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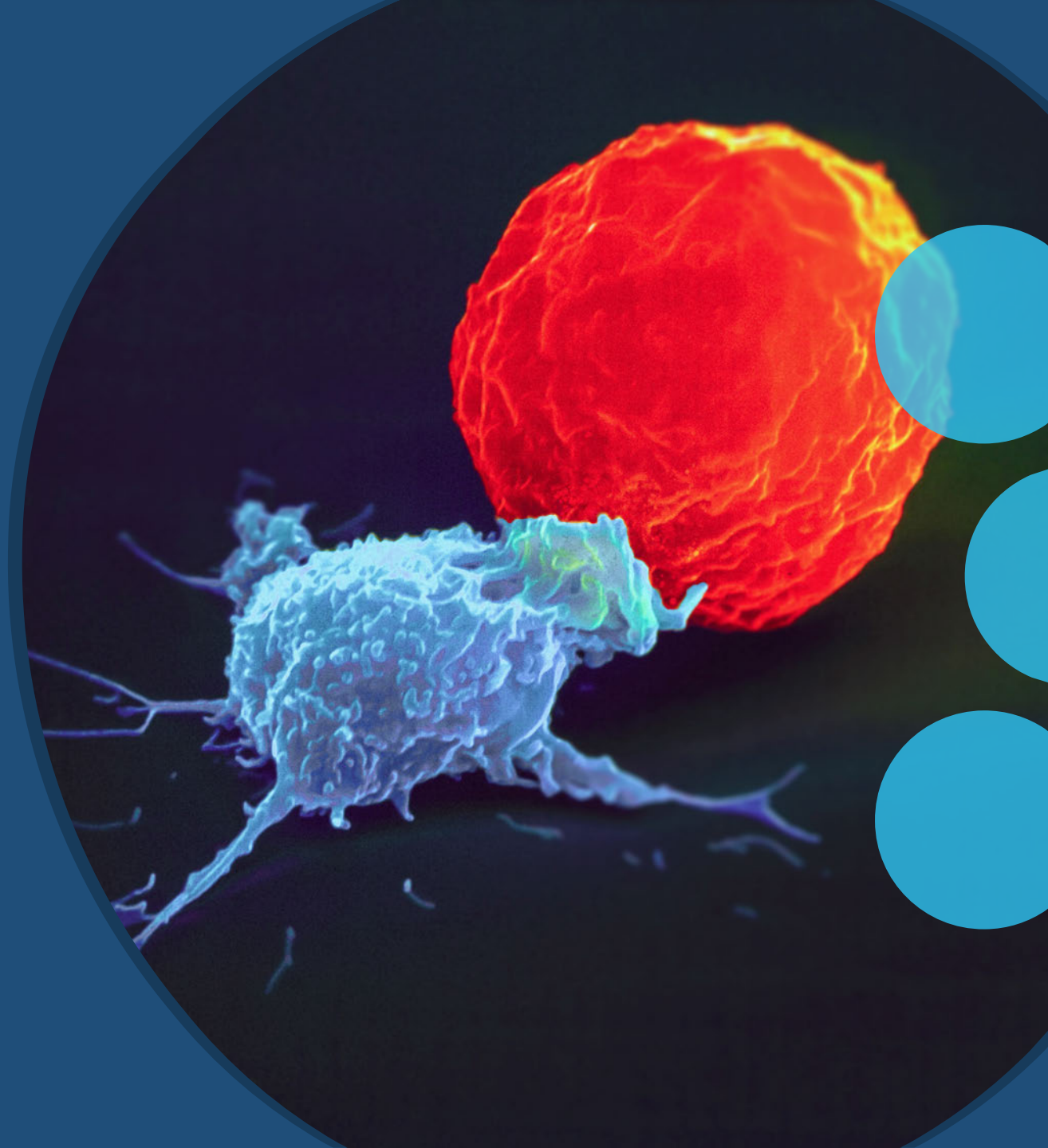
# Allogeneic Natural Killer Cells Engineered to Beat Cancer

November 2020



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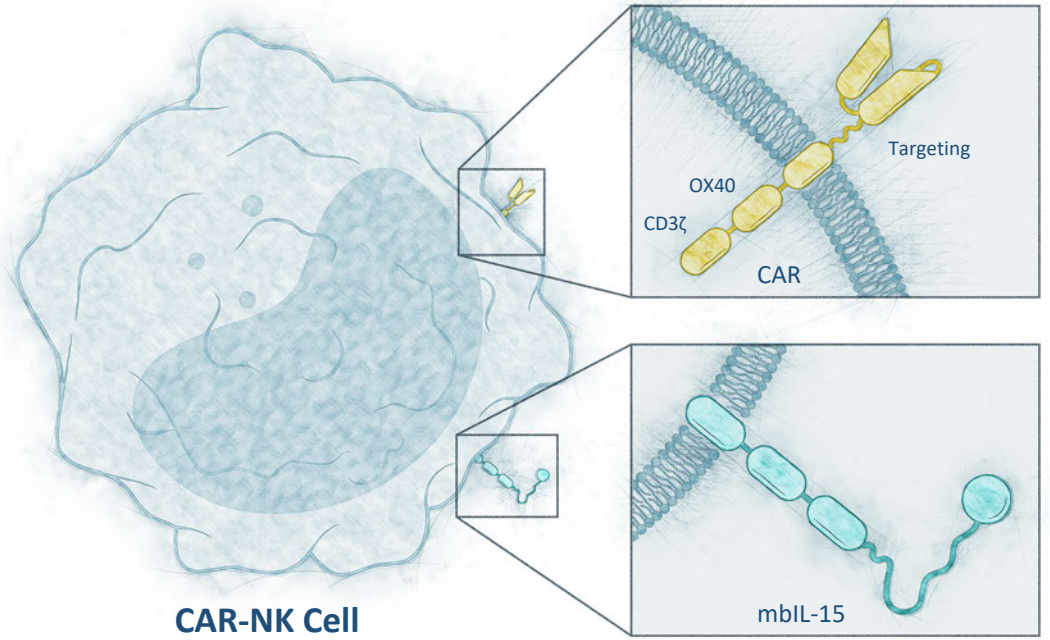
# Highlights: Nkarta engineered CAR-NKs

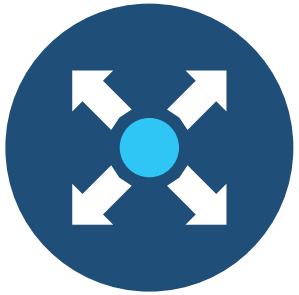
*Natural Killer cells are the cornerstone of innate immune surveillance*

- Allogeneic and off-the-shelf
- Attractive cost of manufacturing
- Proprietary expansion, persistence, tumor targeting and cryopreservation technologies
- Potential for outpatient administration
- Co-lead programs
  - NKX101, Phase 1
  - NKX019, IND expected to file 1Q 21




**Targeting receptor, OX40 costimulatory domain, CD3ζ signaling moiety, membrane bound IL-15**

# Nkarta proprietary technologies



**Expansion**

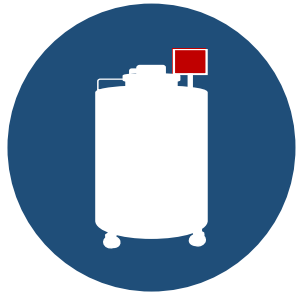
Co-culture with proprietary K562 stimulatory cell line to achieve high cell doses

