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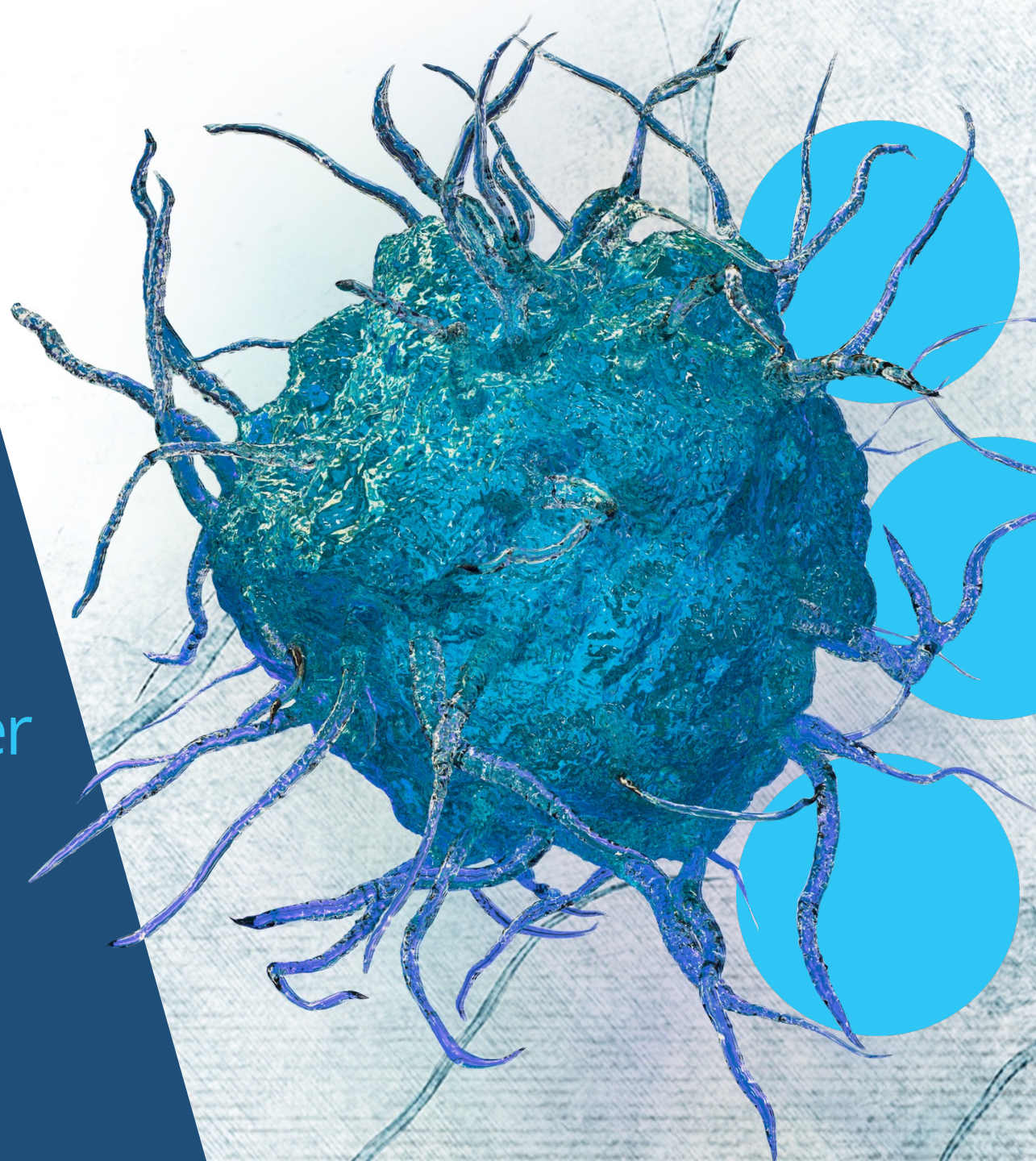
ENGINEERING

Natural Killer Cells

for next generation treatment of autoimmune diseases and cancer

ON DEMAND



March 2024

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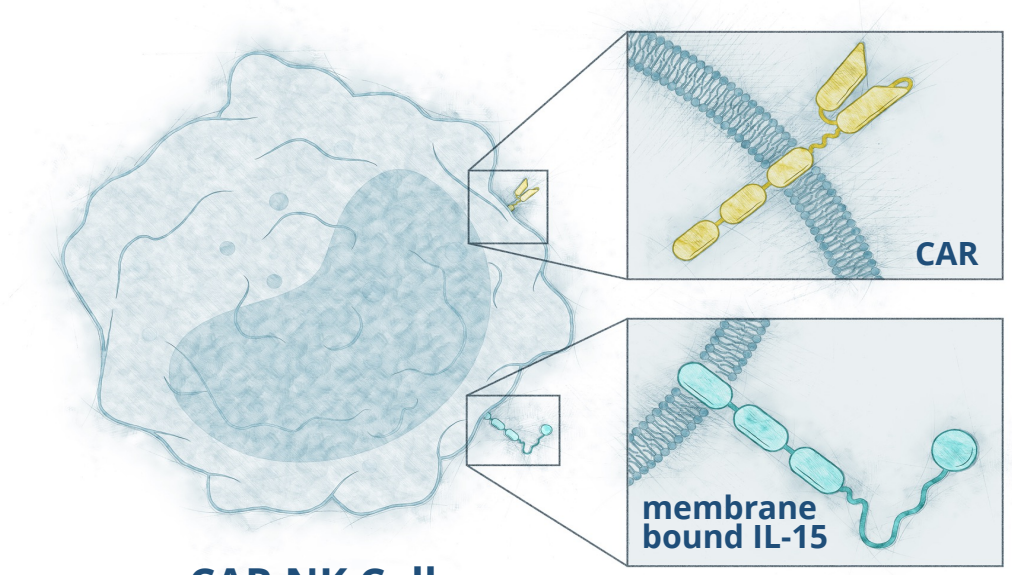
Delivering the future of cell therapy by harnessing the killing ability of natural killer (NK) cells

- Fully allogeneic from healthy, pre-screened donors
- On-demand, off-the-shelf availability for outpatient administration
- Programs in autoimmune disease and oncology
- Clinical program updates expected in 2024
- Projected 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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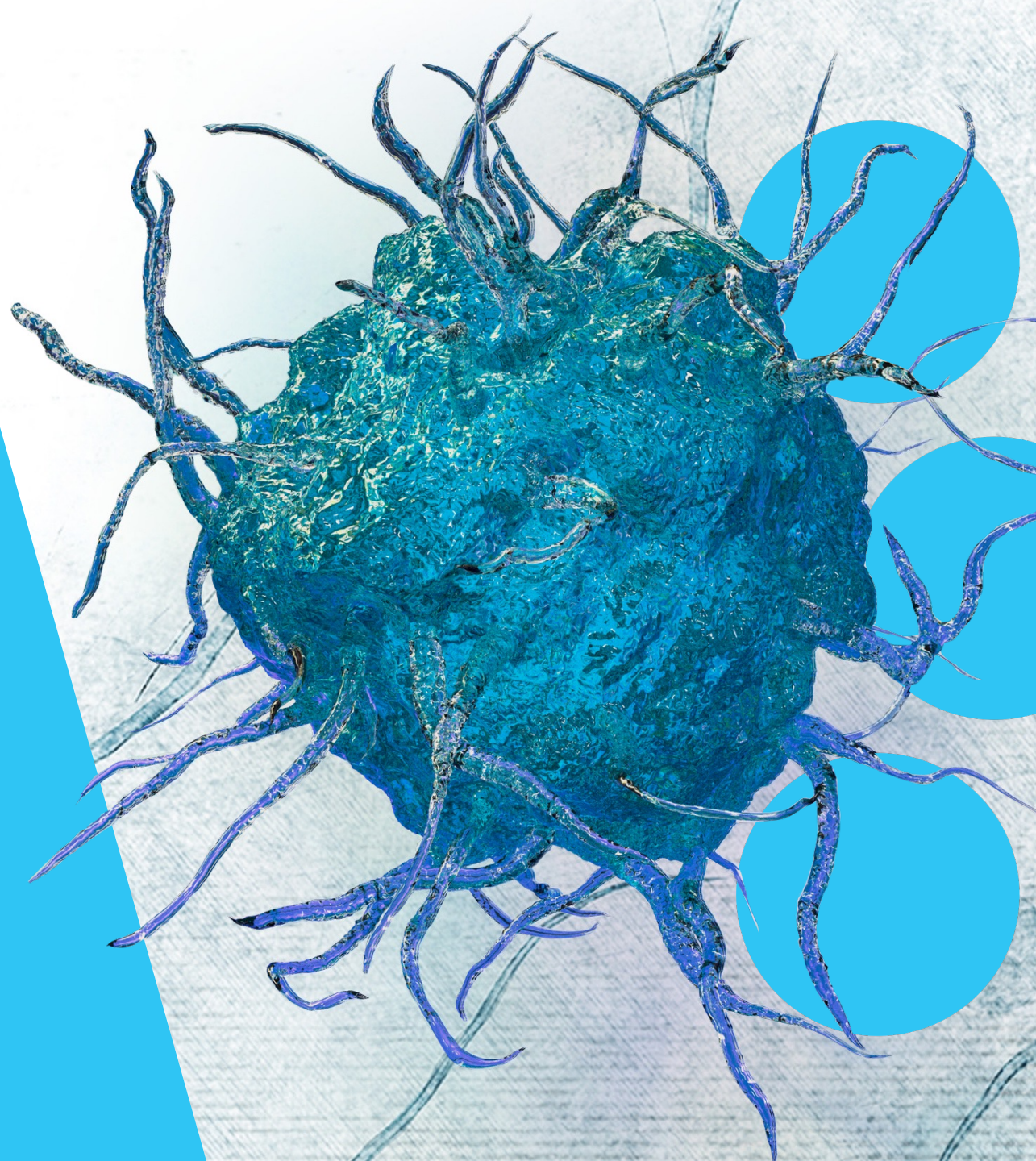
Pipeline with transformational potential

