A Phase 1 Study of NKX019, a CD19 Chimeric Antigen Receptor Natural Killer (CAR NK) Cell Therapy, in Subjects with B-cell Malignancies

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nkarta THERAPEUTICS

NK cell biology has potential to address the limitations of autologous CAR T cell therapy for B-cell malignancies

- Over 500,000 people are diagnosed with B cell-derived cancers each year, including non-Hodgkin lymphoma (NHL) and acute lymphoblastic lymphoma (ALL)[1-3]
  - 30-40% of newly diagnosed patients with aggressive NHL fail first-line treatment[4-7]
  - Only a small percentage of patients with NHL who are chemo-refractory or relapse (R/R) will have prolonged disease-free survival[4]
  - While over 80% of adults with ALL will achieve remission, over half will relapse[8]
- Autologous CD19 CAR T cells altered the treatment landscape for patients with R/R NHL and ALL, though toxicities and manufacturing challenges limit their use
  - Products were not delivered to 7-34% of patients in pivotal CAR T studies
  - Toxicities such as CRS and ICANS are common and can be life-threatening
  - 15-47% of patients in pivotal CAR T studies required ICU admission[9]
- Outcomes for patients who progress after CAR T cell therapy are dismal[10]

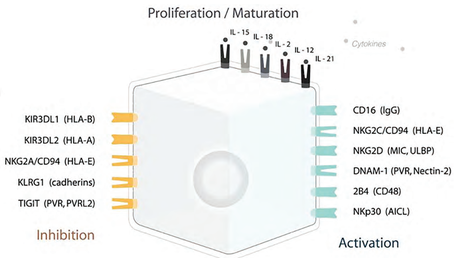
Rates of responses and key toxicities across CAR T cell therapies*

	KYMRIAH®	YESCARTA®	TECARTUS™	BREYANZI®
ORR	50-83% (32-40% CR)	72% (51% CR)	80% (41% CR)	73% (54% CR)
CRS	74-79% (23-49% G3+)	94% (13% G3+)	92% (18% G3+)	46% (4% G3+)
ICANS	58-72% (18-21% G3+)	87% (31% G3+)	81% (37% G3+)	35% (12% G3+)

CR= complete response; CRS = cytokine release syndrome; G3+ = Grade 3 and higher; GVHD = graft versus host disease; ICANS = Immune cell neurotoxicity syndrome; LD = lymphodepletion chemotherapy; NK = natural killer; ORR= overall response rate.

*According to package insert

Distinct NK cell biology has potential to address T cell limitations



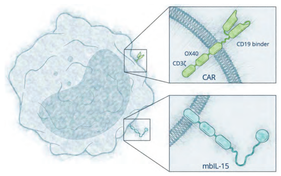
	T cell Biology	NK cell Biology
Anti-tumor activity	Target killing is a product of T cell expansion	Target killing is a product of NK cell numbers
Potential as an allogeneic product	Low without additional gene edits because of TCR and risk for GVHD	High without additional gene edits as no TCR and low to no risk for GVHD
Proliferation upon target recognition	Massive proliferation	Modest proliferation
Cellular kinetics	Slower to develop robust response	Peak activity is more immediate
Lifespan and response	Longer potential lifespan and immunity	Shorter intrinsic longevity and limited memory phenotype[a]

[a]Overcome by multi-dosing and multiple treatment cycles

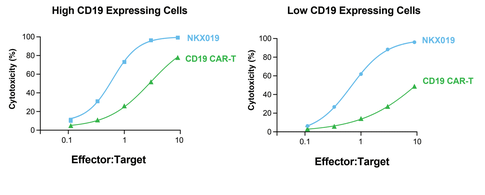
NKX019 is a CD19 CAR NK cell product that has consistent cytotoxicity independent of CD19 expression levels

NKX019: Engineered CAR NK cells with CD19 chimeric antigen receptor, OX40 costimulatory domain, CD3ζ signaling moiety, membrane-bound IL-15