**Persistence**

Expression of proprietary membrane bound IL-15 to enhance time in circulation

**Targeting**

Engineered for expression of optimized CARs



**Cryopreservation**

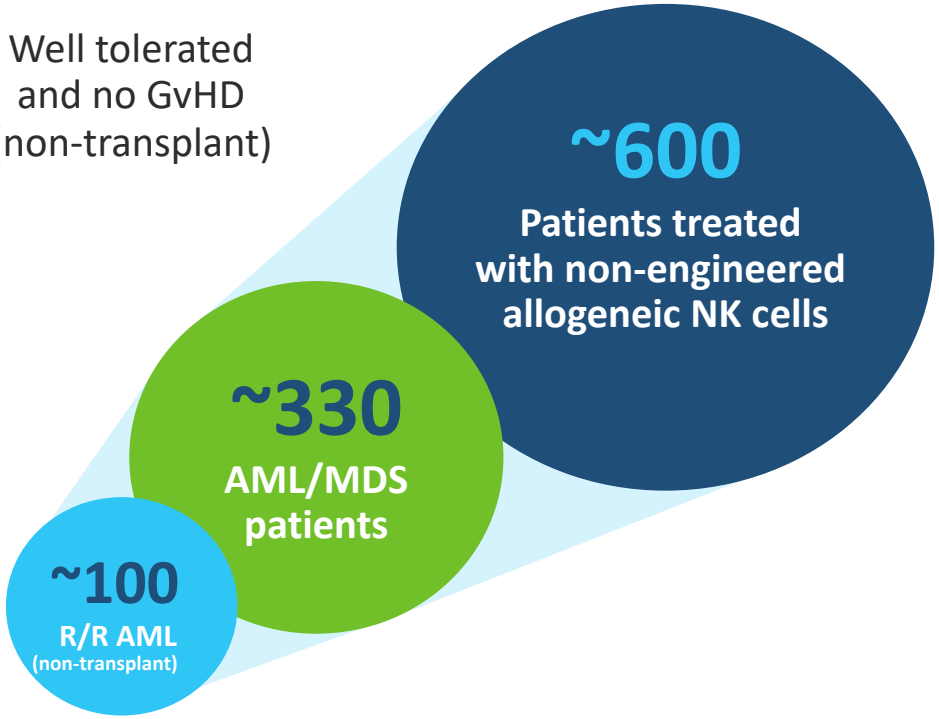
Maintains NK cell viability and potency

# Extensive clinical experience validates NK approach

## NKG2D

Patients have been treated with non-engineered NK cells across ~30 studies

Well tolerated and no GvHD (non-transplant)




~34% aggregate CR rate

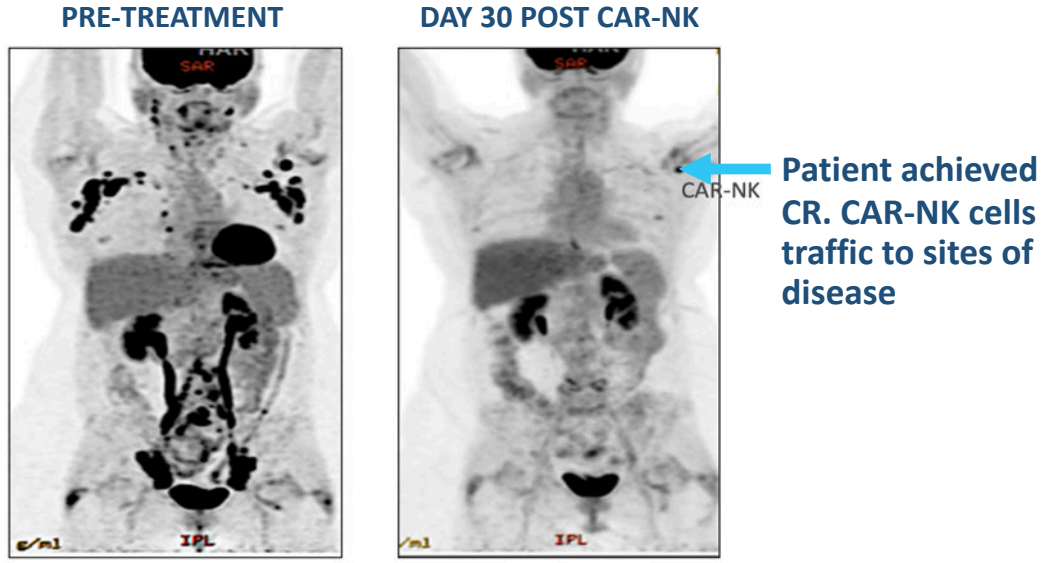
*Velluchamy 2017; Nkarta systematic literature review. CR: Complete remission.*

## CD19

MD Anderson study with CD19 CAR-NK cells

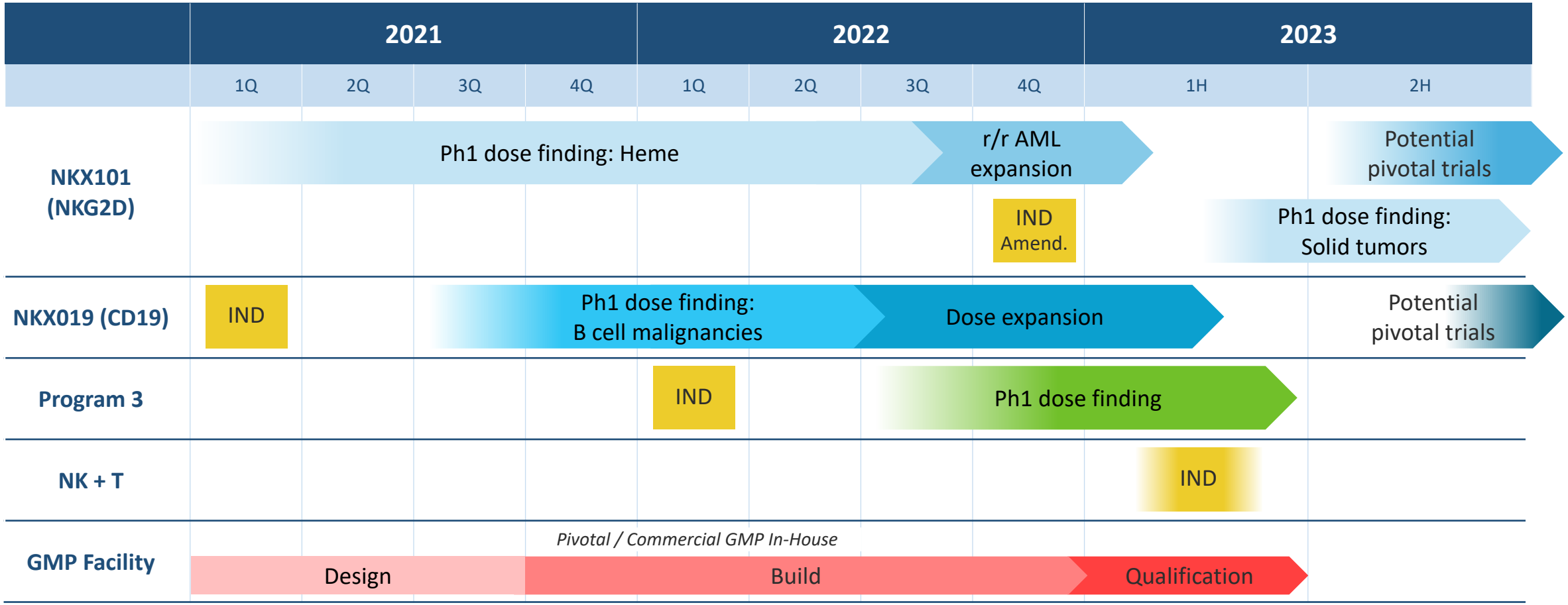
- Published in *New England Journal of Medicine, Feb 2020*

- ✓ 7 / 11 CRs in patients with advanced B cell malignancies
- ✓ No reported CRS, GvHD or neurotoxicity




*Katayoun Rezvani, M.D., Ph.D., et al., N Engl J Med 2020, 382:545-553. DOI: 10.1056/NEJMoa1910607.*
*Takeda Investor Day 2019. CRS: Cytokine release syndrome. GvHD: Graft versus host disease.*

