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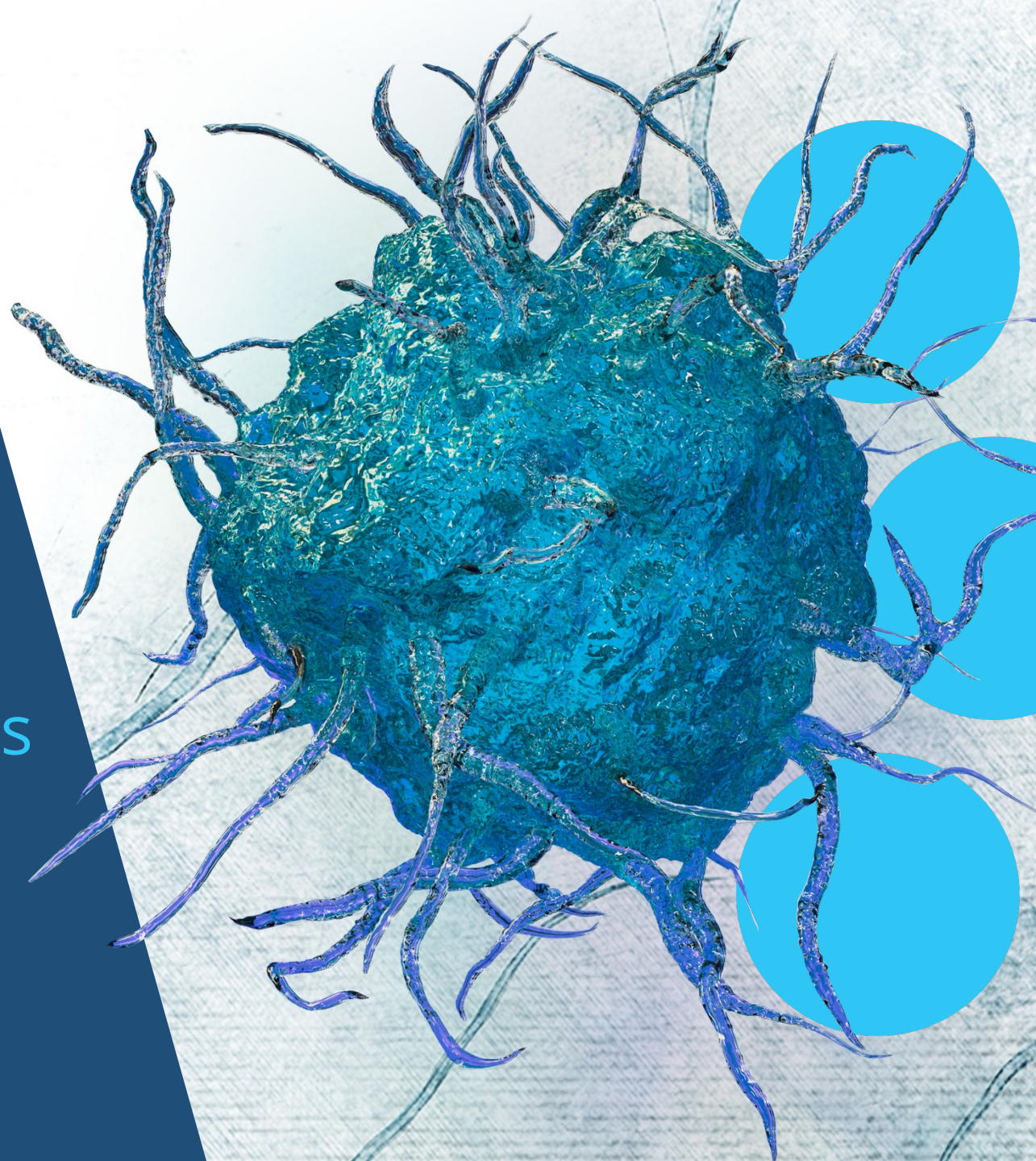
ENGINEERING

Natural Killer Cells

for next generation treatment of cancer and autoimmune diseases

ON DEMAND



FEBRUARY 2024

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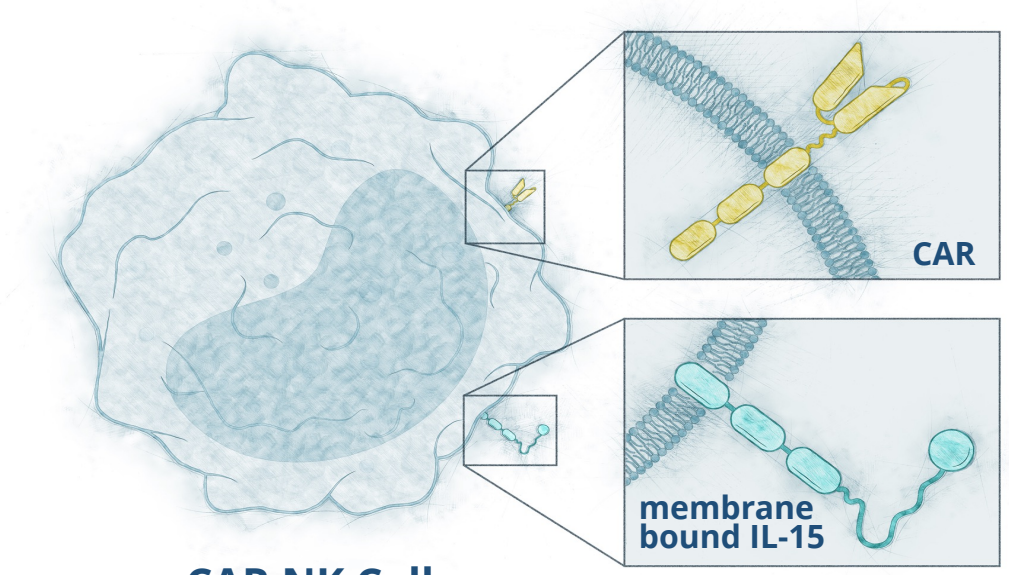
Delivering the future of cell therapy by harnessing the killing ability of natural killer (NK) cells

- Fully allogeneic from healthy, pre-screened donors
- On-demand, off-the-shelf availability for outpatient administration
- Programs in autoimmune disease and oncology
- Multiple clinical updates expected in 2024
- Cash runway into 2026



CAR NK Cell

- CARs engineered for optimal target cell killing
- Candidates engineered with a targeting CAR and membrane bound IL-15

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Pipeline with transformational potential

Program (Target)	Indication	Research	IND-Enabling	Clinical	Status
NKX019 (CD19)	Lupus Nephritis (SLE)				IND cleared 4Q 2023 First patient enrollment expected 1H 2024
NKX019 (CD19)	r/r NHL				Phase 1 dose-compression cohort ongoing Update planned mid 2024
NKX101 (NKG2D)	r/r AML				Phase 1 ongoing Update planned 1H 2024
NKX101 (NKG2D)	Solid Tumors				Gated on proof of concept in r/r AML
NKX070 (CD70)	Heme & Solid Tumors				Collaboration CRISPR THERAPEUTICS
NK + T (Undisclosed)	Undisclosed				Collaboration CRISPR THERAPEUTICS

Autoimmune Oncology

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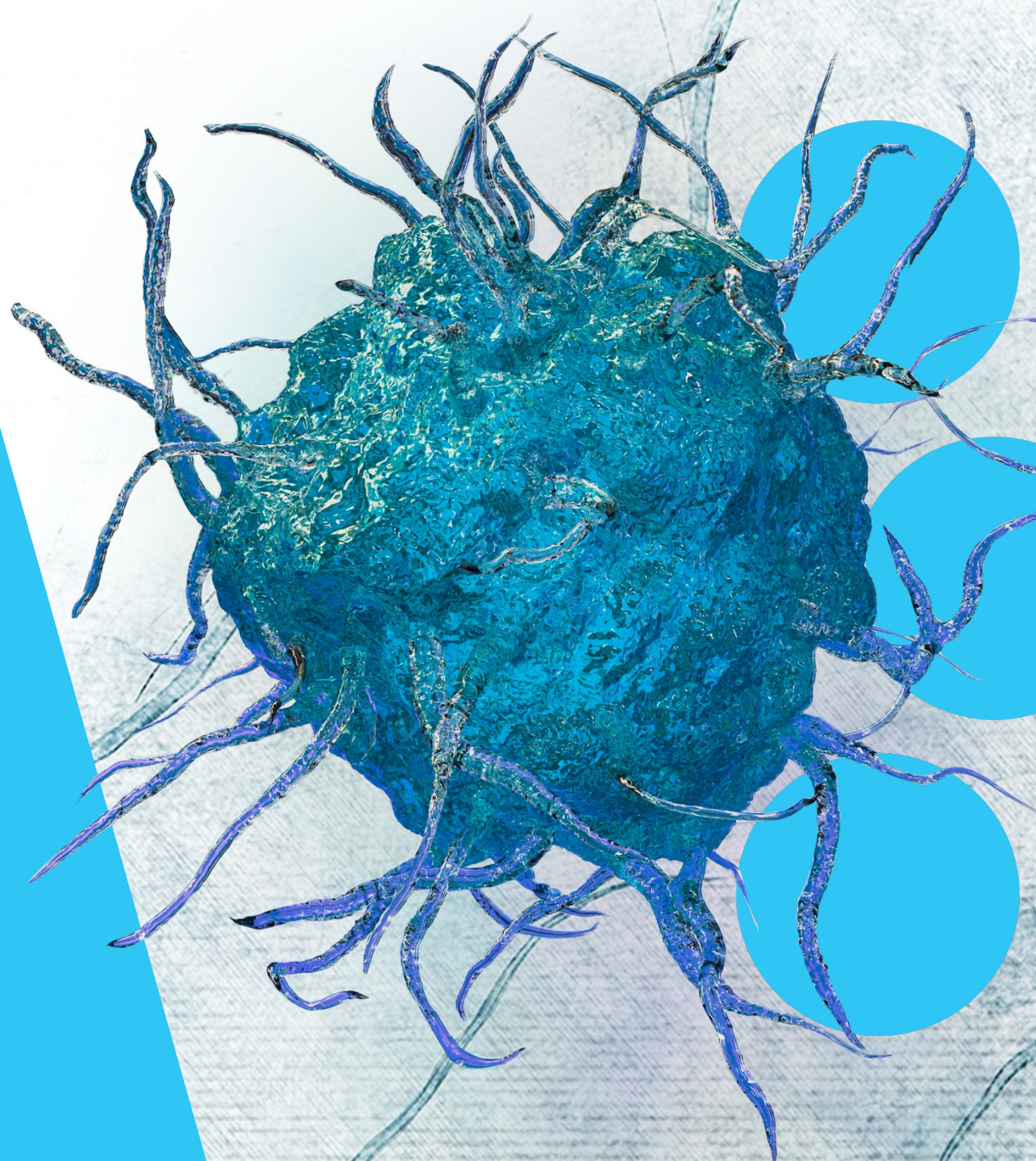
AML, acute myeloid leukemia; NHL, non-Hodgkin lymphoma; r/r: relapsed or refractory; SLE, systemic lupus erythematosus