Program (Target)	Indication	Research	IND-Enabling	Clinical	Status
NKX019 (CD19)	Refractory LN				IND cleared 4Q 2023 First patient dosing 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 follow-up ongoing Patient enrollment closed
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

AML: acute myeloid leukemia; LN: lupus nephritis; NHL: non-Hodgkin lymphoma; r/r: relapsed or refractory

NKX019 in Autoimmune Disease



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

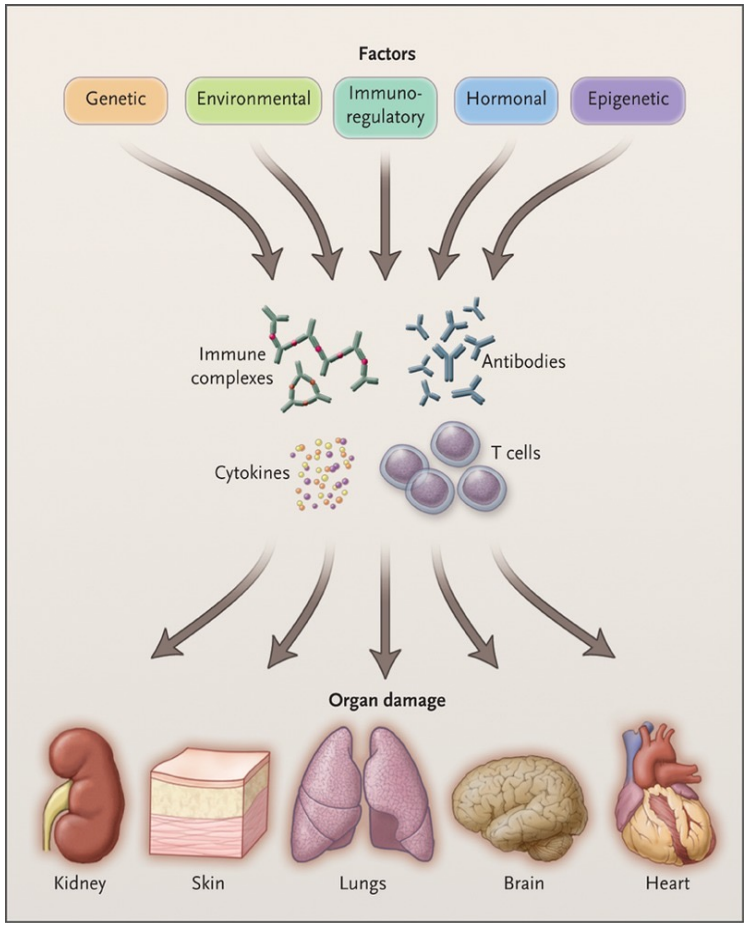
Autoimmune disease is a major unmet need

- 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.

1: Canaccord Genuity, 14 Nov 2023.

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

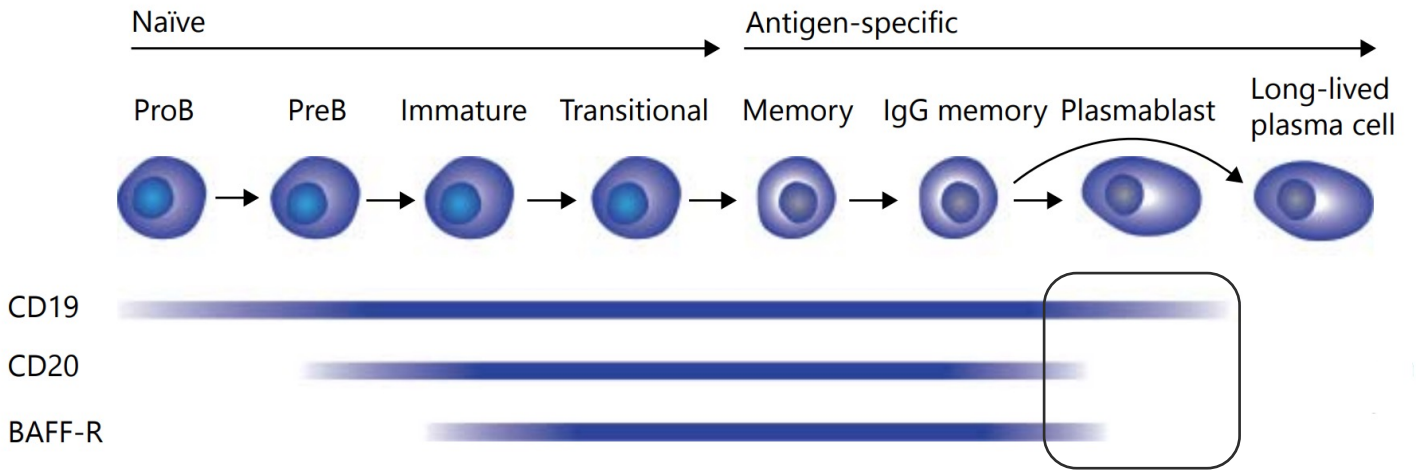
Both target and therapeutic modality likely contribute to benefits of anti-CD19 cell therapy versus antibody approaches to targeting B cells

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

- $CD19^{high}$ $CD20^{dim/neg}$ $BAFF\text{-}R^{dim/neg}$ plasmablasts
- $CD19^{dim/neg}$ $CD20^{neg}$ $BAFF\text{-}R^{neg}$ 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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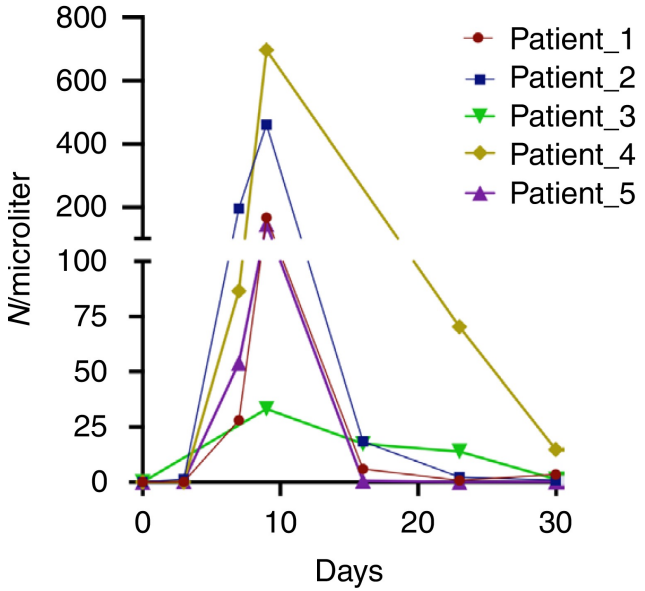
CAR T cell kinetics in autoimmune disease differ greatly from that in oncology