# Pipeline




**NKX101 heme IND cleared 3Q20; in-house clinical GMP facility completed mid 2020**

## MANAGEMENT TEAM

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# Platform

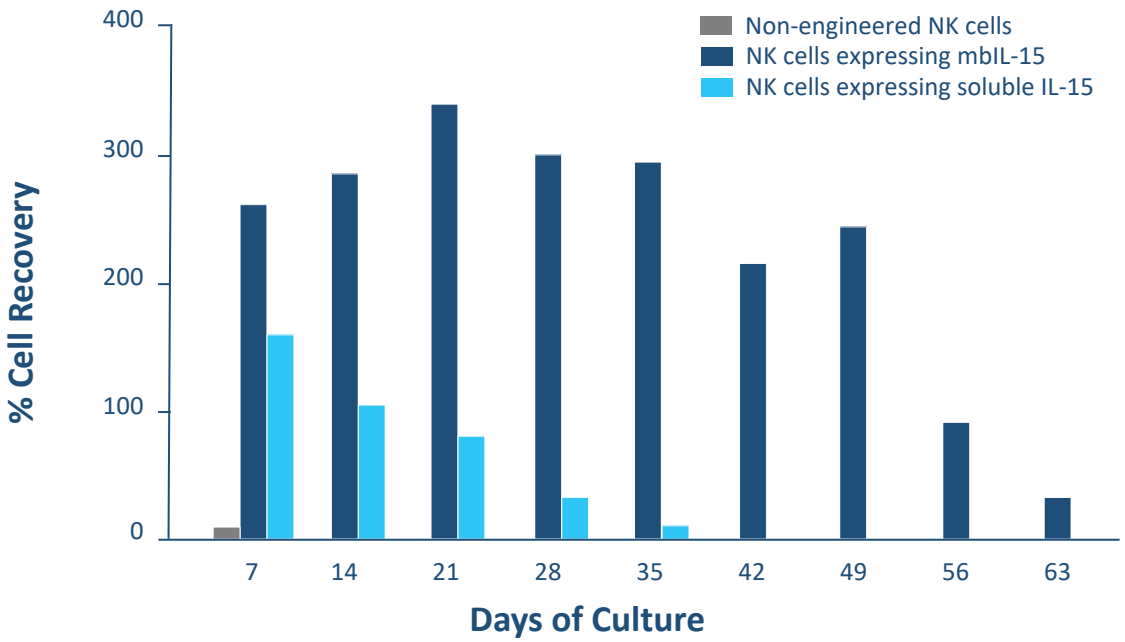
# Nkarta CAR-NKs: engineered to enhance activity

| | APPROVED CAR-T THERAPIES | ALLO CAR-T THERAPIES | NK CELLS | CAR-NK CELLS |
|---|---|---|---|---|
| OPPORTUNITY FOR IMPROVED SOLID TUMOR ACTIVITY | | | | ✓ |
| PERSISTENCE | ✓✓ | ✓ | | ✓ |
| LOW GVHD RISK | ✓ | TBD | ✓ | ✓ |
| LOW RISK OF CRS OR NEUROTOXICITY | | | ✓ | ✓ |
| ALLOGENEIC, OFF-THE-SHELF MANUFACTURING | | ✓ | | ✓ |
| COST OF MANUFACTURING | +++ | ++ | ++ | + |

**Nkarta's platform is designed to generate CAR-NKs engineered to address the limitations of current CAR-T therapies, including safety concerns, tumor targeting, manufacturing time and COGS**

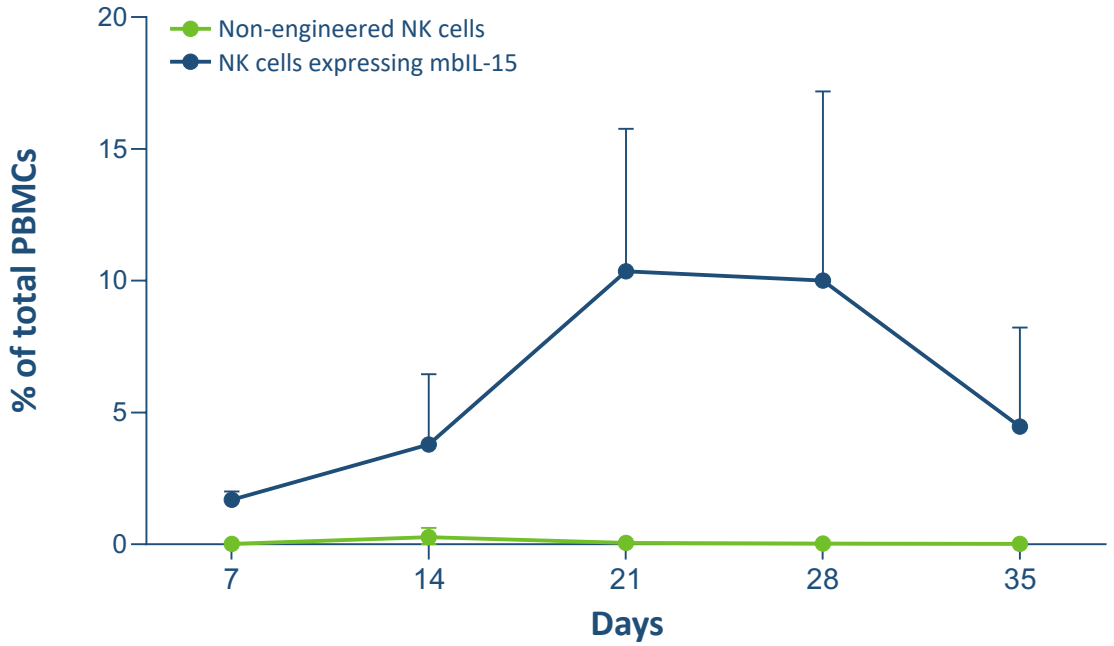
# Superior persistence from membrane bound IL-15

## *In vitro* persistence




*Source: Imamura, Blood 2014*

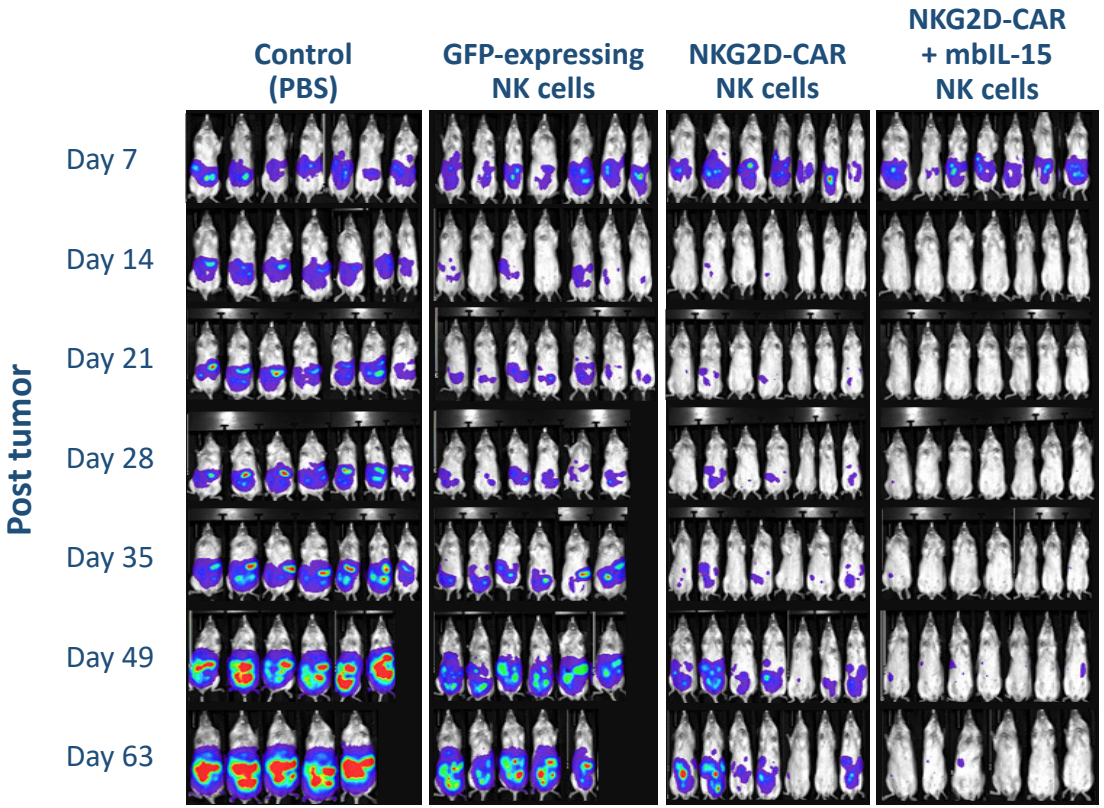
## *In vivo* persistence and expansion in NSG mice