NKX019 in Autoimmune Disease



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Cell therapy offers a promise of a disease-modifying option for patients with refractory autoimmune disease

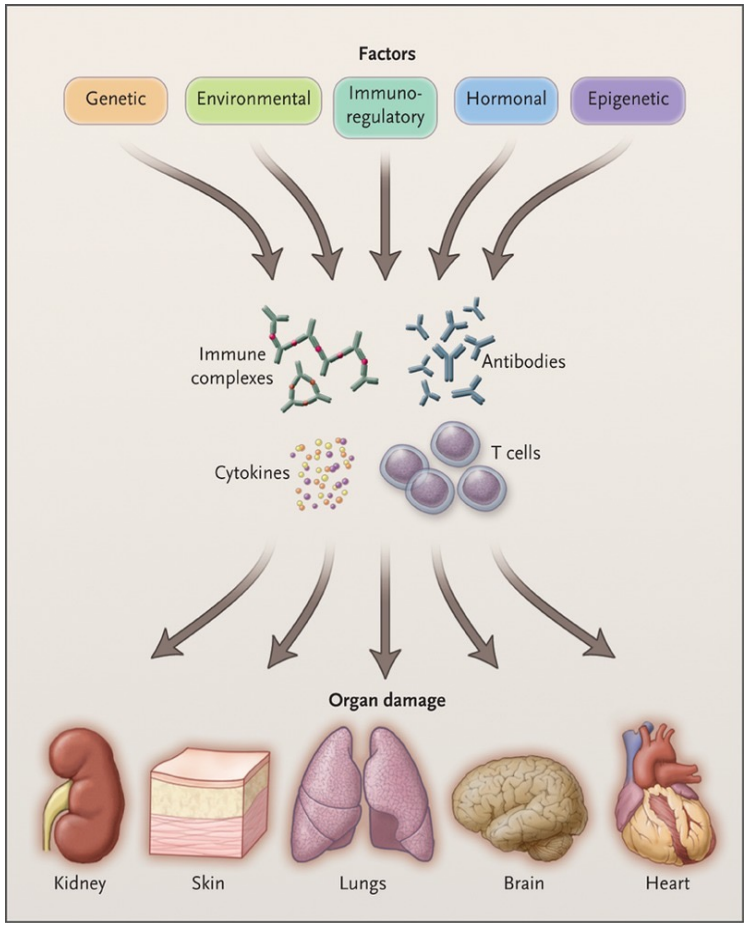
Autoimmune disease is a major unmet need

- Estimated 7 million patients in U.S. with a form of B-cell mediated autoimmune disease[1]
- Pathogenic B cells can drive systemic diseases via combination of intrinsic and extrinsic factors

Effectiveness of current therapies is inadequate and often consists of lifelong immune suppression

CD19-directed cell therapy has challenged the treatment paradigm for autoimmune diseases

- Drug-free remissions after a single treatment in academic trials[2]



Tsokos, *N Engl J Med* 2011; 365:2110-2121.

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1: Canaccord Genuity, 14 Nov 2023.

2: Mackensen et al. *Nature Med*. 28 Oct 22. 2124–2132.

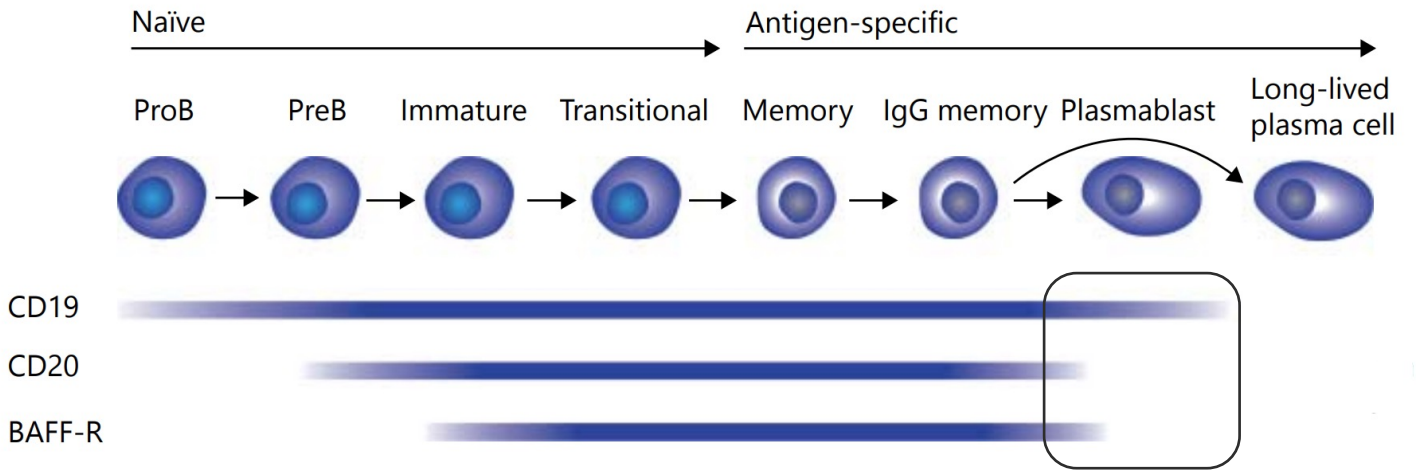
Target, not only modality, may explain benefits of CD19 cell therapy compared to historical responses to B cell-targeting

Benefit of CD19-directed CAR T in SLE may be via elimination of autoantibody-producing cells

- $CD19^{high}$ $CD20^{neg/dim}$ plasmablasts
- $CD19^{neg/dim}$ $CD20^{neg}$ long-lived plasma cells

Current agents that target B cells have inconsistent benefit in SLE

- Rituximab (CD20 antibody)
- Belimumab (BAFF-R antibody)



von Büdingen, et al. *Eur Neurol* 2015;73:238–246.

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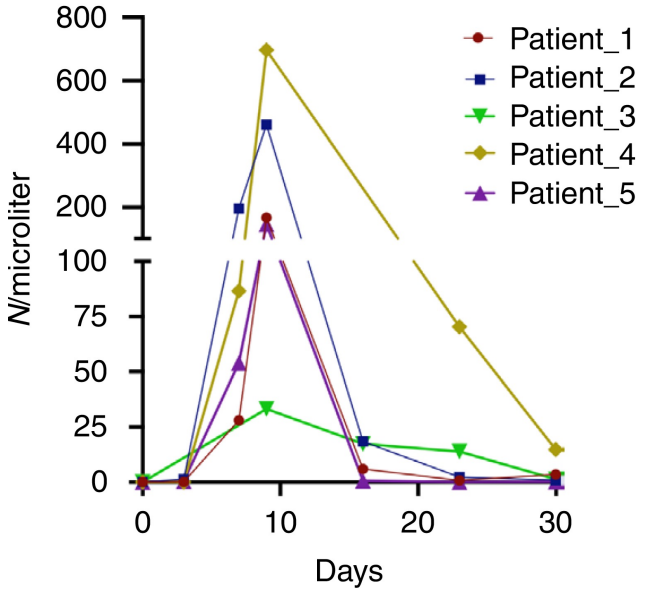
CAR T cell kinetics in autoimmune disease differ greatly from oncology

Transient persistence is followed by rapid elimination in autoimmune disease

- Expansion peaks at ~10 days
- Less antigen burden may explain differences in persistence and exposure

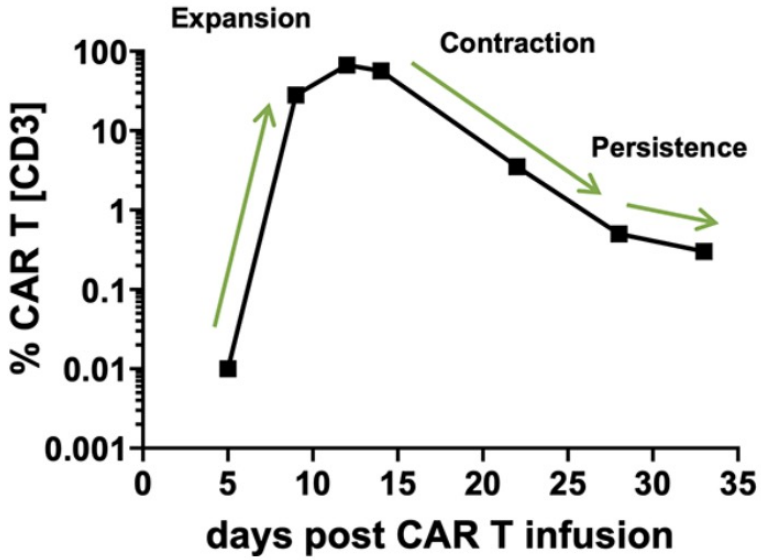
In B cell malignancies, CAR T cells persist long after antigen-dependent expansion

Autoimmune



Mackensen et al. *Nature Med*. 28 Oct 22. 2124–2132.

B cell malignancy



Peinelt, et al. *Front. Immunol.* 2022. 13:830773.