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

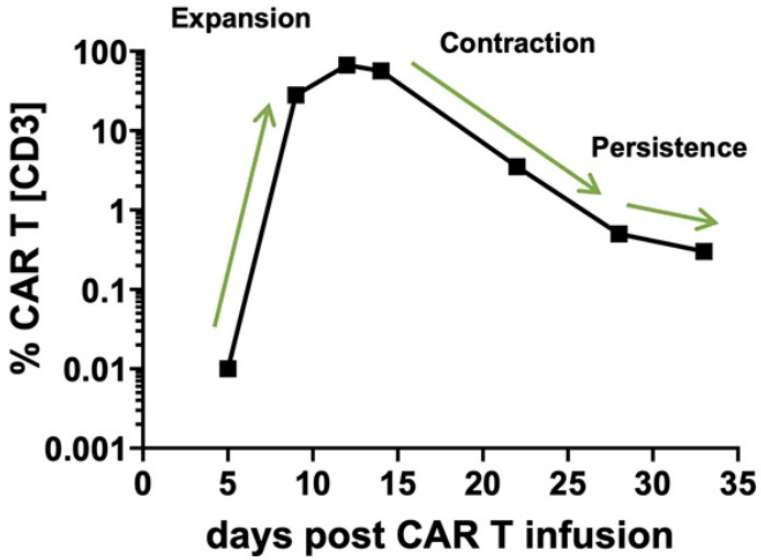
In B cell malignancies, CAR T cells persist long after antigen-dependent expansion

Autoimmune disease



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 drug-free responses in autoimmune disease

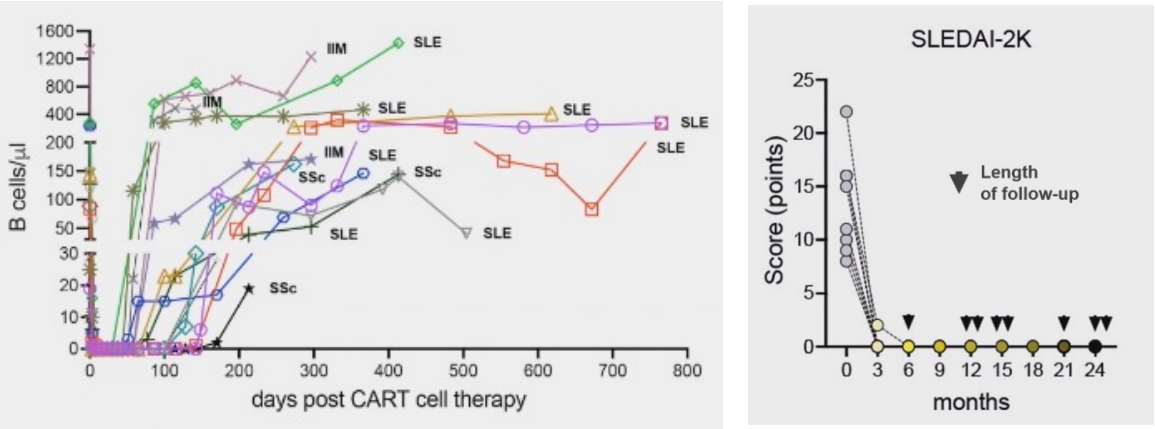
Immune "reset" occurs after B cell suppression in as short as 50 days in autoimmune disease

- Persistent B cell aplasia is NOT required for long-term responses
- Autoantibodies remain negative in most patients and drug-free remissions persist for up to 29 mo[1]

Prolonged B cell aplasia is common in oncology (median ~18 mo[2]), especially in responders

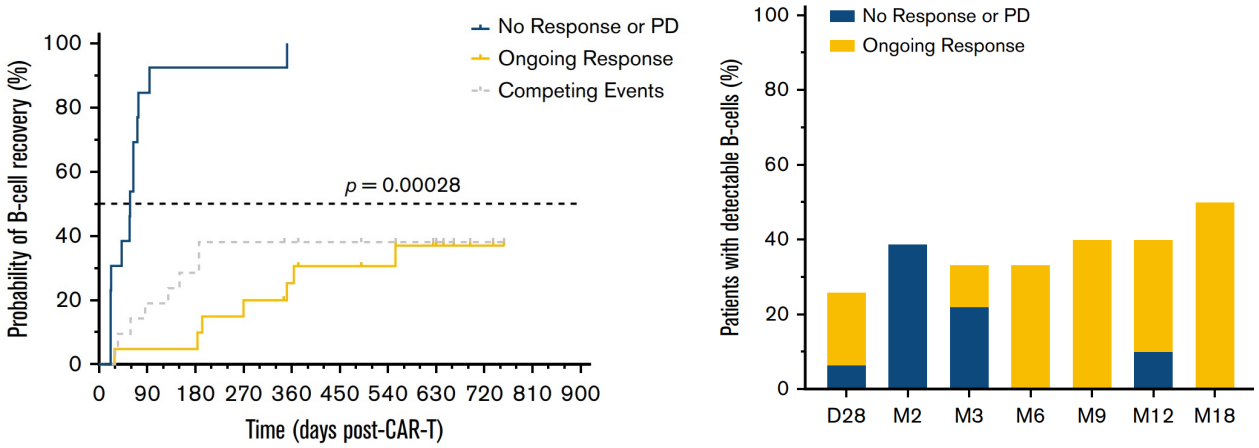
- Absence of B cells is used as clinical proxy for detection and activity of CAR T cells
- B cell recovery within 3 months of infusion is associated with disease progression

Autoimmune disease



Muller et al. Abstract 220, ASH 2023.

B cell malignancy



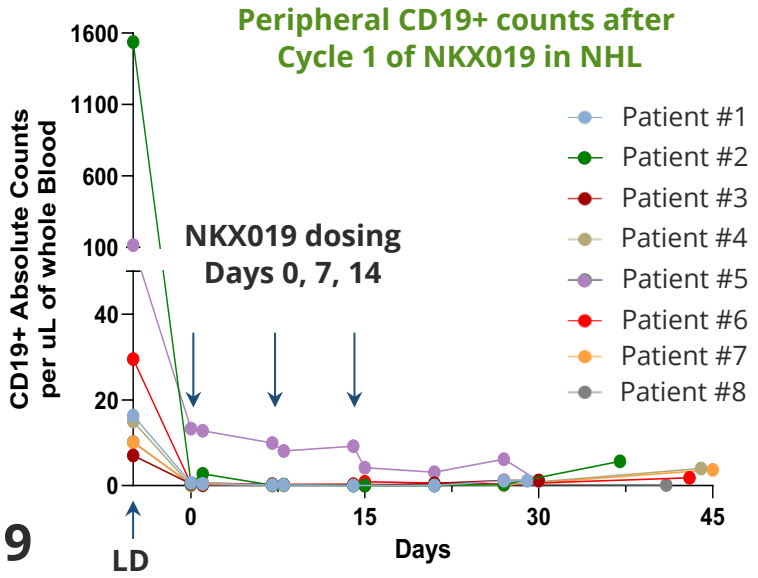
Baird, et al. 2021. *Blood Advances 5(1):143-155.*

1: Mueller, et al. *NEJM. 2024; 390:687-700.*
2: Bhoj, et al. *Blood. 2016 Jul 21; 128(3): 360–370.*

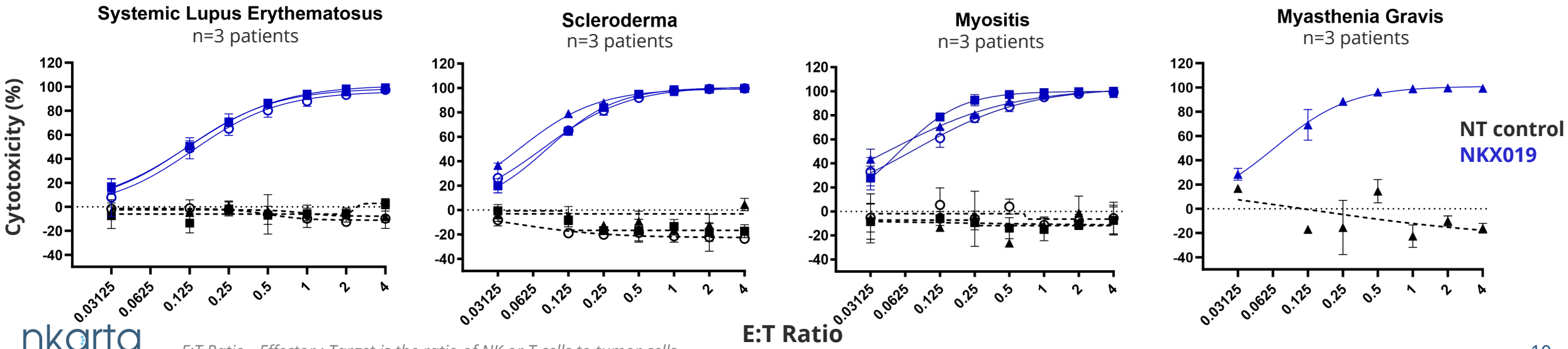
NKX019 targets and kills C19+ cells from patients across indications

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 by NKX019**



E:T Ratio - Effector : Target is the ratio of NK or T cells to tumor cells.