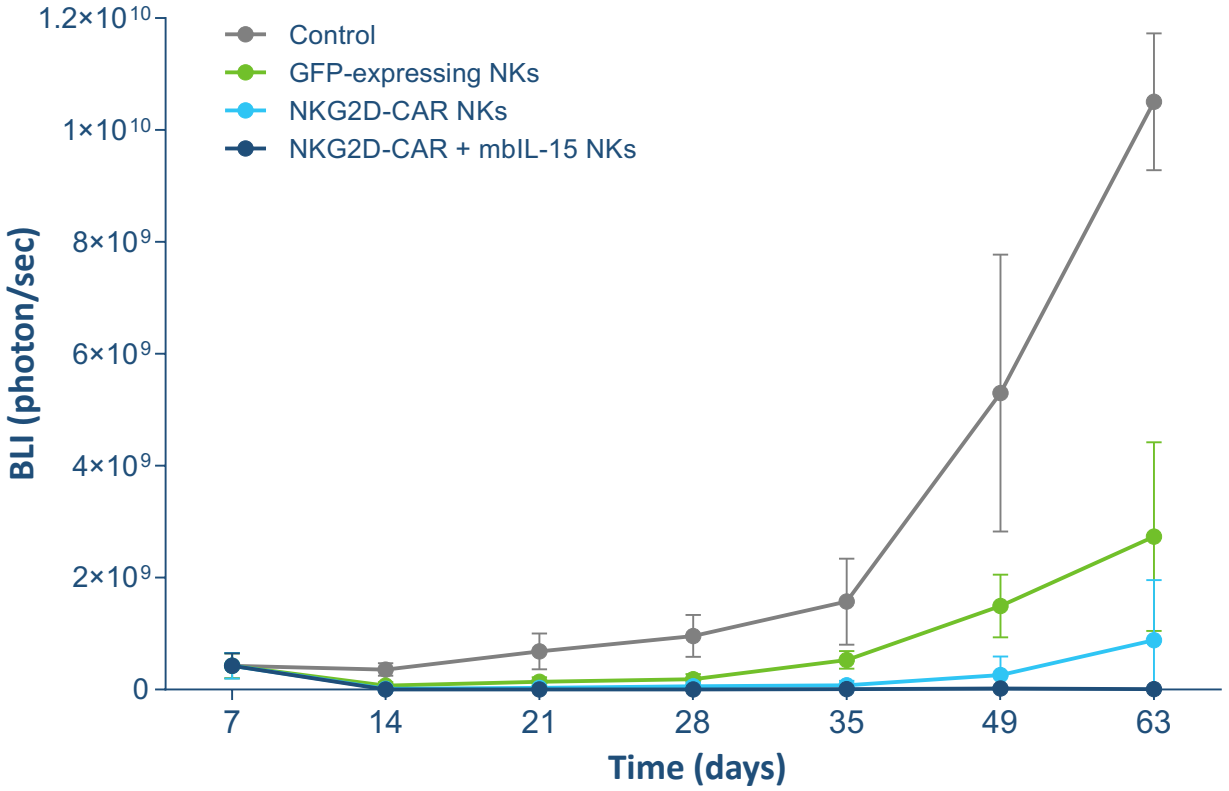



*Source: Nkarta. N = 5 per arm.*

**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 activity

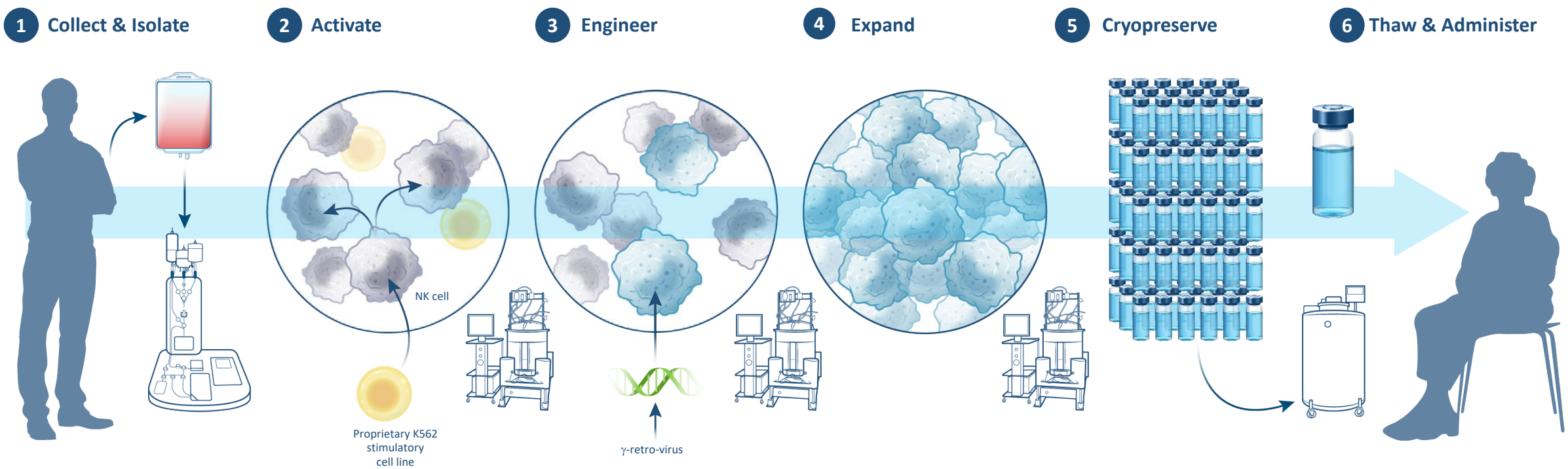



*Source: Nkarta. U2OS osteosarcoma model; 3 x $10^6$ NK cells administered on D7. Graphical data at right are average BLI of mice above.*

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

# Allogeneic, commercially-enabling manufacturing




NK cells collected from healthy donors by leukapheresis.

NK cell expansion using proprietary stimulatory cells.

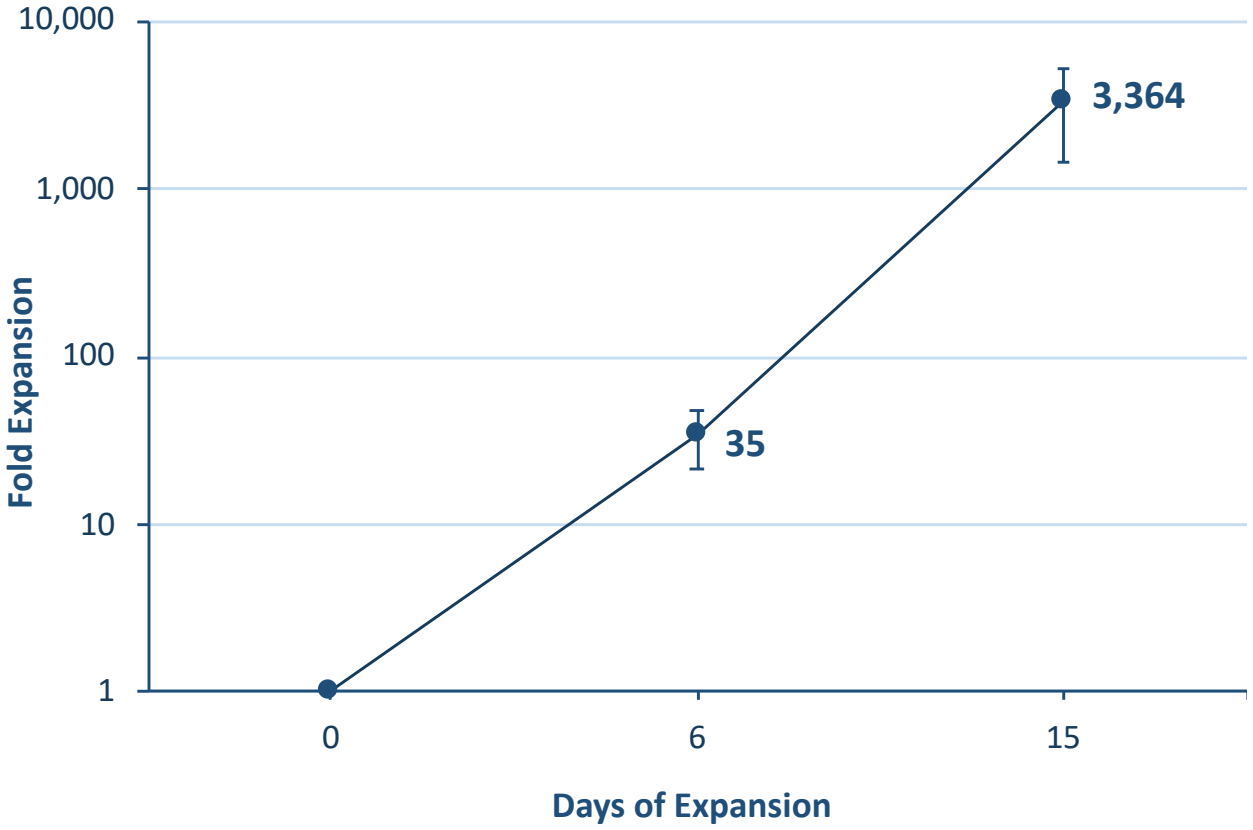
Expanded NK cells are transduced to express mbIL-15 and CAR.