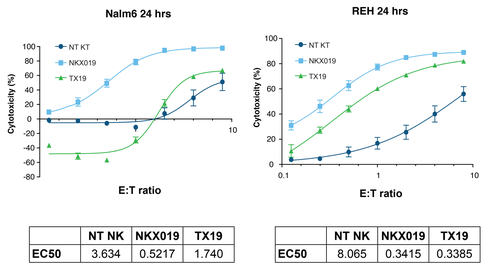
- mbIL-15 serves as an autocrine growth factor for NK cells, potentially obviating the need for systemic cytokine support



NKX019 kills B cell-derived tumor cells despite significantly reduced surface expression of CD19 compared to CD19 CAR T cells



NKX019 has superior early activity and comparable delayed target cell killing compared to CD19 CAR T cells[11]



	NT NK	NKX019	TX19
EC50	3.634	0.5217	1.740

	NT NK	NKX019	TX19
EC50	8.065	0.3415	0.3385

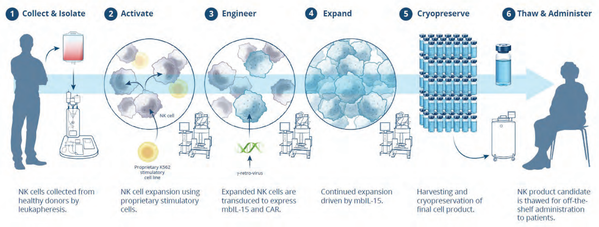
	NT NK	NKX019	TX19
EC50	4.383	0.3619	0.3463

	NT NK	NKX019	TX19
EC50	1.914	0.1815	~0.02661

NT NK = non-engineered NK cells; TX 19 = CD19-directed CAR T-cells

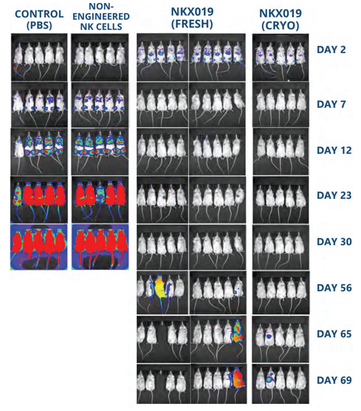
Nkarta's proprietary manufacturing technology has the potential to produce multiple cryopreserved doses with no loss of cytotoxicity compared to fresh cells

Manufacturing process is scalable



- Manufacturing process is scalable
  - In house GMP facility allows maximal flexibility and control
- Cryopreserved, off-the-shelf NKX019 allows for clinical evaluation in a multicenter trial
  - Anti-tumor activity not compromised
  - Easily support multiple doses and cycles

Cryopreserved and thawed NKX019 remains potently cytotoxic in vivo



NKX019-101* is a Phase 1 study evaluating the safety and activity of NKX019 monotherapy in patients with R/R NHL or B-ALL

Cryopreserved and thawed NKX019 remains potently cytotoxic in vivo

Dose expansion cohorts

All cohorts except 2A-B are CAR T naïve

Cohort 1A (N = 6-12) **NHL Dose finding**

- **Cohort 2A-A:** Aggressive LBCL
- **Cohort 2A-B:** Aggressive LBCL after CAR T
- **Cohort 2A-C:** Mantle cell lymphoma
- **Cohort 2A-D:** Indolent lymphoma
- **Cohort 2A-E:** Waldenström macroglobulinemia
- **Cohort 2A-F:** CLL/SLL

Dose finding cohorts recruit in parallel

Cohort 1B (N = 6-12) **B-ALL Dose finding**

- **Cohort 2B-A:** B-ALL

*ClinicalTrials.gov Identifier: NCT05020678

Key Objectives

- Assess safety and tolerability, including dose-limiting toxicity (DLT)
- Identify MTD and/or RP2D
- Characterize PK, PDn, and immunogenicity
- Assess anti-tumor activity (efficacy)
- HLA, KIR and other immune regulatory ligand match/mismatch with safety and tolerability, PK, PDn, and anti-tumor activity

DLT definition

- ≥ NCI CTCAE Grade 3 non-hematological toxicity
- ≥ Grade 2 acute GVHD that is steroid refractory in non-transplant recipients

Study NKX019-101 provides an off-the-shelf therapeutic option for patients with refractory malignancies