B cells that recover after NKX019 are naïve and non-class switched

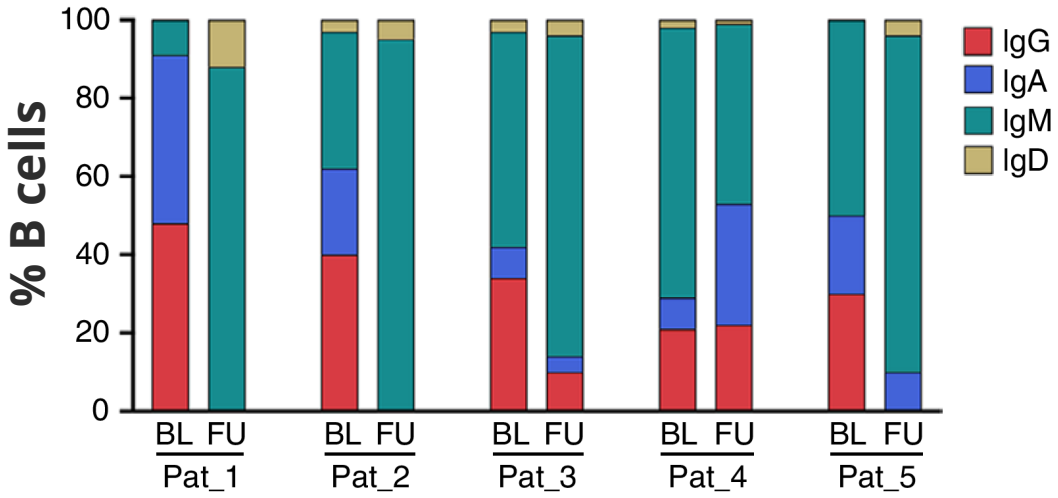
Evaluation of B cell receptor (BCR) heavy chains can identify naïve B cell phenotypes

- Naïve B cells express IgM and IgD (non-class switched isotypes)
- After activation, B cells undergo class switching and express IgG and IgA antibodies

Class switching appears to be required for the generation of autoantibodies in SLE[1]

B cell isotype distribution after treatment with NKX019 in NHL trial is comparable to that with CD19 CAR T

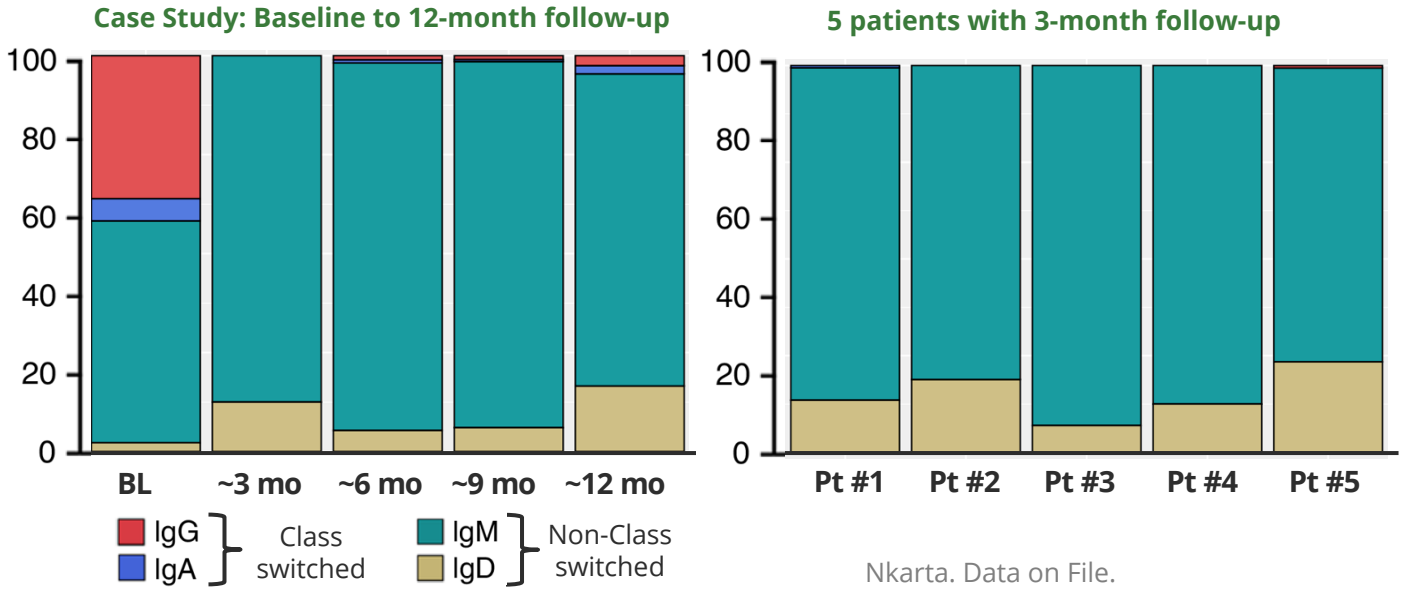
CD19 CAR T Cells in SLE



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

BL: baseline; FU: follow-up; SLE: systemic lupus erythematosus

NKX019 in NHL



Nkarta. Data on File.

1: Liu, et al. *Autoimmunity*. 2004, Sep-Nov 37; (6-7): 431-443.

RNA profile confirms naïve B cell predominance after NKX019 treatment

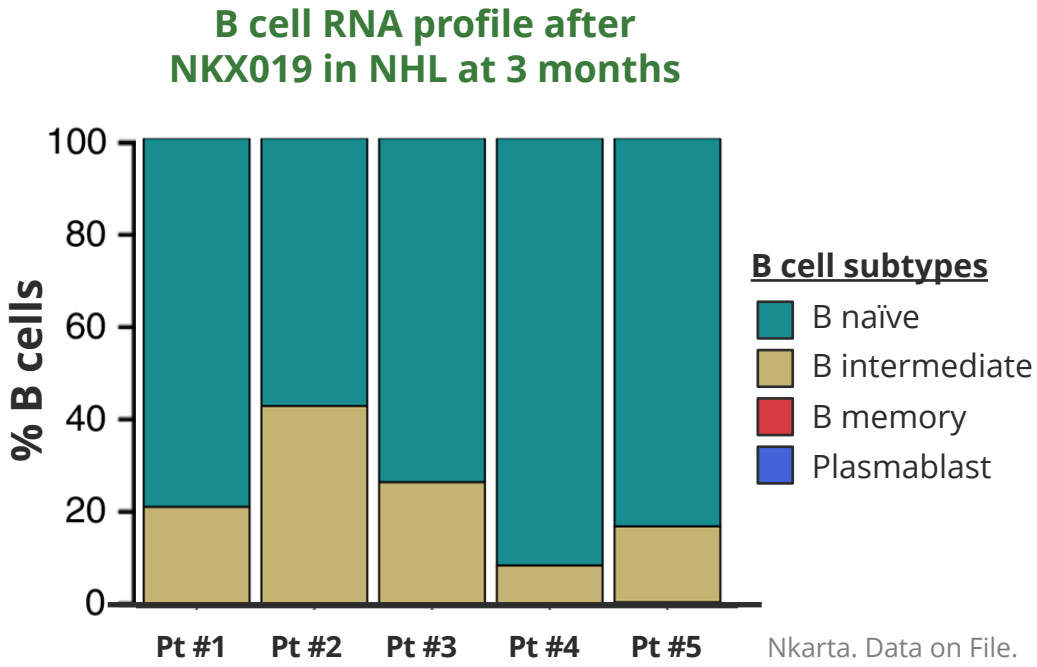
Various B cell subsets have expression profiles identifiable by single cell RNA (sc-RNA)