Continued expansion driven by mbIL-15.

Harvesting and cryopreservation of final cell product.

NK product candidate is thawed for off-the-shelf administration to patients.

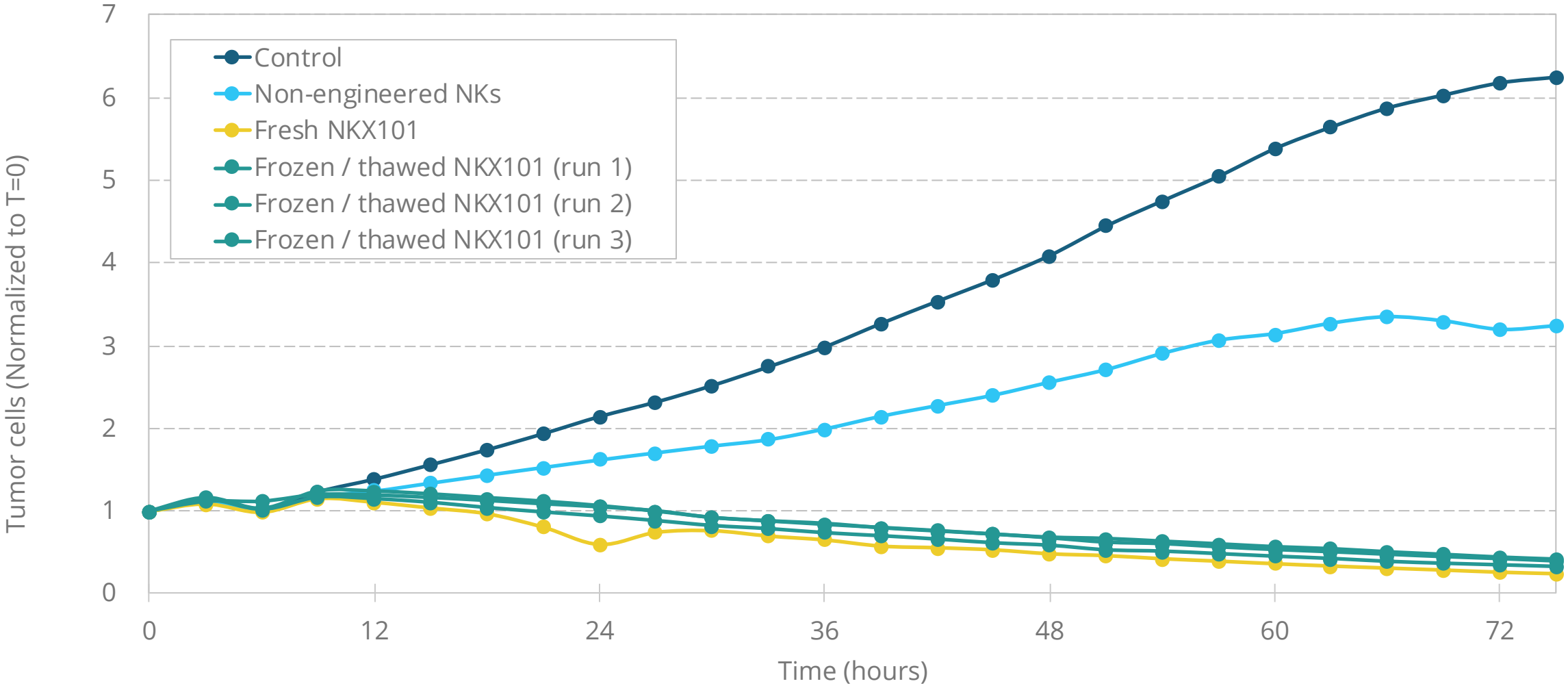
# Proprietary expansion to enable large scale manufacturing




*Data above are from the process development of NKX019 for cGMP manufacturing and are an average of 5 expansions from 4 different donors.*

- Extensive optimization enables truly off-the-shelf products
- In-house cGMP manufacturing suite construction recently completed
- Projected cost of commercial manufacturing at peak:
  ~$2,000 / dose (500 doses / batch)

# Cryopreserved NKX101 retains *in vitro* cytotoxicity




**Cryopreserved NKX101 retains cytotoxicity similar to fresh NKX101 in a long-term assay**

# In-house clinical GMP facility: construction complete

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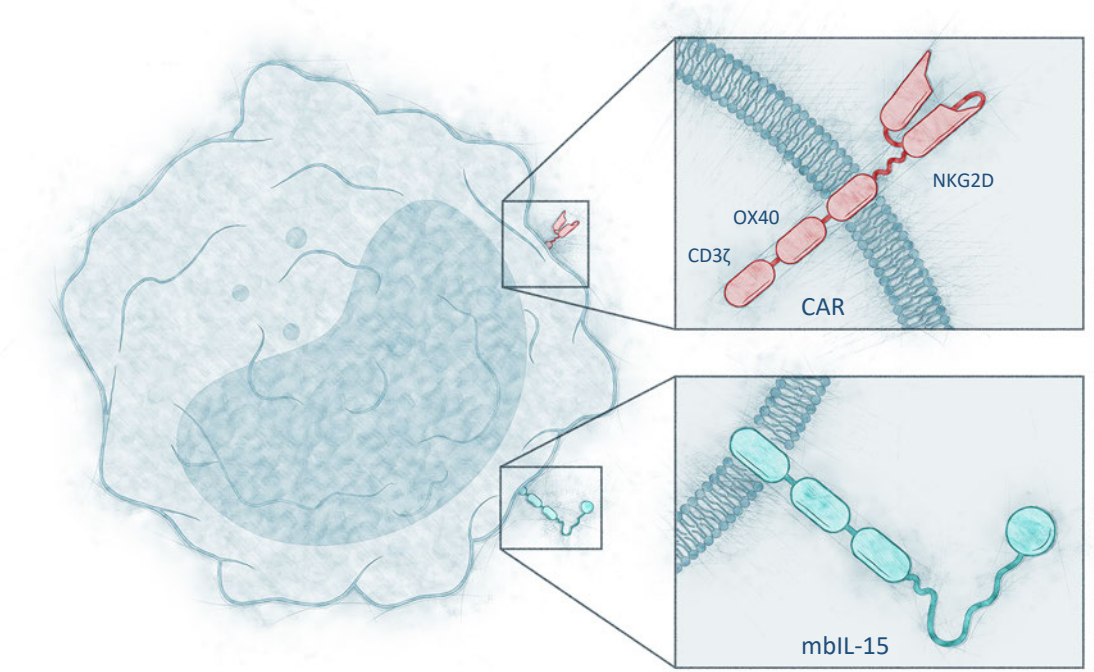
# Pipeline

# 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




**NKX101: NKG2D activating receptor, OX40 costimulatory domain, CD3ζ signaling moiety, membrane bound IL-15**

# NKG2D: ligands enriched in tumors, demonstrated responses

## NKG2D ligand expression is documented in multiple tumor types

| TUMOR TYPE | REFERENCE |
|---|---|
| **AML, ALL, CML, CLL** | Hilpert, *J Immunol* 2012 |
| **MULTIPLE MYELOMA** | Carbone, *Blood* 2005 |
| **HCC** | Kamimura, *J Hep* 2012 |
| **BREAST** | de Kruif, *BMC Can* 2012 |
| **OVARIAN** | McGilvray, *Int J Can* 2010 |
| **LUNG** | Okita, *Can Imm Immunother* 2016 |
| **COLON** | McGilvray, *CCR* 2009 |
| **MELANOMA** | Vetter, *J Inv Derm* 2002 |
| **OSTEOSARCOMA** | Lu, *Neoplasma* 2008 |
| **GLIOMA** | Weiss, *CCR* 2018 |