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Transient B-cell suppression can provide treatment-free responses in autoimmune disease

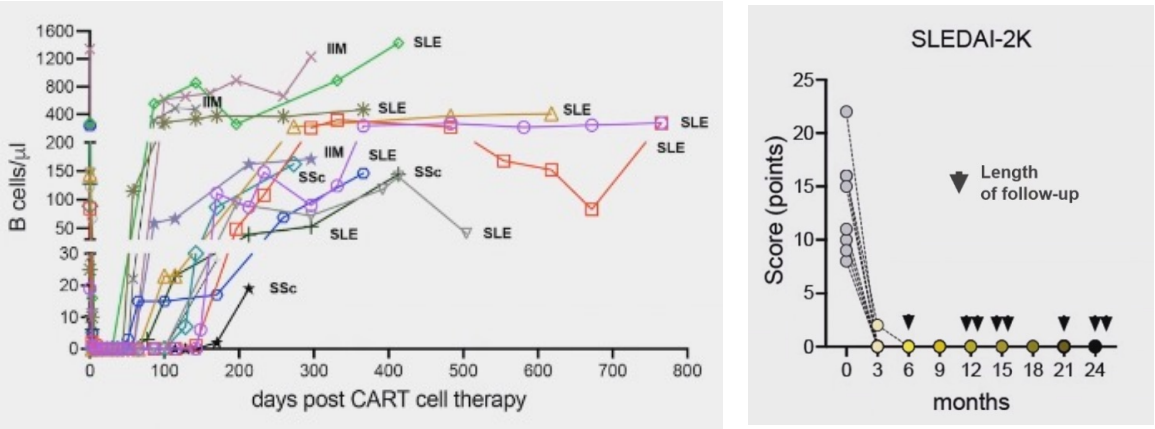
Immune "reset" occurs after B cell suppression as short as 50 days in autoimmune disease

- Persistent B cell aplasia is NOT required for long-term responses
- Autoantibodies remain negative in most patients and drug-free remissions persist

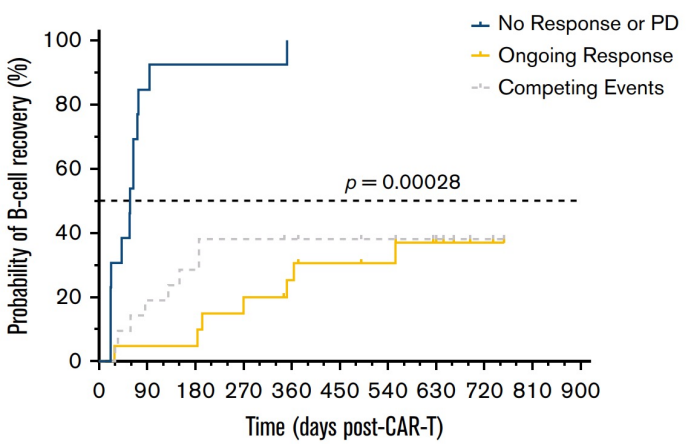
Prolonged B cell aplasia is common in oncology (median ~18 mo[1]), especially in responders

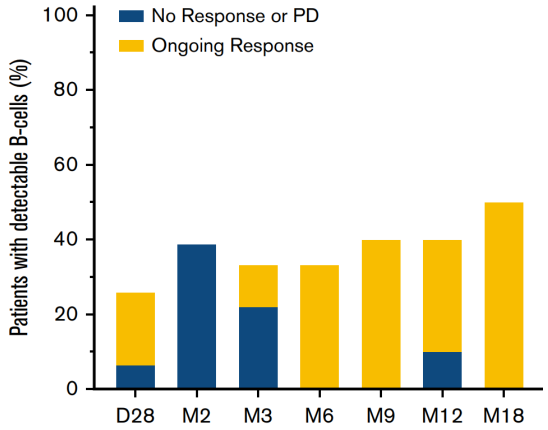
- Absence of B cells is used as clinical proxy for detection and activity of CAR T cells
- B cell recovery within 3 months of infusion is associated with disease progression

Autoimmune



B cell malignancy





Muller et al. Abstract 220, ASH 2023.

1: Bhoj, et al. *Blood. 2016 Jul 21; 128(3): 360–370.*

Baird, et al. 2021. *Blood Advances 5(1):143-155.*

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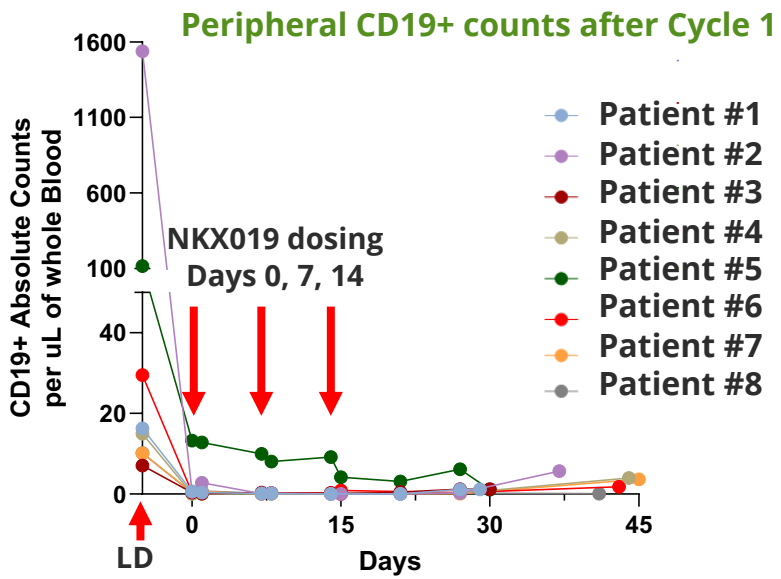
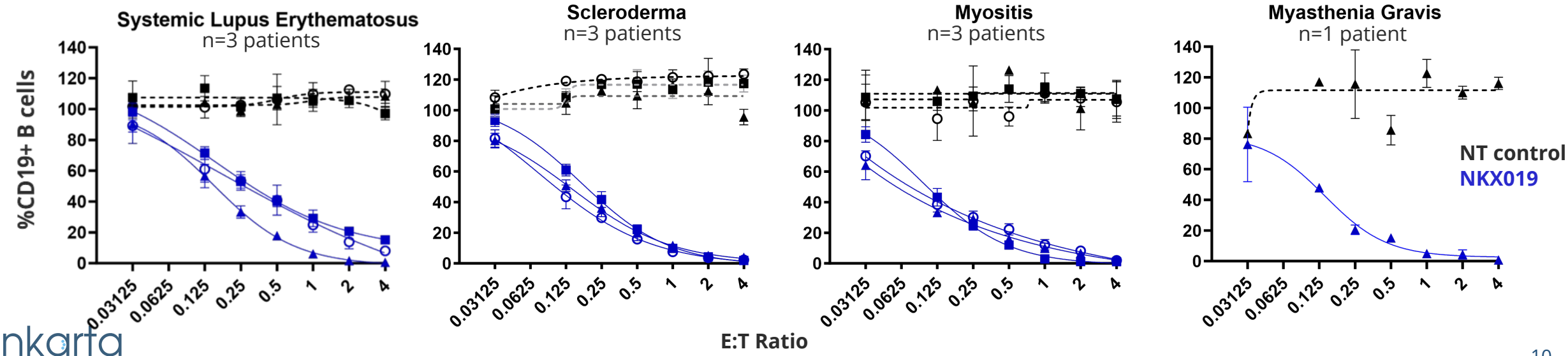
NKX019 targets and kills cells from patients across indications

Patient samples from ongoing NHL trial show effective elimination of CD19+ cells from circulation by NKX019

- Normal and malignant cells cleared with a single cycle
- One cycle includes lymphodepletion and 3 doses of NKX019
- Deep suppression achieved by day 30

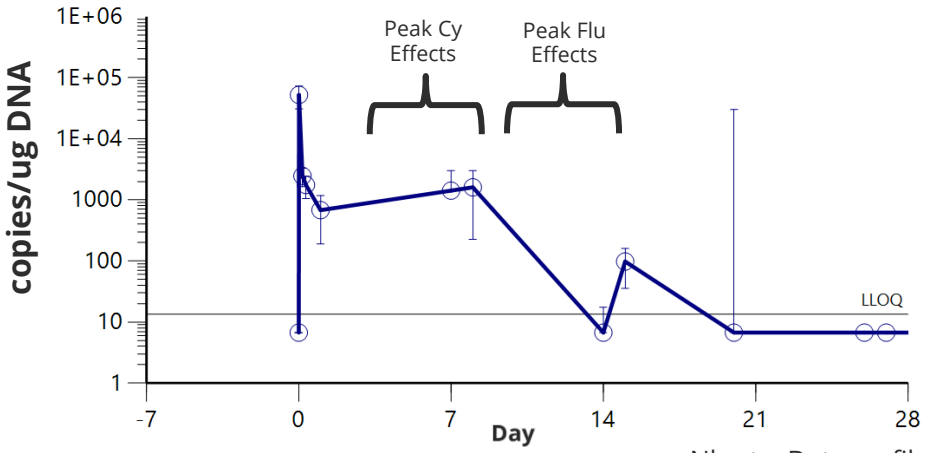


***In vitro* studies using blood from patients with various autoimmune diseases show consistent B cell killing**



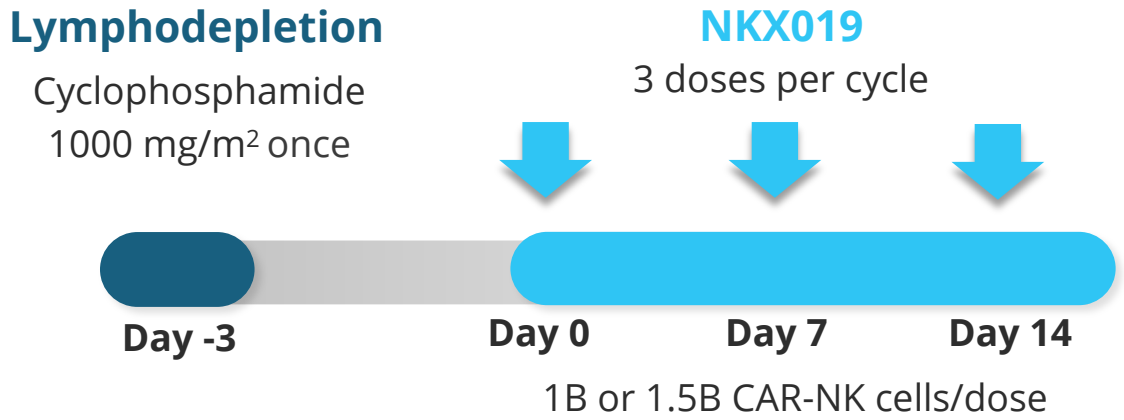
Disease-tailored lymphodepletion with cyclophosphamide alone could provide a critical advantage for patients with autoimmune disease

CAR NK Pharmacokinetics



Nkarta. Data on file.