- Provides additional insight beyond surface expression (e.g. flow cytometry)

Recovery after treatment with NKX019 in NHL trial results in a naïve population

- Naïve B cells and intermediate B cells which are “transitioning” to memory B cells
- Little to no recovery of autoantibody-producing plasmablasts or memory B cells

Comparable to recovery after CD19 CAR T in autoimmune disease

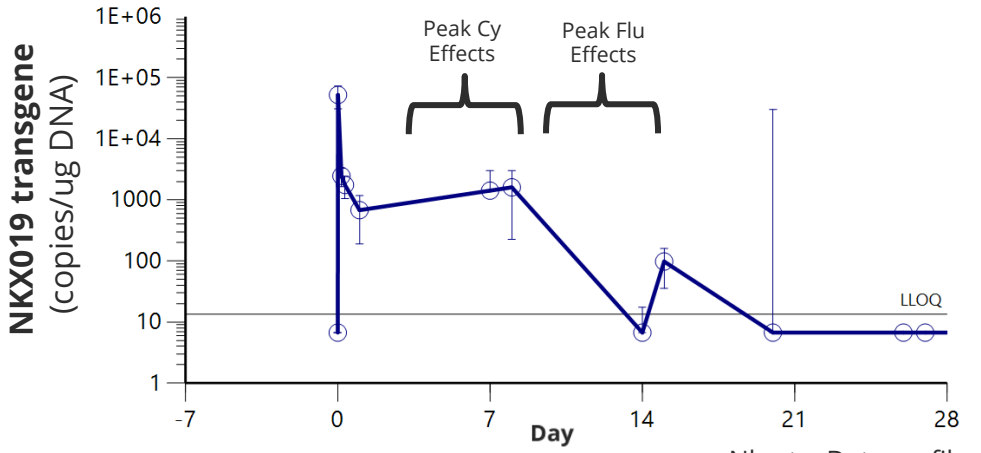


Nkarta. Data on File.

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

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

CAR NK Pharmacokinetics



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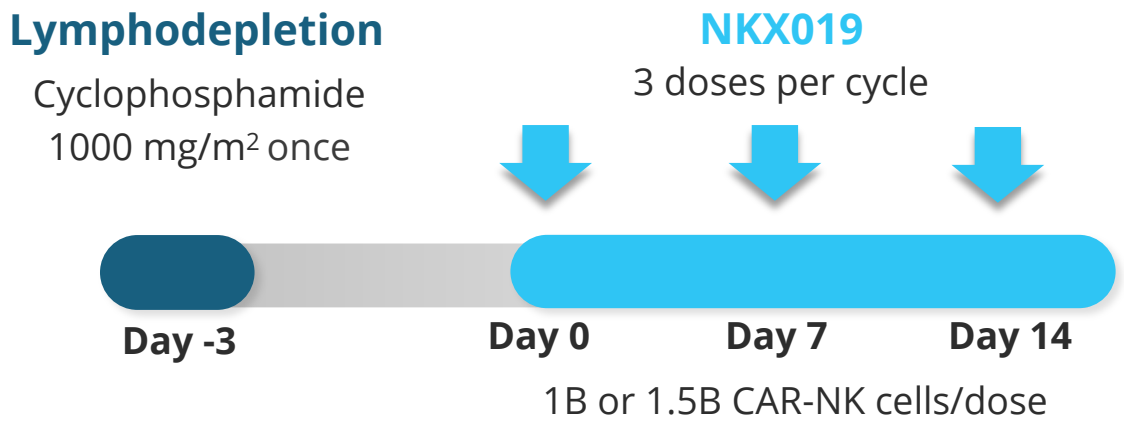
NKX019 Protocol in Autoimmune Disease



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

- Same dose is used by rheumatologists for management of autoimmune disease
- Possible regulatory advantage leveraging prior studies and real-world evidence

Cy: cyclophosphamide; Flu: fludarabine; LD: lymphodepletion

1: Fludarabine USPI.

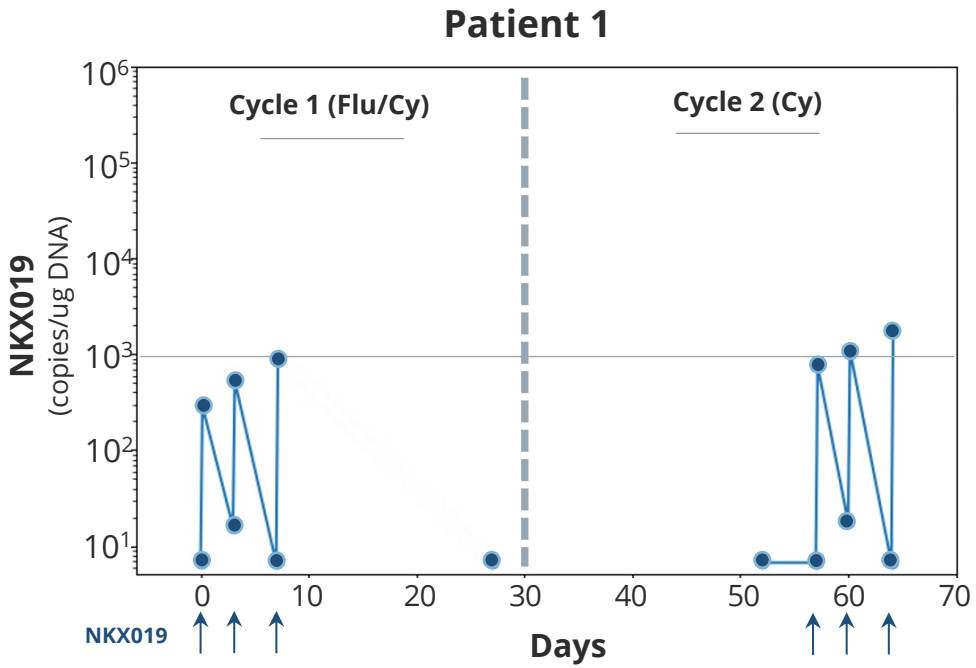
Cy-alone LD results in similar exposure of NKX019

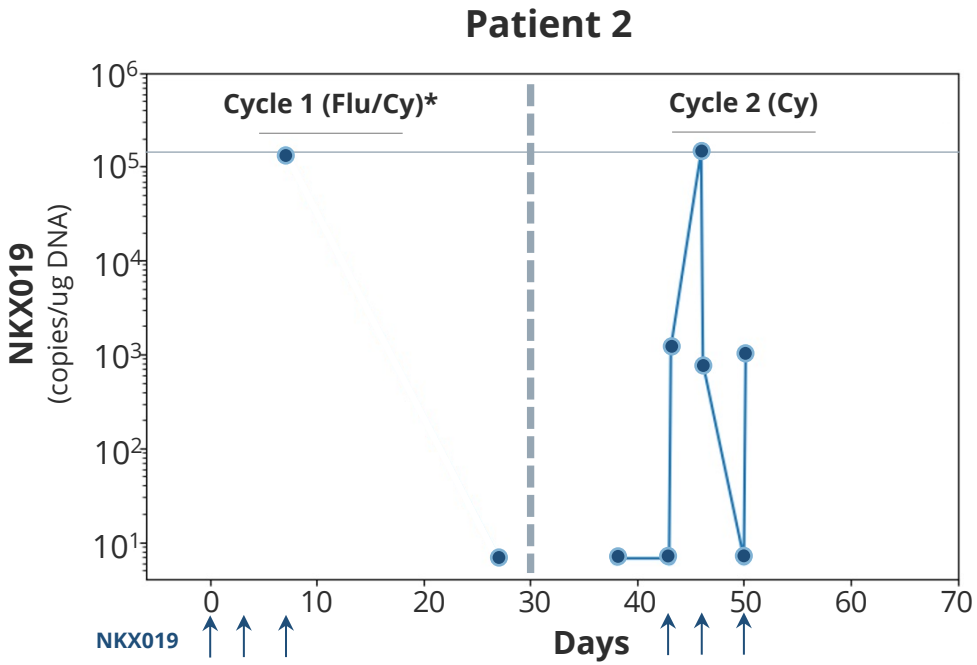
Current trial of NKX019 for NHL allows omission of fludarabine during LD

- Regardless of LD, patients receive NKX019 on Days 0, 3, and 7 following 2 days of rest

Two patients have received subsequent cycles with Cy-only LD after Flu/Cy LD for Cycle #1