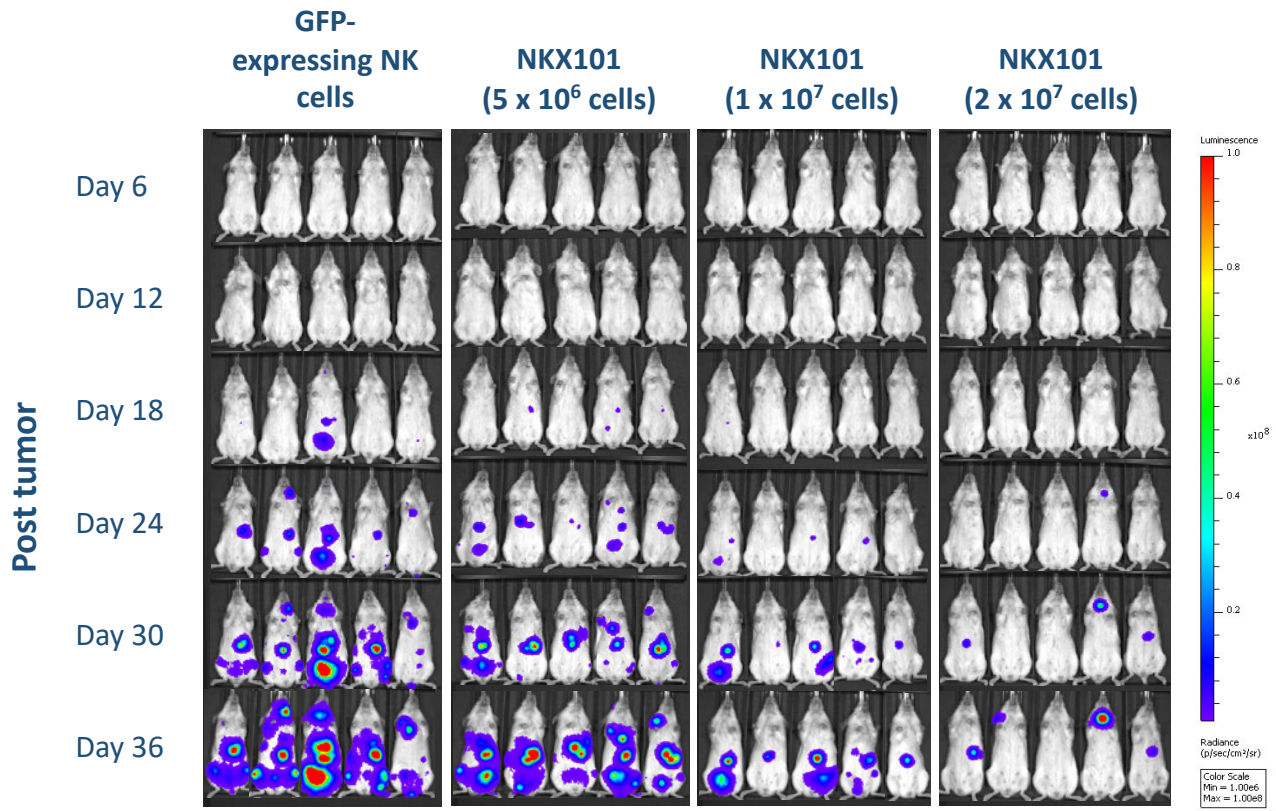
## Clinical responses observed in R/R AML with non-engineered allo-NKs validate NKG2D

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

**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: Acute myeloid leukemia (AML)

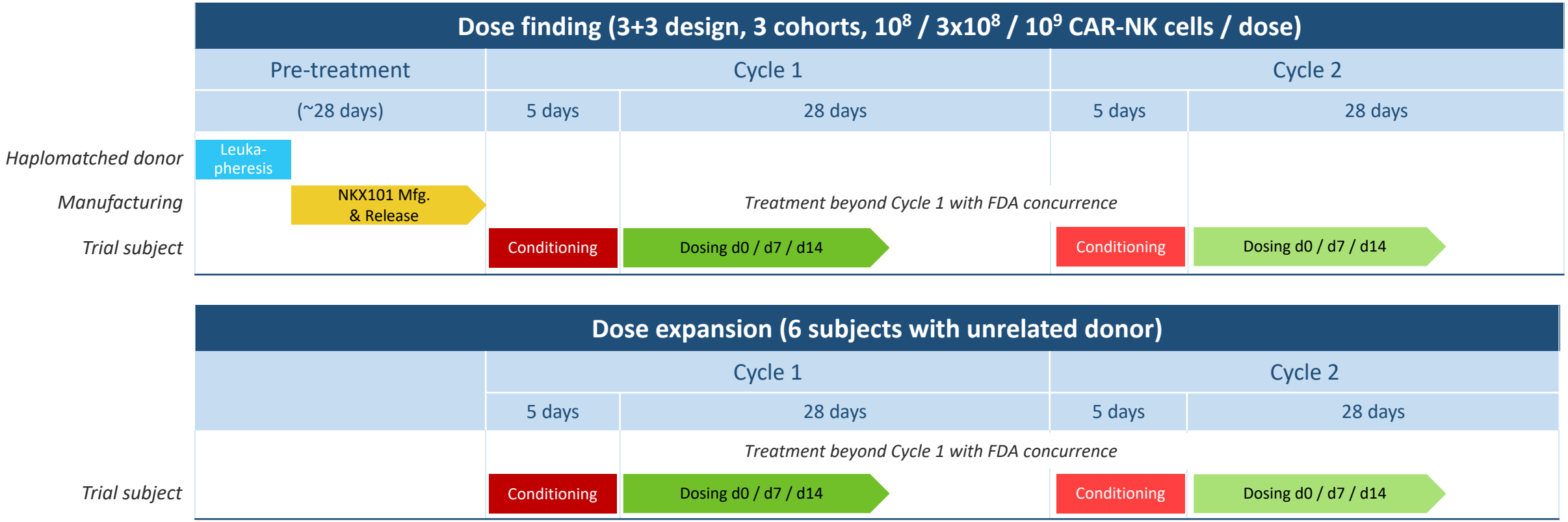
- AML US incidence: ~21K / yr
  - 5-year survival rate ~28%
- NKG2D targets are over-expressed in AML blasts
- Clinical activity with non-engineered NKs
- Phase 1 multi-center clinical trial in r/r AML and higher-risk MDS patients currently enrolling: NCT04623944




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

*Sources: SEER database; Veluchamy, Front Immunol 2017; Brayer ASH 2018; Hilpert, J Immunol, 2012*

# NKX101: Heme dose finding and expansion

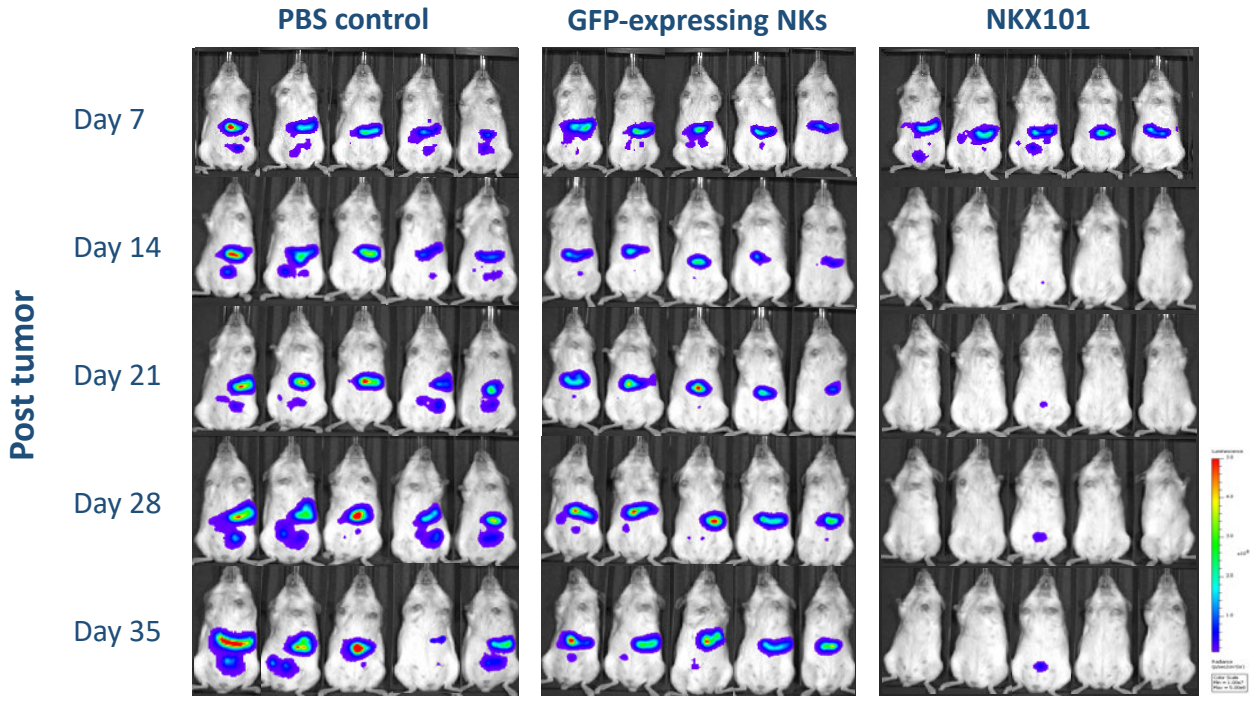



**In addition to haplomatched subjects, the dose expansion cohort is designed to evaluate subjects treated with off-the-shelf NKX101 – our expectation for pivotal trials and commercial use**