Key Inclusion Criteria	Key Exclusion Criteria
Adult ≥ 18 years of age	Burkitt Lymphoma, primary CNS lymphoma, Transformation to Hodgkin lymphoma
ECOG ≤ 1	Known active CNS disease or isolated extramedullary leukemia
Histologically or cytologically confirmed diagnosis of relapsed / refractory NHL or B-ALL defined by WHO 2016 classification[12]	• Any chemotherapeutic, targeted small molecule drug, investigational therapeutic or radiation within 14 days prior or 5 half lives • Any anti-NHL/ALL monoclonal/antibody within 28 days
NHL/CLL: • Received ≥ 2 prior lines of appropriate therapy except subjects with MCL & WM who must have ≥ 1 line of therapy • Measurable or detectable by disease-specific classification including Lugano classification[13,14], iwCLL[15] or iwWM[16]	• Prior allogeneic or autologous transplant within 100 days prior to the first dose of NKX019 • Ongoing ≥ Grade 2 acute GVHD or ≥ moderate chronic GVHD • Use of any prior CD19 CAR T or any NK cell therapy except in those cohorts evaluating subjects with prior CAR T treatment
ALL: WBC count ≤ 30 × 10^9/L Detectable disease per NCCN[17] criteria, including MRD level	• Autoimmune disease requiring chronic therapy • Active systemic infection, cardiac dysfunction or CNS disorder • Other prohibited comorbid conditions and concomitant medications
Exposure to disease-appropriate therapies including anti-CD20 antibody, anthracycline, BTKi, BCL-2i, and TKi	Presence of residual non-hematologic toxicity from prior therapies that has not resolved to ≤ Grade 1
Documented CD19+ status by local assessment, if treated with prior CD19-targeted therapy	Previous or concomitant malignancy within 2 years of study entry
Adequate organ function	Pregnant or lactating female

3 doses of NKX019 administered after lymphodepletion; 2 dose levels evaluated

	Cycles 1-5													
	LD Chemotherapy				NKX019 I.V. Administration; 28-day cycle									
Study Day	−5	−4	−3	−2	−1	0	1	2-6	7	8	9-13	14	15	16-19	20	21-26	27
Study Treatment	×	×	×			×			×			×					
Safety	×					×	×		×	×		×	×		×		
PK	×					×	×		×	×		×	×		×		×
Efficacy	×																×

- 3 doses of NKX019 per cycle after standard fludarabine/cyclophosphamide lymphodepletion chemotherapy
  - 300 mg/m² of cyclophosphamide and 30 mg/m² of fludarabine
- Up to 5 treatment cycles, each with 3 doses of cells and lymphodepletion, based on tumor response and tolerability
- 2 NKX019 dose levels planned: 3×10^8, 1×10^9 viable CAR NK cells per dose
- All products are derived from healthy, unrelated adults for off-the-shelf administration with no HLA matching required
- Minimum 24-hour monitoring on NKX019 dosing days; 2-hour drive proximity to study center for 1-week post-NKX019 infusion
  - Potential to decrease monitoring to 8 hours in later cohorts if protocol-specified safety criteria are met
- DLT observation period: Day 0-27 of treatment cycle
- Preliminary efficacy assessment: NHL (excluding CLL and WM): Lugano[13,14], CLL: iwCLL[15], WM: iwWM[16], ALL: NCCN[17]

Summary

- Unmet need for patients with R/R NHL and B-ALL despite autologous CAR T therapies
- Preclinical studies demonstrate superior in vitro and in vivo activity of NKX019 against target cells with reduced CD19 expression compared to CAR T cells
- NKX019 retains potent cytotoxicity after cryopreservation
- NKX019 is being evaluated in an international multicenter study utilizing Nkarta's proprietary manufacturing and cryopreservation technologies to support multiple cycles
- NKX019-101 is a first-in-human trial of allogeneic NKX019 monotherapy
- in patients with R/R B-cell malignancies with poor prognosis and limited treatment options
  - NKX019 monotherapy is administered after lymphodepletion; 2 dose levels of NKX019 are planned to evaluate safety, tolerability, PK, PD, and preliminary efficacy
- **Trial is currently enrolling in US and Australia: NCT05020678**

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