NKX019 Protocol in Autoimmune Disease



Early C_{max} of NK cells may lessen need for prolonged suppression provided by fludarabine

- LD is tailored to limit chemotherapy exposure as delayed peak effect offers less benefit for NK cells
- Elimination of fludarabine also lessens risks of cytopenias, infection, and secondary MDS[1]

Historical use of single agent Cy at same dosage offers additional benefits

- Rheumatology providers and patients more familiar with Cy
- Possible regulatory advantage leveraging prior studies and real-world evidence

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Cy: cyclophosphamide; Flu: fludarabine
LD: lymphodepletion

1: Fludarabine USPI.

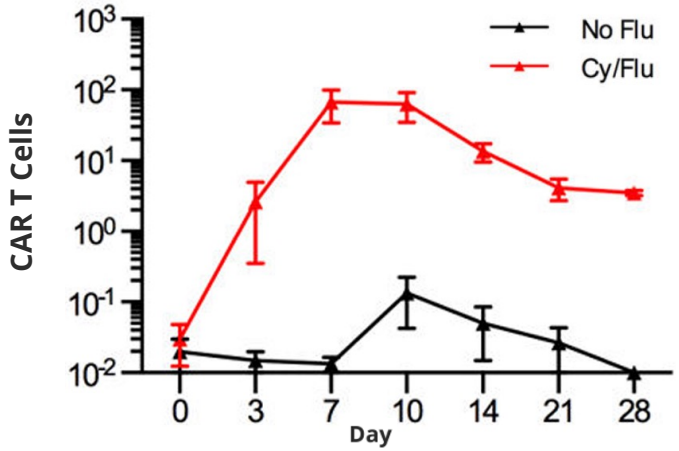
Autologous CD19 CAR T cells require fludarabine-containing LD for maximal exposure due to induction of endogenous cytokines, especially IL-15

Despite no immune barrier, autologous CAR T cells depend on multi-agent LD for elimination of "cytokine sink" to facilitate expansion

- Fludarabine-sparing LD results in limited CAR T expansion and benefit
- IL-15 levels peak shortly after infusion and correlate with expansion

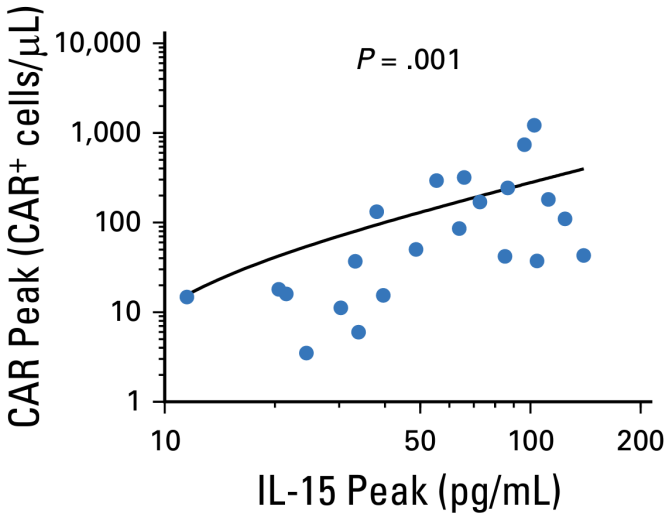
Lower peak IL-15 levels associated with decreased responses in CAR T[1]

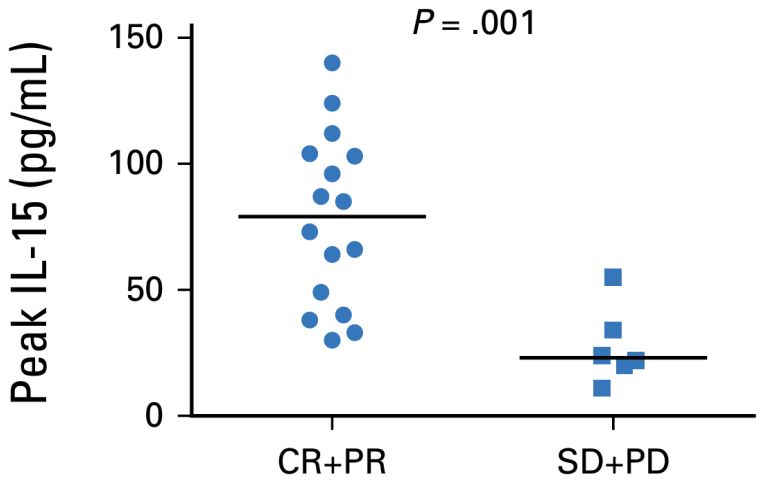
LD without fludarabine results in lower CAR T expansion and persistence



Turtle, et al. *Sci Transl Med.* 2016 Sep 7;8(355).

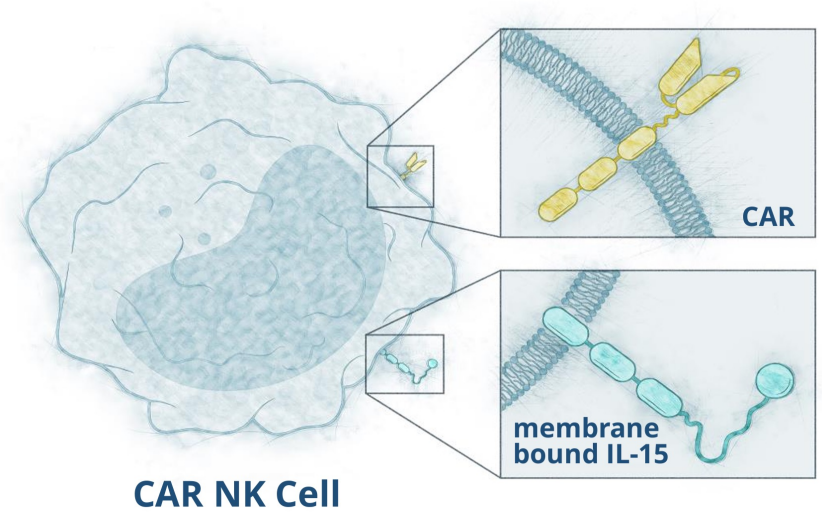
Higher peak IL-15 after LD correlates with CAR T expansion and responses

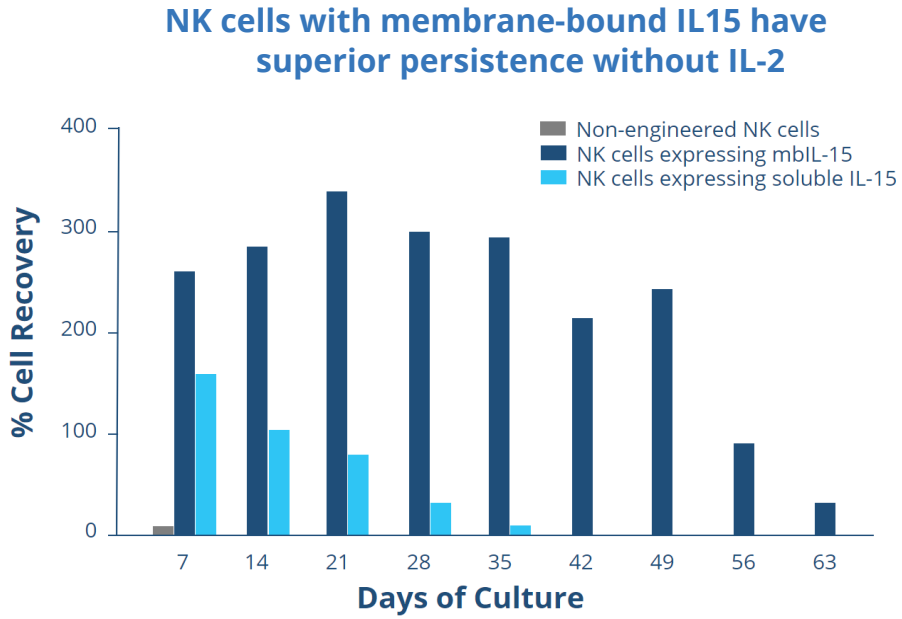




1: Kochenderfer, et al. *J Clin Oncol*. 2017 Jun 1;35(16).

NKX019 engineering allows cytokine independence, further enabling disease-tailored LD





Autocrine stimulation by membrane-bound IL-15 (mb-IL15) provides pro-survival signal

- mb-IL15 allows NKX019 to survive several weeks without supplemental cytokines like IL-15 or IL-2
- Construct causes no secreted IL-15 and has limited cross-cell stimulation

Imamura, et al. *Blood* 2014 Aug 14;124(7):1081-8

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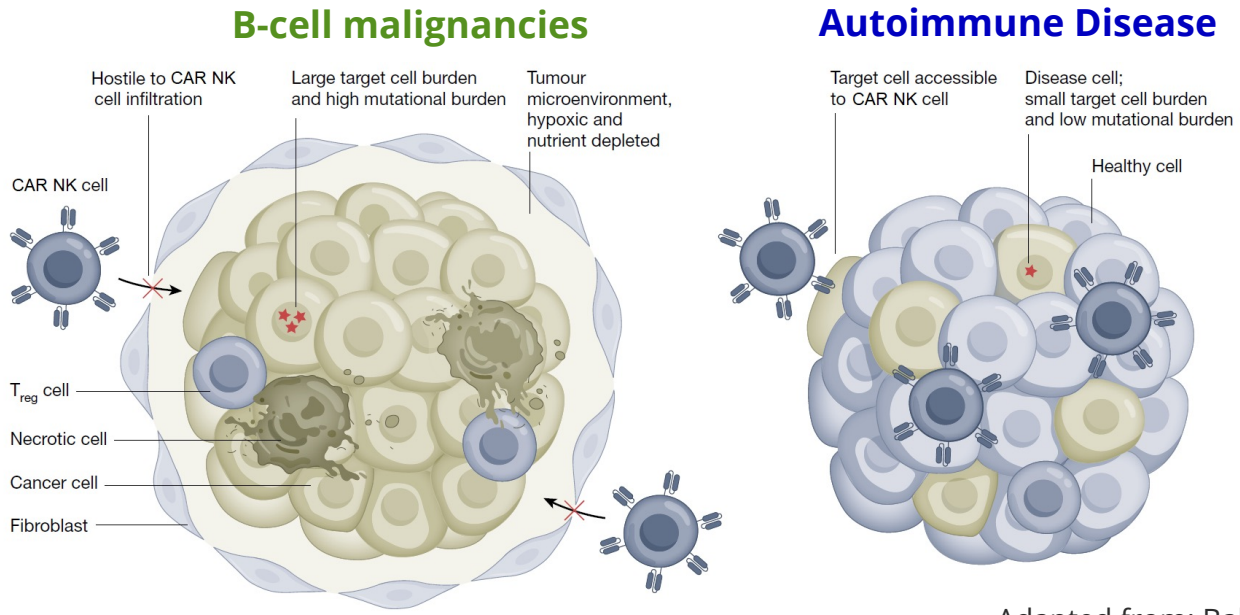
Autoimmune B cells may be more accessible than malignant B cells

While CD19 allows effective targeting of normal and abnormal cells of B cell lineage, multiple factors may make B cells in autoimmune disease more accessible to killing

- Widespread antigen escape via downregulation or loss of CD19 by malignant B cells
- Tumor microenvironment preventing trafficking and infiltration
- Large cell burden and tumor infrastructure



Adapted from: Baker, et al. *Nature* 2023 Jul;619(7971):707-715.