- Allows direct comparison of exposure between cycles
- Cy-only LD gives comparable PK to Flu/Cy, including peak exposure





*Multiple PK timepoints missed

LD: lymphodepletion; NHL: non-Hodgkin lymphoma; PK: pharmacokinetics

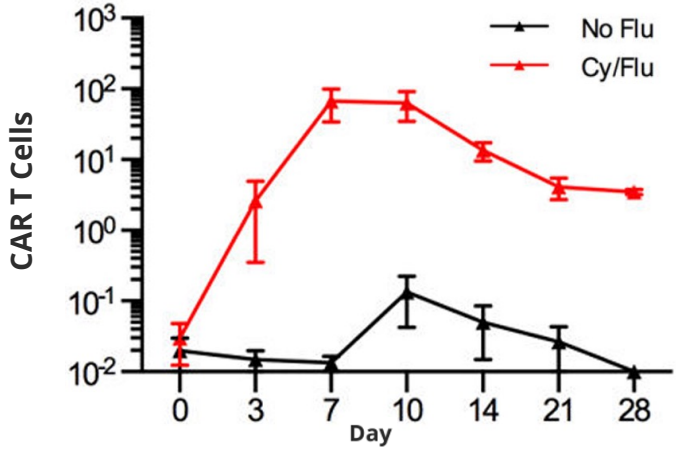
Autologous CD19 CAR T cells require fludarabine-containing LD for maximal exposure due to induction of endogenous cytokines, especially IL-15

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

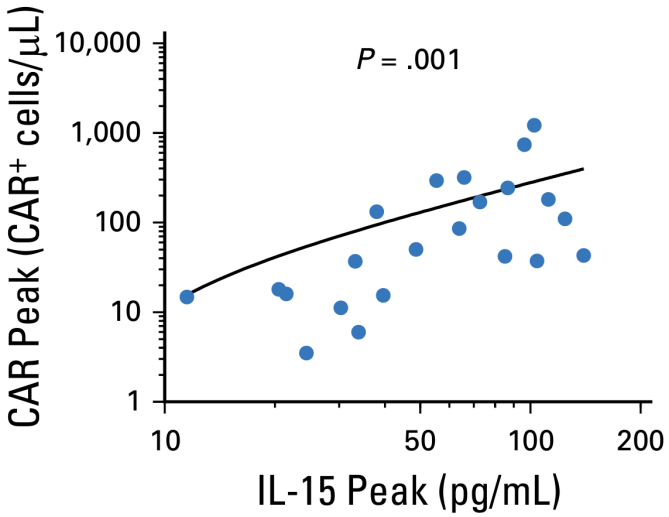
Lower peak IL-15 levels associated with decreased responses in CAR T[1]

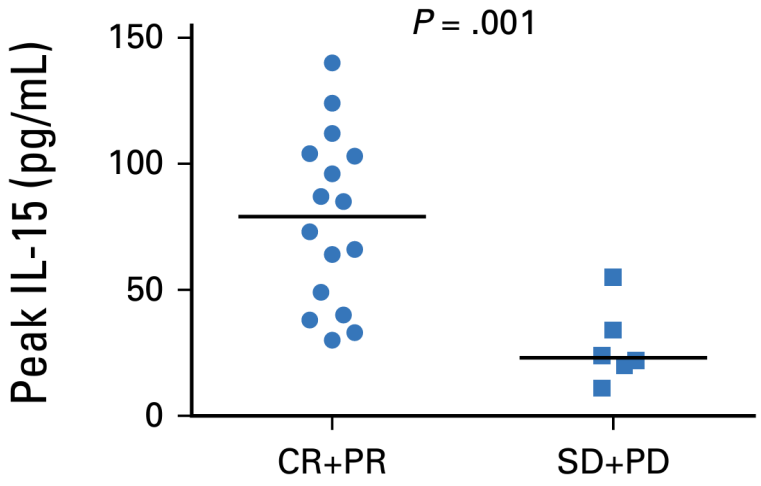
LD without fludarabine results in lower CAR T expansion and persistence



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

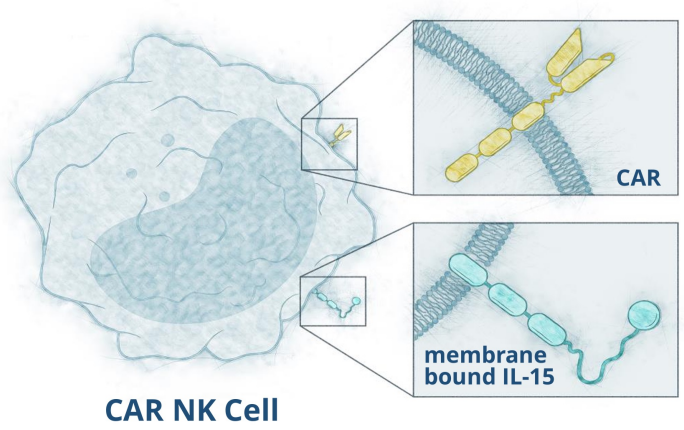
Higher peak IL-15 after LD correlates with CAR T expansion and responses



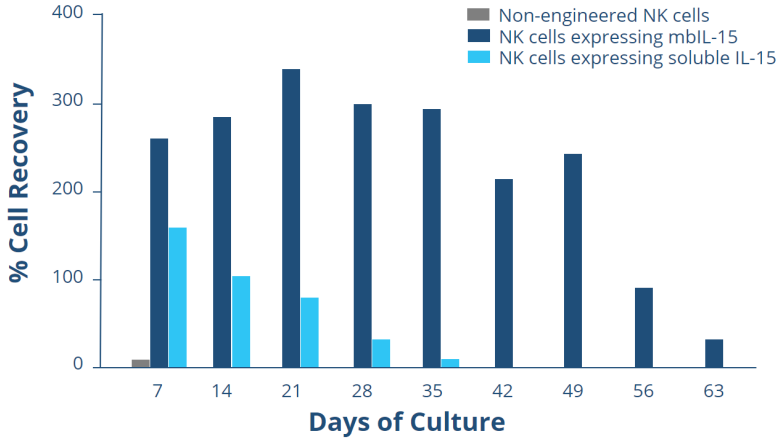


1: Kochenderfer, et al. *J Clin Oncol*. 2017 Jun 1;35(16).

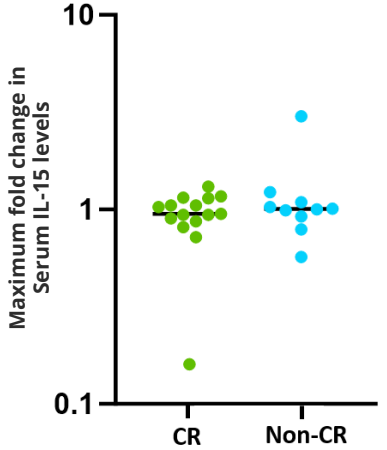
NKX019 engineering allows cytokine independence, for both persistence and response, further enabling disease-tailored LD



NK cells with membrane-bound IL-15 have superior persistence without IL-2



Serum IL-15 elevation is not required for CR with NKX019 for NHL



Nkarta, corporate presentation. Dec 2022.

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

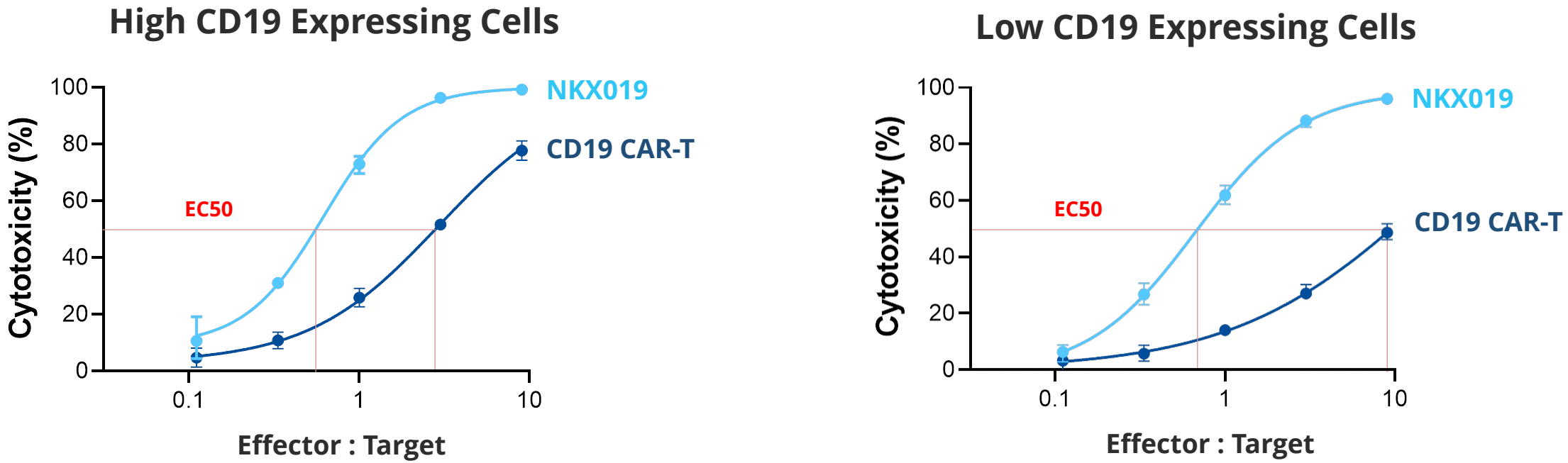
- mb-IL15 allows NKX019 to survive several weeks without supplemental cytokines like IL-15 or IL-2
- Construct causes no secreted IL-15 and has limited cross-cell stimulation