# NKX101: 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

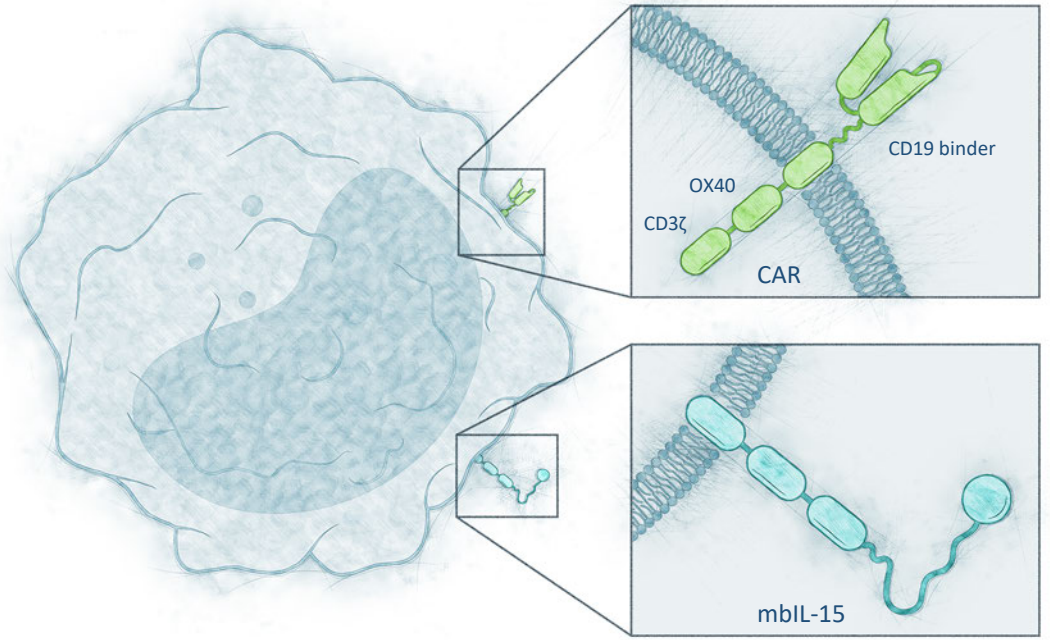



SNU449 HCC xenograft model
3 x $10^6$ NK cells injected at day 7 post-tumor

*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; IND 1Q21

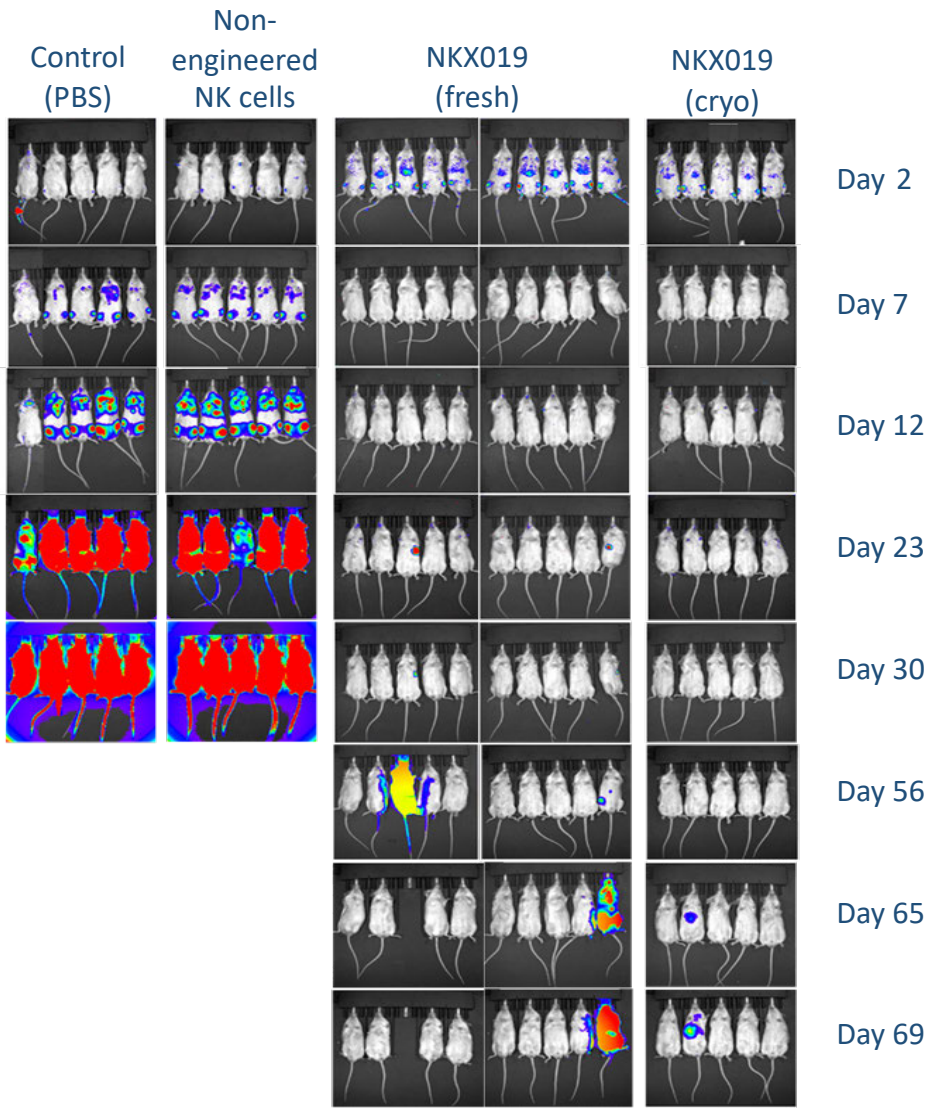
- Large opportunity after CAR-T approvals:
  - Gr3+ CRS: 13–49%; Gr3+ neurotoxicity: 18–31%
  - Limited number of specialized sites can treat
  - 9–34% of patients in pivotal trials didn't receive cells (primarily due to mfg. challenges)
- Rezvani (MDACC / Takeda) CAR19-NK:
  - 7 / 11 CRs in patients with B-cell malignancies (median 4 prior rounds Tx)
  - No reported CRS, GvHD or neurotoxicity
- Phase 1 in B-cell malignancies
  - Off-the-shelf NKX019
  - $3x10^8$ starting dose, 2 dose finding cohorts
  - Several dose expansion cohorts thereafter