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CD19 CAR NK cells may be ideally suited for autoimmune disease

NK cells reach peak activity at infusion for rapid target activity

- Maximal immediate effect without *in vivo* expansion
- T cells require expansion and necessitate a different LD approach

Allogeneic NK cells are cleared by host immunity

- Low risk of prolonged B-cell aplasia which is not required for response
- Long-lived CAR T cells have FDA-issued risk of T-cell malignancy[1]

Superior safety and accessibility in non-malignant setting

- On-demand availability without need for cumbersome infrastructure at treatment centers
- Low risk of expansion-related toxicities including CRS and ICANS

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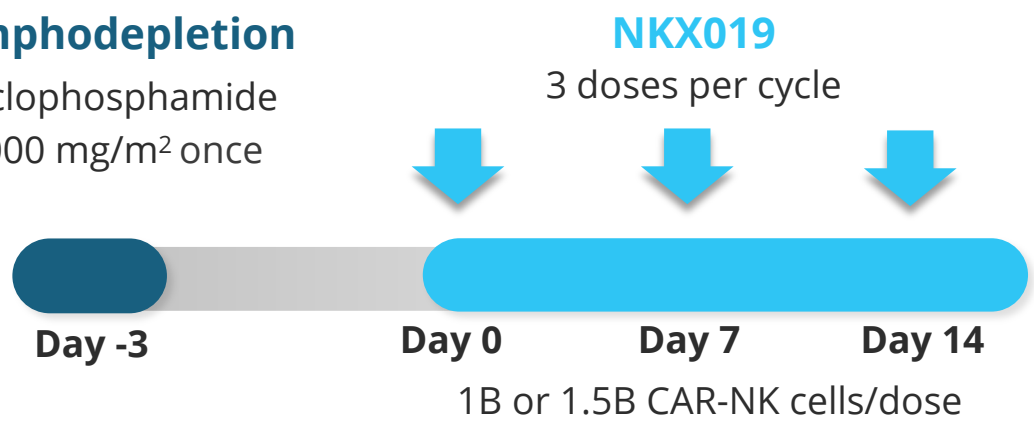
1: Nelson. *Lancet*. Vol 402. 2181. December 9, 2023

NKX019 CAR NK for autoimmune diseases:
A multicenter, open-label, phase 1 study



Endpoints:

- Safety and tolerability
- Pharmacokinetics
- Renal function
- Autoantibody serology

Off the shelf administration reduces burden to patients and providers

First patient dosing expected 1H 2024

Opportunity to investigate broader applicability of NKX019 in multiple autoimmune diseases

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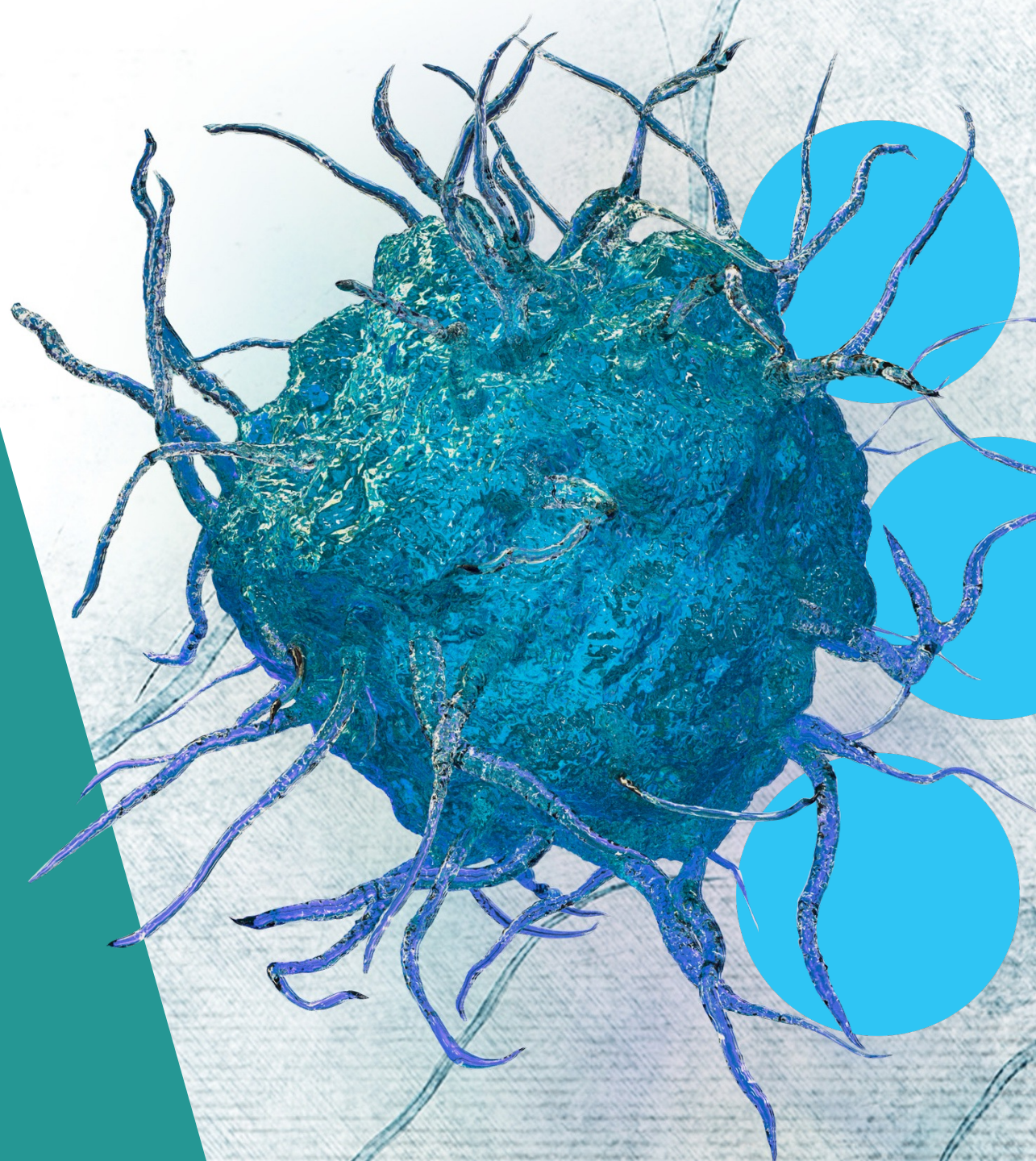
CAR: chimeric antigen receptor

NKX019 and NKX101 in oncology



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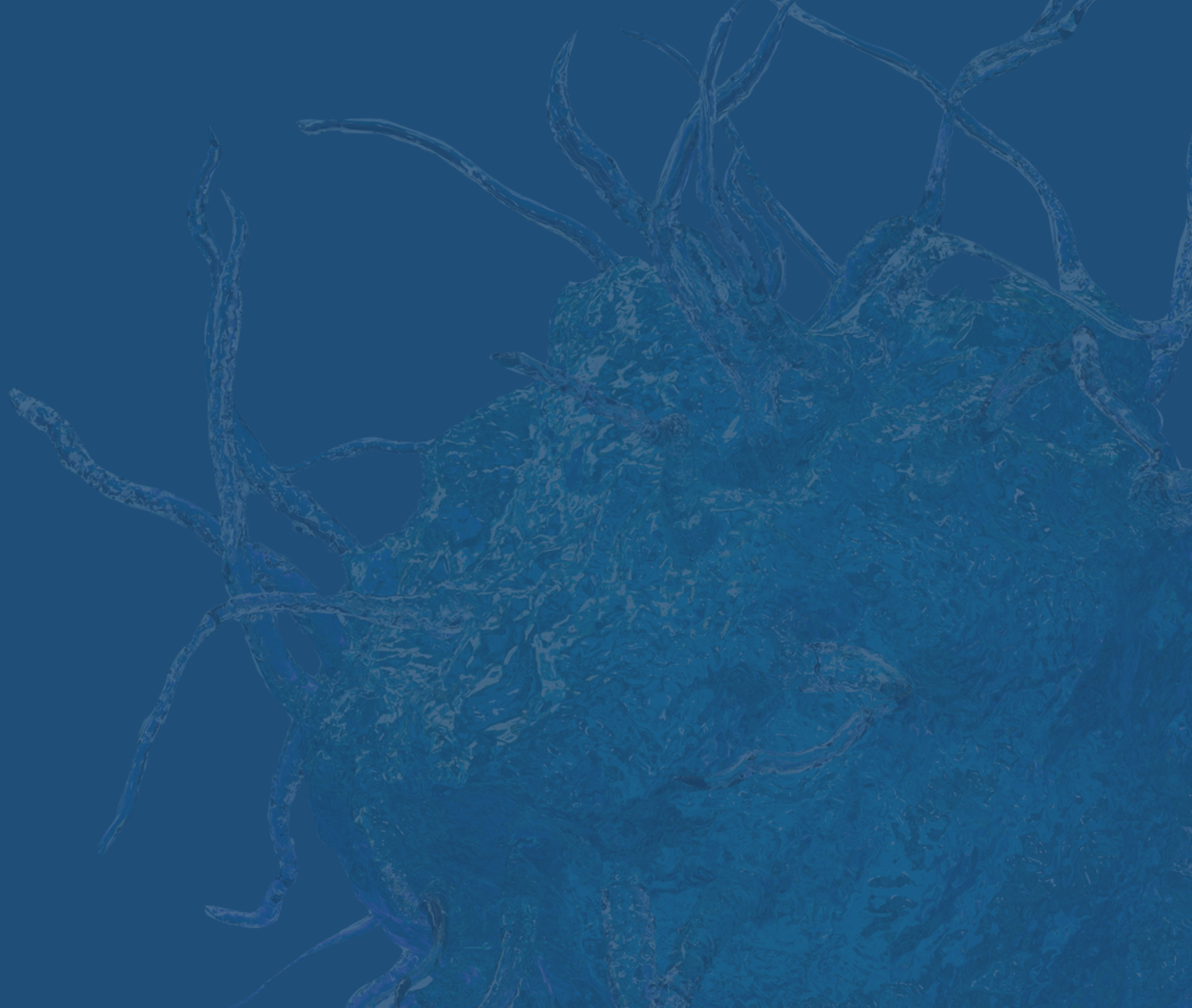
NKX019