Unlike CD19 CAR T, there is no association between elevated IL-15 after NKX019 and CR in NHL

CR: complete response; IL-2: interleukin-2; IL-15: interleukin-15; NHL: non-Hodgkin lymphoma

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

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



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

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.

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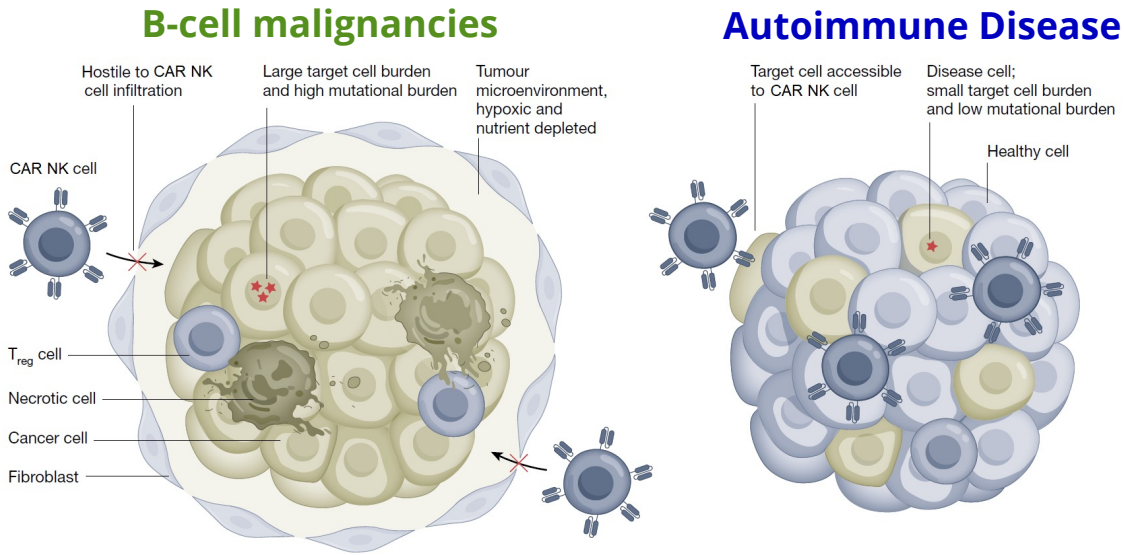
Autoimmune B cells may be more accessible than malignant B cells

While CD19 allows effective targeting of 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

Fewer target cells favors NK cell antigen-independent dosing, potentially increasing E:T ratio



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

E:T Ratio - Effector : Target is the ratio of NK or T cells to tumor cells.

NKX019 trafficking facilitates B cell killing throughout the body

NK cells traffic throughout the body, including to traditionally privileged sites

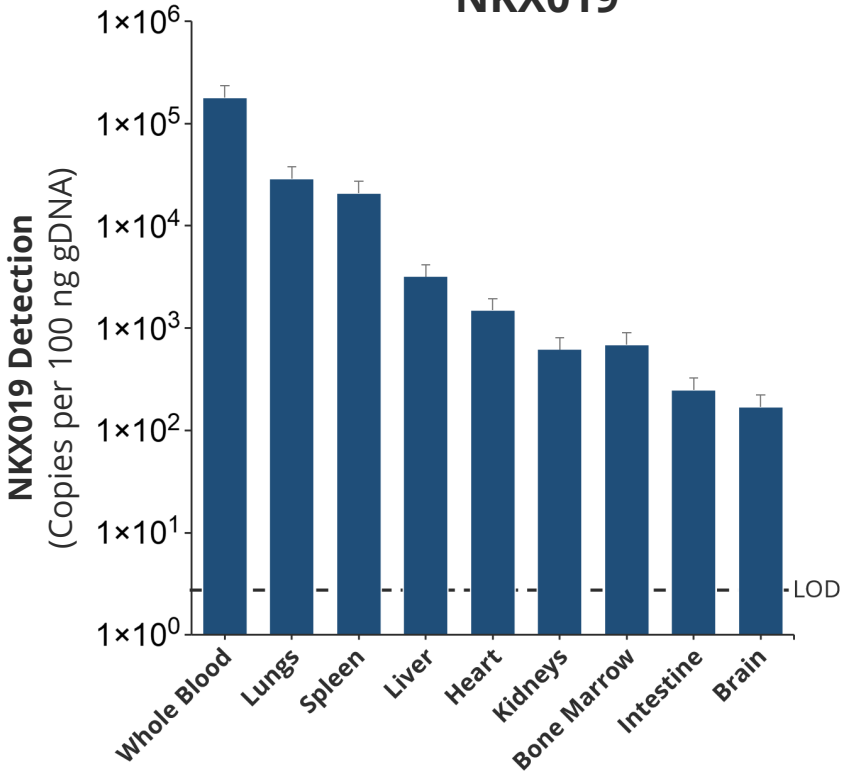
- Under pathological conditions, including autoimmune diseases, NK cells redistribute between tissues and organs[1]

NKX019 distributes broadly in animal models

Patients with B-cell malignancies have achieved CR with NKX019 despite widespread disease

- NHL cleared from bone marrow, lymph nodes, liver, spleen, etc
- Malignant B cells offer effective proxy for biodistribution of normal B cells

In vivo Distribution of NKX019



Nkarta, Data on File.

CR: complete response; LOD: limit of detection; NHL: non- Hodgkin lymphoma

1: Peng, et al. Clin Rev Allergy Immunol. 2014 Oct;47(2):119-27

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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

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

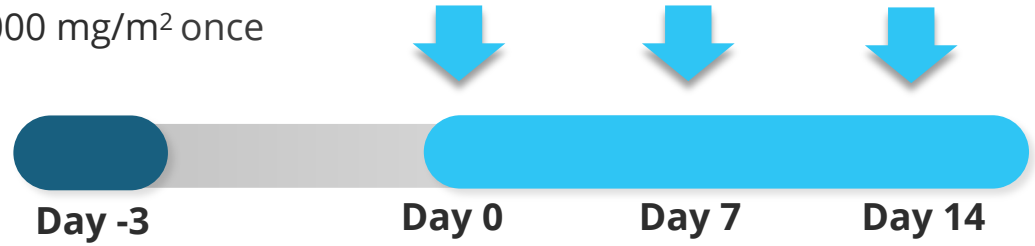
NKX019 for autoimmune diseases:
A multicenter, open-label, phase 1 study