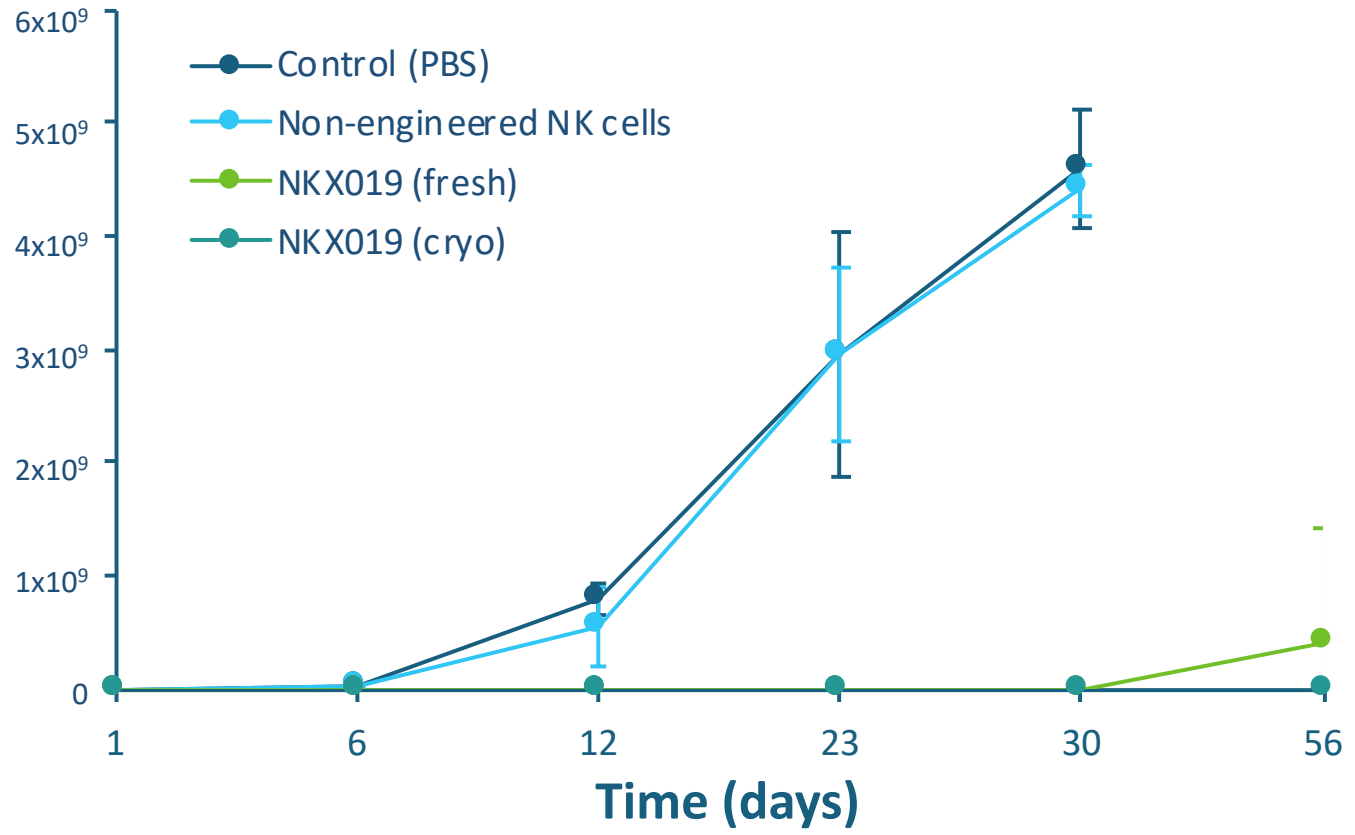



**NKX019: Proprietary CD19 binder, OX40 costimulatory domain, CD3ζ signaling moiety, membrane bound IL-15**

*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.*

# NKX019: Activity in lymphoma model




Nalm-6 lymphoma model. $10^7$ 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**

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# Corporate

# Intellectual property

## PLATFORM

### NK cell expansion
- Multiple issued patents and pending applications
- Compositions and methods of expansion/treatment
- Expiry ~2024 to ~2038

### NK cell persistence
- Allowed US application and multiple pending OUS applications
- Expiry ~2035

### Pipeline
- Provisional applications
- Compositions & treatment methods
- Expiry ~2039 to ~2040

## NKX101

### NKG2D target
- Issued US patents and multiple pending US/OUS/PCT applications
- Claims to various NKG2D targeting constructs & treatment methods
- Expiry ~2034 to ~2039

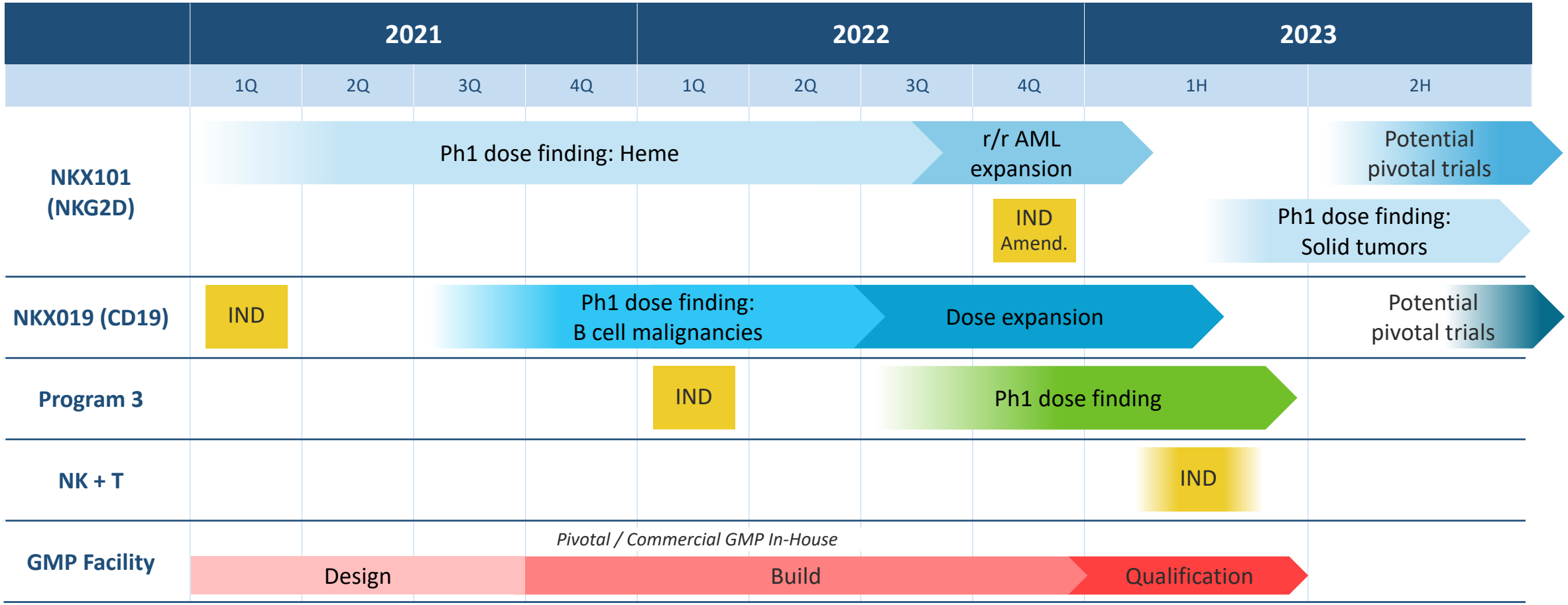
### Local NKX101 delivery
- Provisional applications
- Local delivery to tumors
- Expiry ~2039

### Combo Therapy
- Provisional applications
- NKG2D construct + adjunct therapy
- Expiry ~2039

## NKX019

### CD19
- Provisional applications
- Cells expressing tumor-targeting receptor & cytotoxic effector
- Expiry ~2040

# Anticipated Milestones

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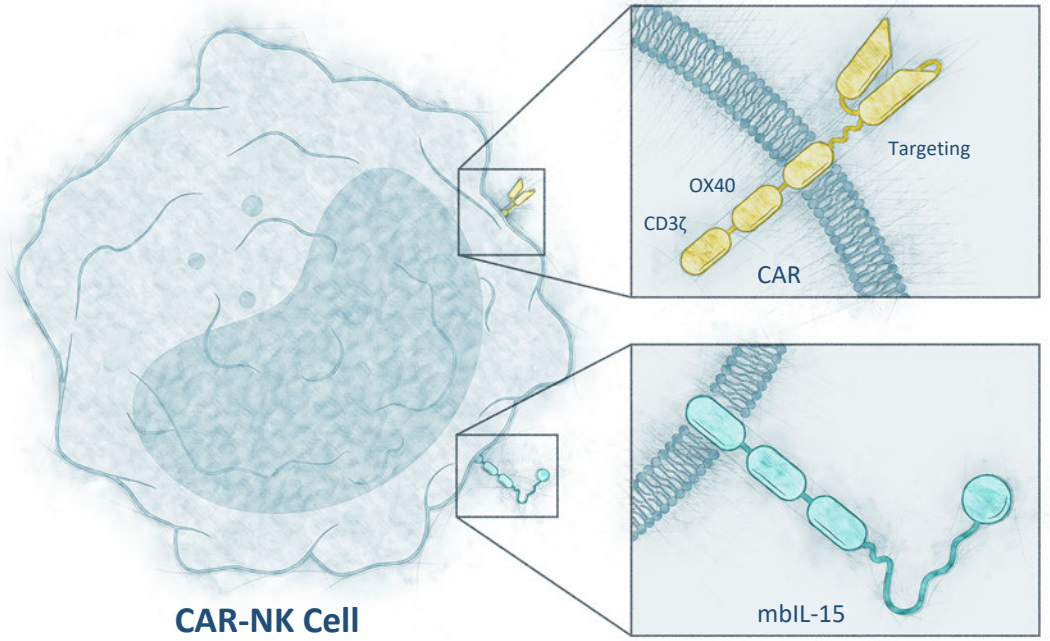


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# Thank you!