CD19 CAR NK in r/r non-Hodgkin lymphoma



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Autologous CAR T-cell therapy has set the bar for cellular therapies in r/r NHL but has limitations

CAR T-cell therapy is not broadly accessible

- Only 20-30% of patients with LBCL who could benefit from CAR T receive it
- Patients often need to change providers and receive bridging chemotherapy

Potential toxicity requires proximity to a specialized inpatient treatment center

- Over 25% of patients require ICU care
- Grade 3+ CRS: 13 to 49%, Grade 3+ ICANS / neurotoxicity: 18 to 31%

Only 30-40% of patients with LBCL treated with CAR T-cell therapy have 6-month CR

- No ability to re-dose for incomplete response
- Outcomes among those that relapse are poor

YESCARTA USPI; KYMRIAH USPI; BREYANZI USPI; Azoulay et al, 2020; Tomas, et al. 2022.

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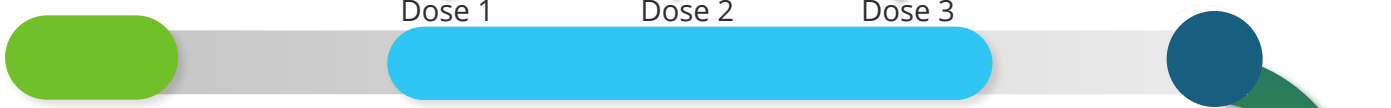
CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit; LBCL, large B-cell lymphoma; NHL, non-Hodgkin lymphoma.

NKX019 for B-cell malignancies: A multicenter, open-label, phase 1 study in r/r NHL

Lymphodepletion
- Cyclophosphamide
- Fludarabine

NKX019
3 doses per 28-day cycle

Efficacy assessment



Multiple cycles allowed to **deepen response**
Subjects in **CR** may receive additional cycle as **consolidation**

Subjects with prior response and subsequent progression may receive **retreatment**

NCT05020678

7 of 10 — **CR in Phase 1 dose escalation cohort[1]**

No ICANS, neurotoxicity, or GVHD of any grade and only transient fevers within 24 h of infusion

4 of 4 — **CR in retreatment of patients with progression after NKX019**

Study amended to increase dose intensity and prevent relapse

1. Dickinson, et al. Oral presentation at EHA 2023, program section s347.

CAR, chimeric antigen receptor; CR, complete response;; r/r, relapsed/refractory; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome

NKX019 Amendment: Compressed Dosing

Dose compression cohort enrolling patients with large B-cell lymphoma (LBCL), targeting patients who have received *prior CD19 CAR-T cell therapy*

New compressed dosing schedule to intensify exposure to NKX019 in the first week after LD

NKX019 on Days 0, 3, and 7
following standard LD with Flu/Cy

Previous cohorts received NKX019 on Days 0, 7 and 14

Study amendment also includes

- Potential higher doses of CAR NK cells
- Tailored LD with Cy monotherapy for patients with prolonged cytopenias
- Elimination of inpatient requirement
- Streamlined protocol assessments to reduce burden on sites and patients

Next clinical update planned for mid-2024

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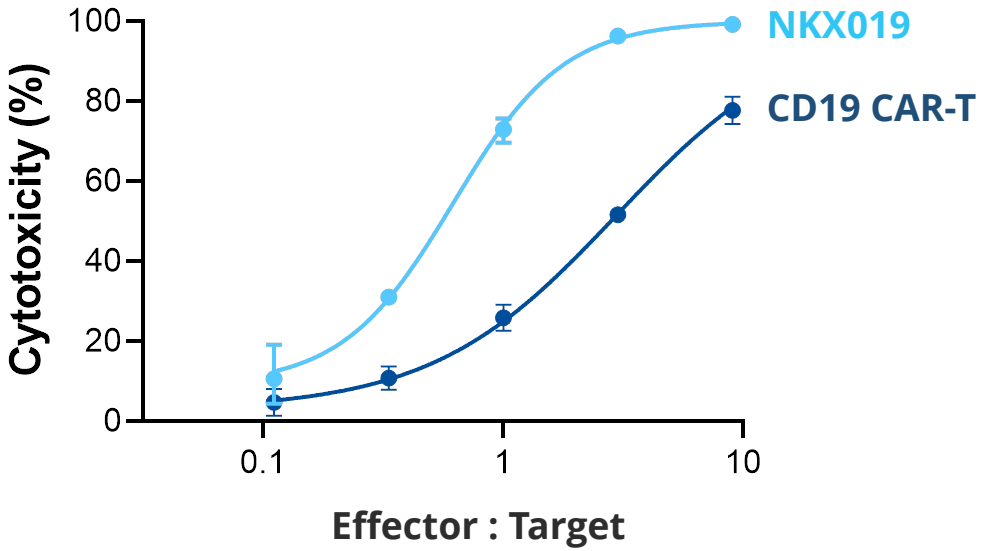
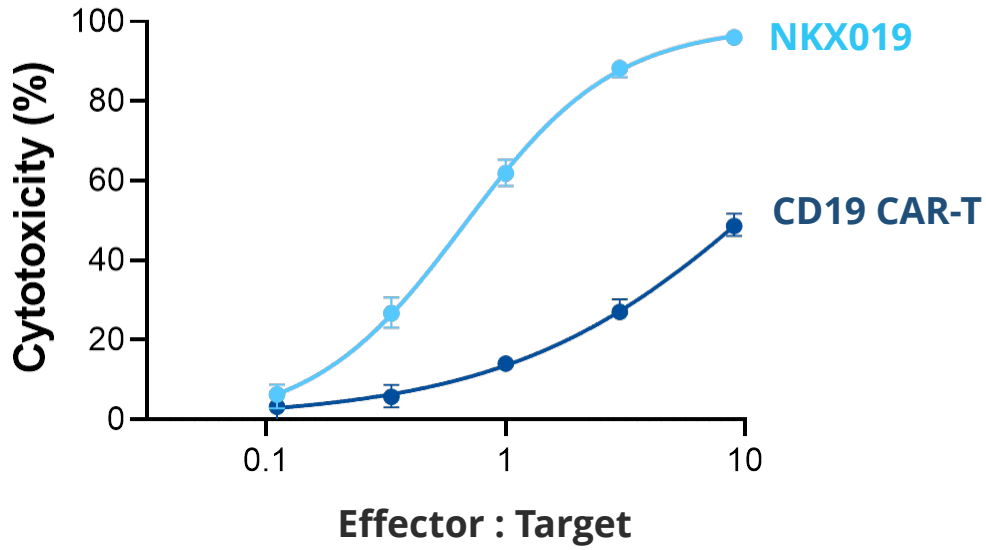
CAR, chimeric antigen receptor; cy, cyclophosphamide; flu, fludarabine; LD, lymphodepletion

NKX019 has superior target cell killing compared to CD19 CAR T cells, even with low levels of CD19 expression

High CD19 Expressing Cells



Low CD19 Expressing Cells



CD19 downregulation allows normal and malignant B cells to escape CAR T cells[1]
NKX019 maintains superior killing in B cell tumor cells expressing low CD19 levels[2]
Potentially allows a deeper B cell immune reset in autoimmune disease

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Nalm6 cells engineered to express varying levels of CD19 were obtained from R. Majzner, Stanford; Effector : Target is the ratio of NK or T cells to tumor cells.

1: Fioretti, et al. Cancer Immunol Immunother. 2023 Jan;72(1):257-264.
2: Dickinson, et al. Blood (2021) 138 (Supplement 1): 3868.