Lymphodepletion

Cyclophosphamide
1000 mg/m^2 once

NKX019

3 doses per cycle



1B or 1.5B CAR-NK cells/dose

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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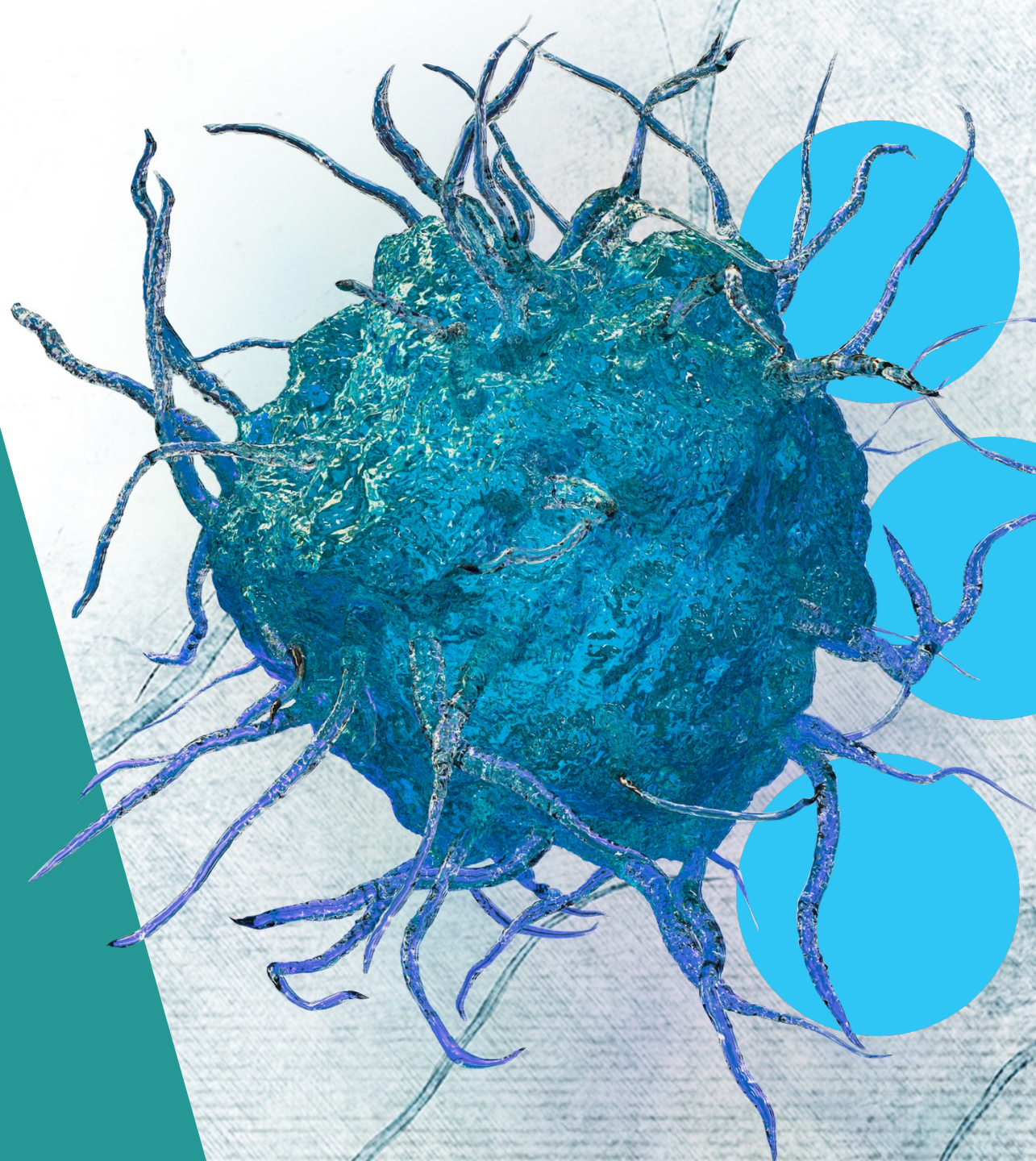
CAR: chimeric antigen receptor

NKX019 in Oncology



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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

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.

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

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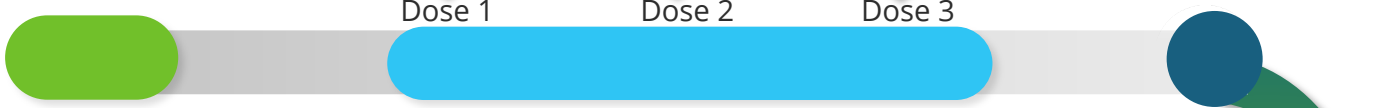
NKX019 for B-cell malignancies: A multicenter, open-label, phase 1 study in r/r NHL

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

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

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.

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NKX019 Amendment: Compressed Dosing as an Outpatient

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

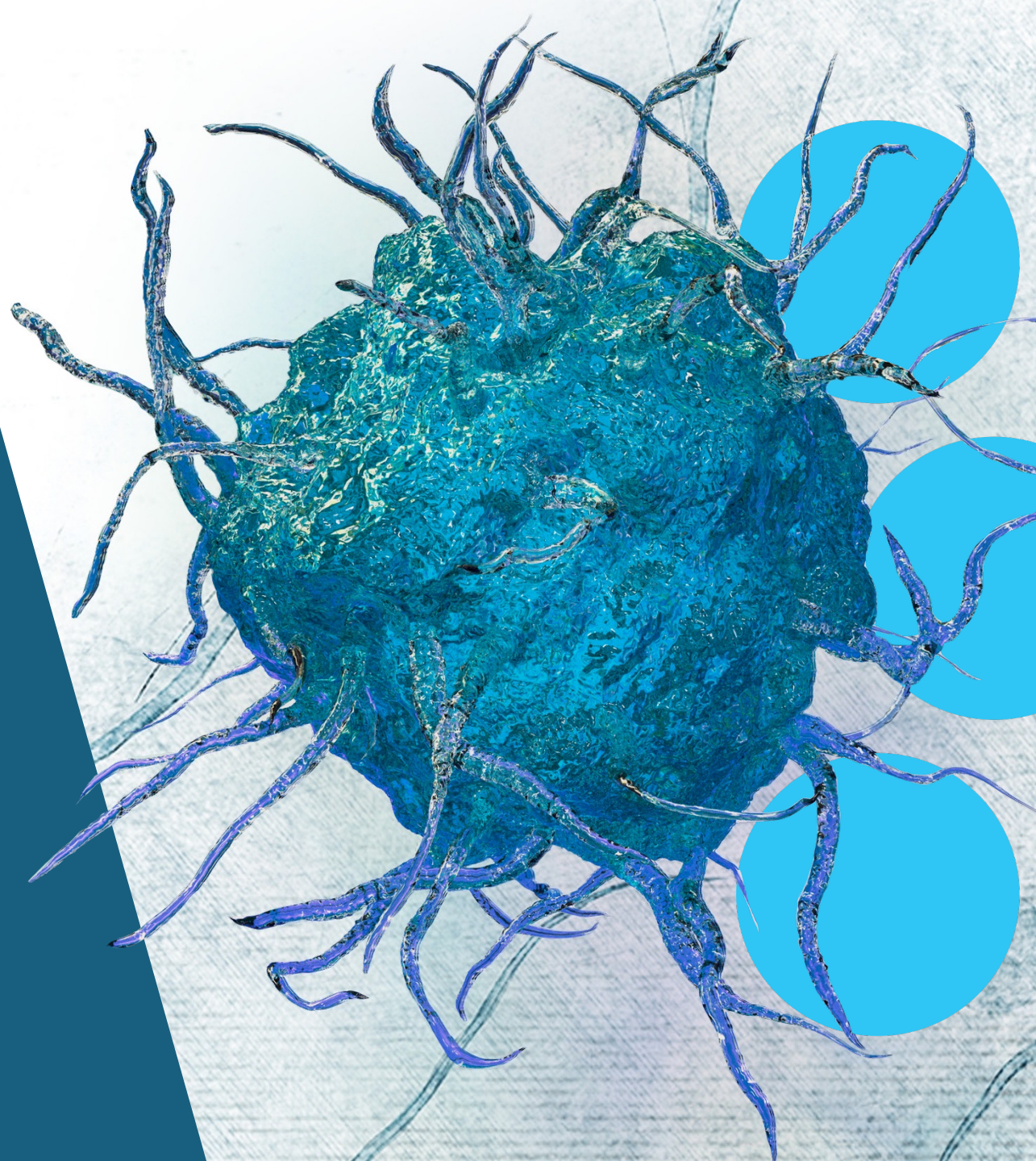
Study amendment also includes

- 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

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

Summary



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Autoimmune expansion | 2024 updates | Cash runway

- Pipeline prioritization focuses on NKX019 development in autoimmune disease
- Disease-tailored lymphodepletion leverages NK cell biology and supports differentiated safety/accessibility profile
- Further investment in NKX019 oncology gated by clinical signals from next data update
- $250.9 M in cash and cash equivalents as of 31 Dec 2023*; projected cash runway into 2026

Anticipated 2024 clinical milestones in autoimmune

1H 2024	*NKX019 in lupus nephritis* Dose first patient and program update

* Includes short-term investments and restricted cash

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