NKX101

NKG2D CAR NK in r/r acute myeloid leukemia

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AML is a rapidly progressing leukemia with a poor prognosis

Heterogenous group of blood cancers treated with risk-adapted chemotherapy

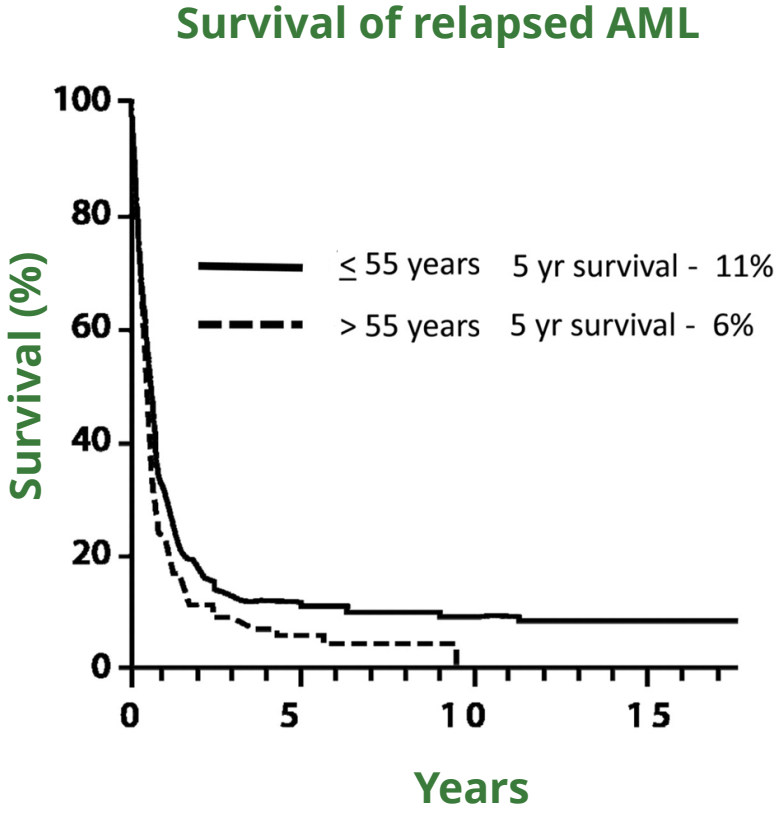
- Most patients will ultimately die from relapse or complications from therapy

Allogeneic HCT is best chance of long-term cure

- Limited to patients who are fit
- **Pre-HCT CR** improves outcomes

Outcomes for patients who relapse or have refractory disease are especially poor

- Low response rates with standard chemotherapy
- 12-18% CR rate, including venetoclax-based regimens



1: Canaccord Genuity, 14 Nov 2023.
2: Mackensen et al. *Nature Med*. 28 Oct 22. 2124–2132.

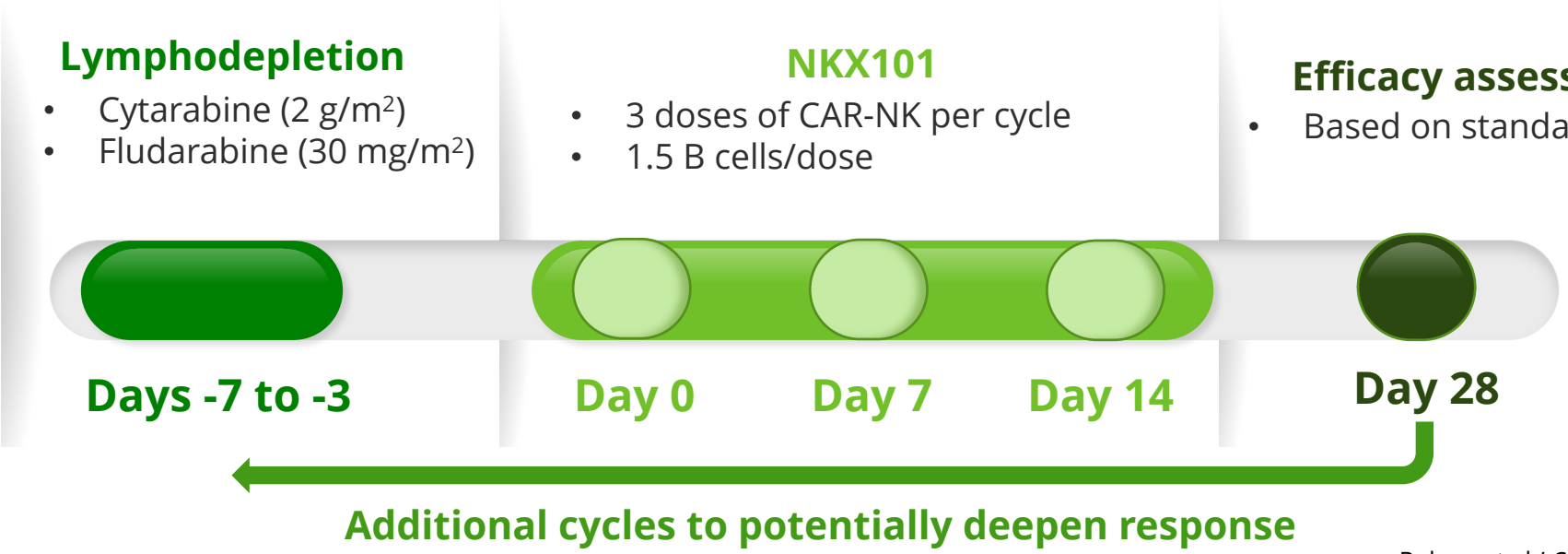
NKX101 for relapsed/refractory AML following disease-tailored LD

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



NCT04623944

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

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

ASH 2023: Updated follow-up of patients with r/r AML

4 of 6 patients achieved CR/CRi

- High-risk features such as prior HCT, TP53 mutation and high blast burden
- 3 of 4 remained in CR/CRi at 4 months

Safety profile consistent with available therapies

- No CRS, ICANS or GvHD of any grade
- Myelosuppression and infection were the most common ≥Grade 3 toxicities

Next clinical update planned for 1H 2024

- 12-20 additional patients
- Additional follow-up for initial patients

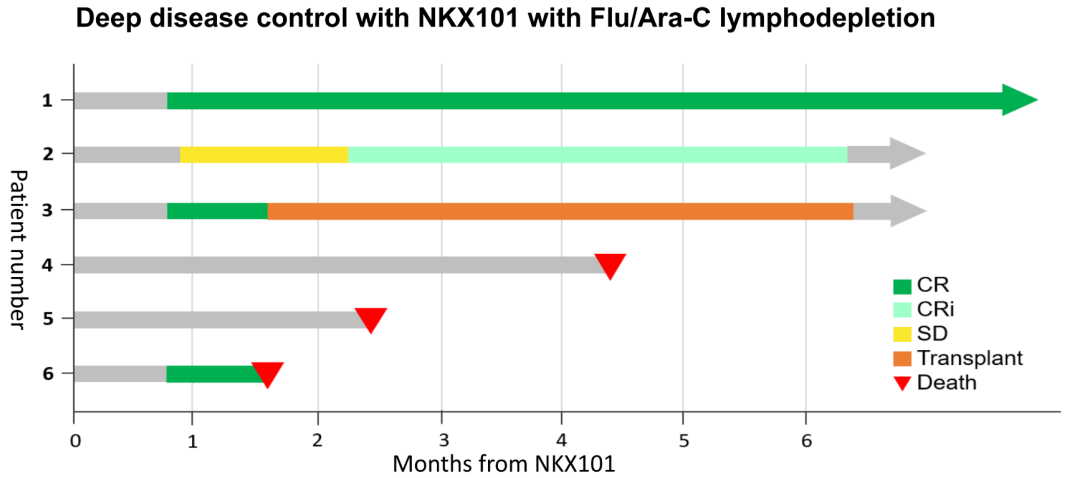


Figure 1. Four of six patients had CR/CRi (67%), with three achieving CR. Patients 1 and 6 had no detectable minimum residual disease (MRD) by flow cytometry after one treatment cycle. Patient 3 had MRD of 0.18% after one cycle and was immediately taken to consolidative hematopoietic cell transplant. 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.

Sauter, et al. ASH 2023

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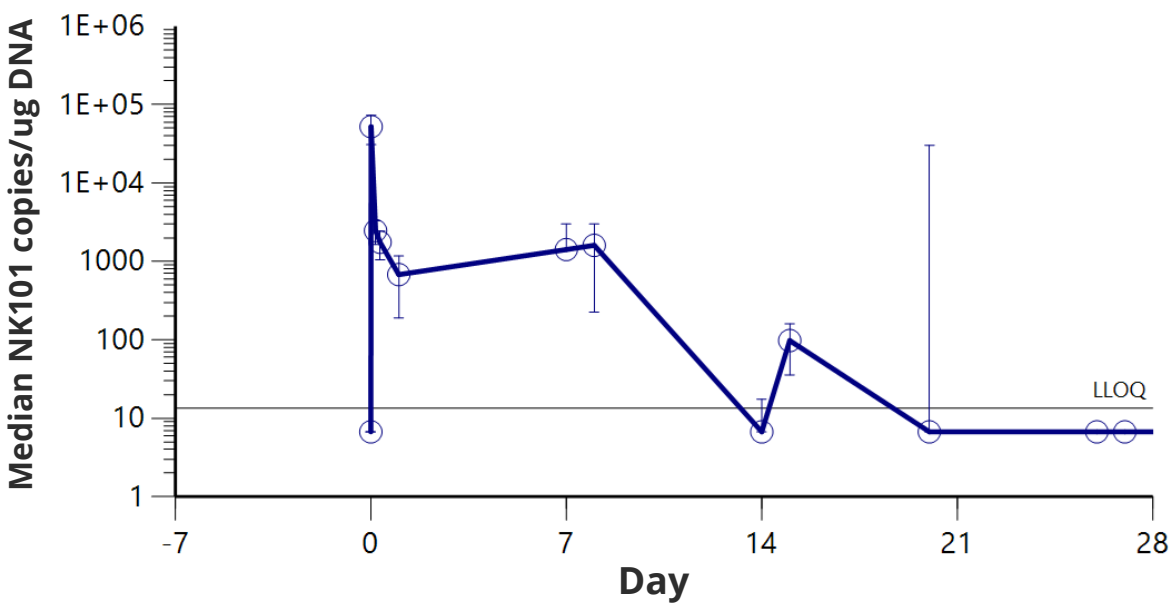
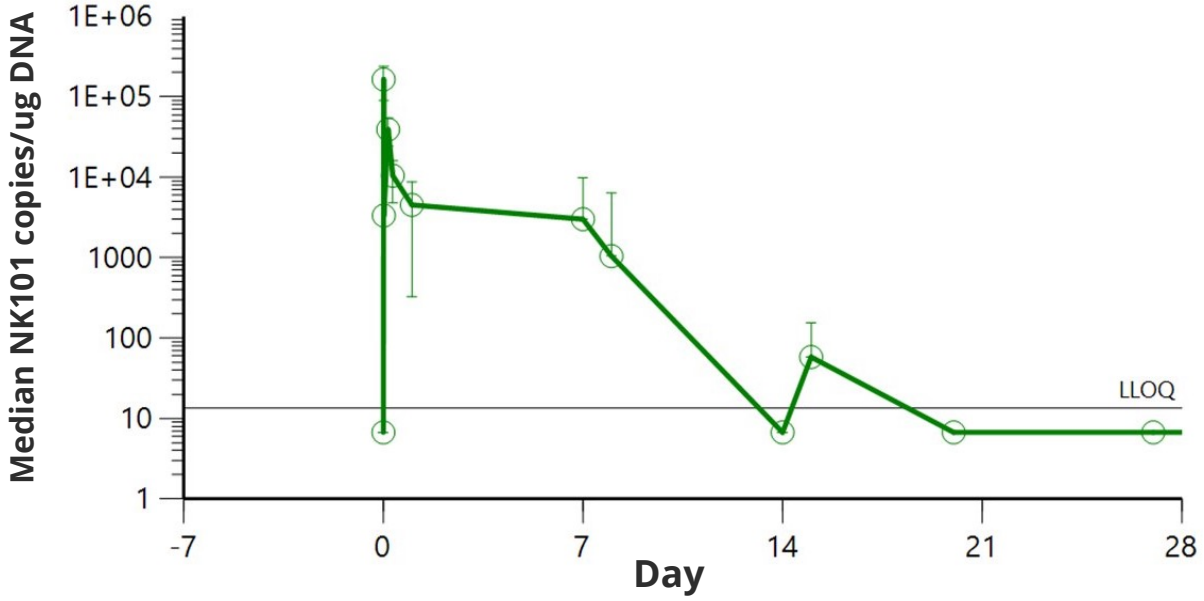
AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CR, complete response; CRi, complete response with incomplete count recovery; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; GvHD, graft versus host disease; r/r, relapsed or refractory

Disease-tailored lymphodepletion does not compromise PK

Fludarabine/Cyclophosphamide



Fludarabine/Ara-C



- NKX101 dosed on days 0, 7, and 14
- Exposure consistent with previously published data using haploidentical NK cells[1]
- No need for exogenous IL-2 or other cytokine support

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

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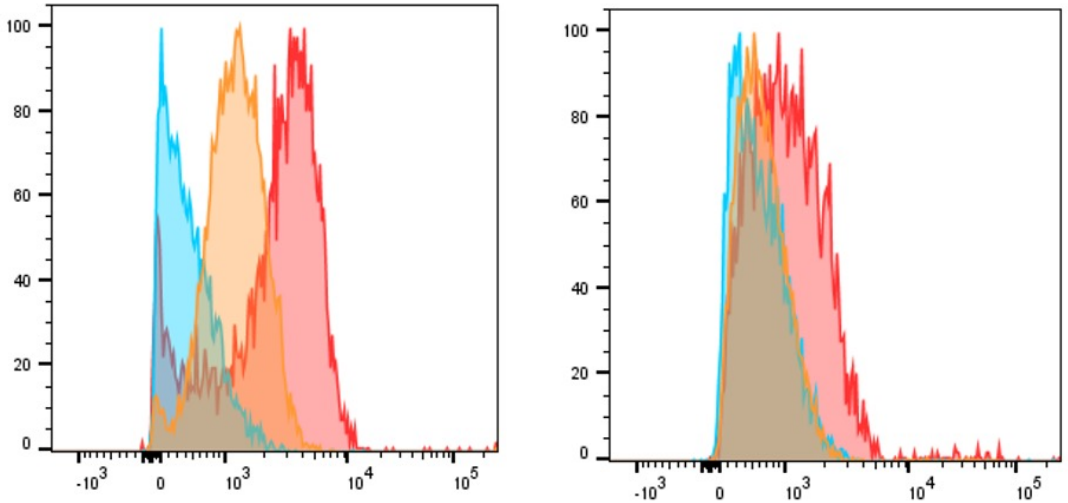
Ara-C upregulates NKG2D ligands and increases sensitivity to NK cell killing

Ligands are upregulated with stress, including chemotherapy

- NKG2D CAR binds to 8 known ligands
- Mediates natural target cell elimination

Ligand staining after 24 hrs of Ara-C Exposure



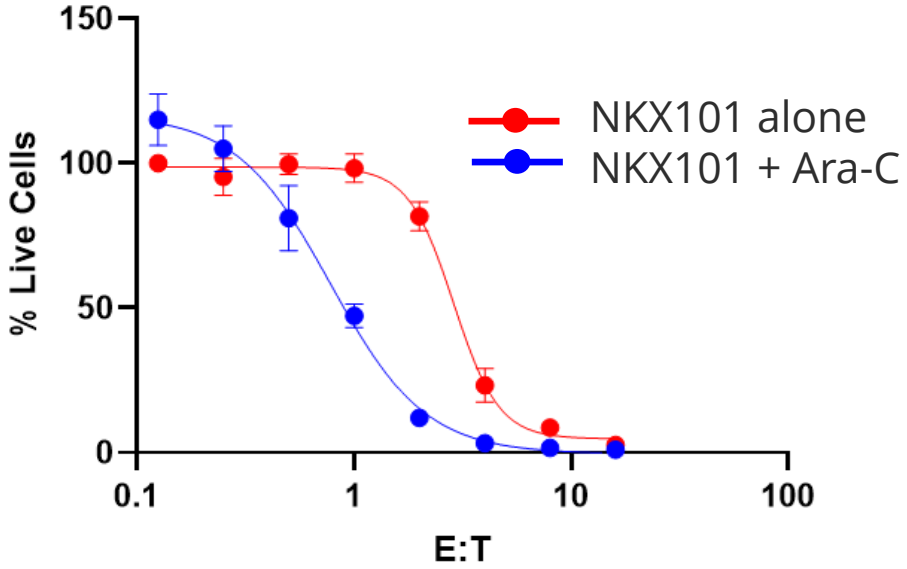
MIC A/B

ULBP1-6

Blue: Isotype
Orange: Untreated
Red: Ara-C treated

Pre-treatment of AML cells increases sensitivity to NK killing in vitro

- Dose dependent effect
- May increase opportunity for CAR-mediated killing



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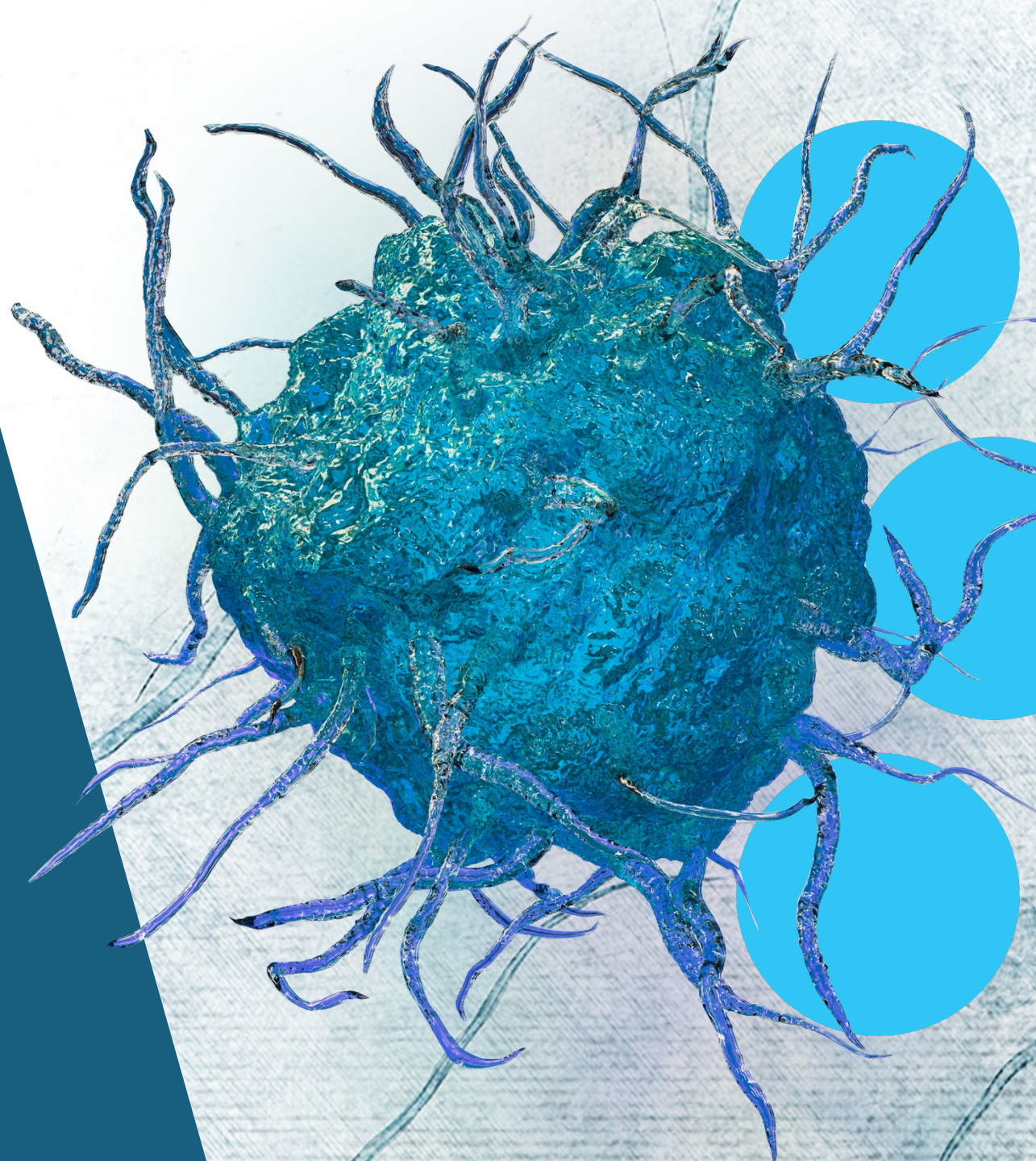
Summary



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Autoimmune expansion | 2024 updates | Cash runway

- Pipeline expanded into autoimmune disease
- Further investment in oncology gated by clinical signals from next data updates
- $278.4 M in cash and cash equivalents as of 30 Sept 2023
- Projected cash runway into 2026
- Multiple clinical updates expected in 2024

Anticipated 2024 clinical milestones

1H 2024	*NKX019 in lupus nephritis* - Dose first patient and program update
1H 2024	*NKX101 in AML* - Clinical data from 12 to 20 new patients in flu/Ara-C cohort
Mid 2024	*NKX019 in NHL* - Clinical data from dose compression cohort in patients with LBCL after prior CAR-T