PATIENT-TAILORED TREATMENT WITH THE CD19-DIRECTED CAR NK CELL THERAPY, NKX019 IS SAFE AND FEASIBLE, INCLUDING DOSE OPTIMIZATION AND SUCCESSFUL RETREATMENT

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OBJECTIVES

Background

Cell therapies have transformed the treatment paradigm for some refractory hematologic malignancies and are increasingly being evaluated for non-malignant conditions, including autoimmune diseases. These therapies share the goal of safe and effective target cell killing, often enhanced by genetic manipulation, such as engineering the expression of a targeting chimeric antigen receptor (CAR) on the cell surface. The successful development of these products is contingent upon understanding the unique features of both cell type and source.

Autologous CAR T vs. Allogeneic CAR Natural Killer (NK)

Autologous CAR T cells have been the most used cell source to date, and the therapies created from these products are characterized by several factors:

- Dependence on LD to eliminate the host cytokine sink to allow for massive in vivo expansion upon target recognition
- Generally dosed once followed by long-term persistence in the body

Logistic challenges which preclude widespread adoption of this therapy include:

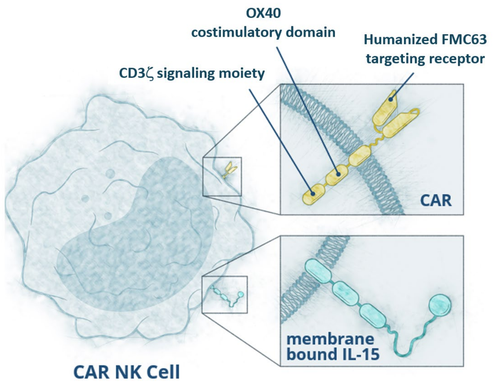
- Custom manufacturing which delays treatment
- Potential for severe T-cell mediated toxicities due to in vivo expansion
- Inability to deepen response or retreat after initial response and progression[1]

In contrast, allogeneic NK cells:

- Require LD for temporary suppression of host immunity
- Have limited expansion and persistence cells so must be dosed at a therapeutic level
- Can be dosed multiple times

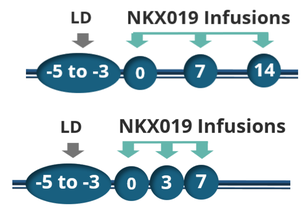
In study NKX019-101, we evaluated a CAR NK product (NKX019) and utilized understanding of NK cell biology to determine a safe dose level and regimen.

NKX019 is an allogeneic, CD19-targeted CAR natural killer (NK) cell therapy, derived from healthy donors and is cryopreserved for off-the-shelf administration. NKX019 expresses a humanized CD19 CAR with CD3 zeta and an OX40 costimulatory domain, as well as a membrane bound form of IL-15, providing an autocrine growth factor to improve NK cell persistence after infusion.



METHODS

Figure 1: NKX019 Administration Cycle



NKX019-101 (NCT05020678) is an open label, multicenter, Phase 1 trial for adults with relapsed/refractory B-cell malignancies who have received ≥2 prior lines of therapy. Subjects are treated with LD followed by three doses of NKX019, constituting one cycle of treatment. These doses were initially given on days 0, 7, and 14 after LD and the protocol was subsequently amended to dose on days 0, 3, and 7 (Figure 1). Dose escalation began at 300 x 10^8 CAR NK+ cells/dose and escalated to 2 x 10^9 CAR NK+ cells/dose

Subjects could receive additional treatment cycles to deepen response from partial response (PR) to complete response (CR), for remission consolidation, as well as for retreatment of initial CR and subsequent relapse.

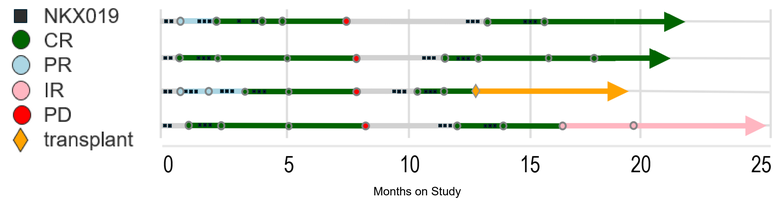
Multiple cohorts were enrolled including NKX019 monotherapy and with NKX019 in combination with rituximab (the latter not described in this abstract).

RESULTS

As of Jan 2024, 26 subjects with NHL in the monotherapy cohort had been dosed. 19/26 (73%) subjects achieved CR or PR across all dose levels. NKX019 has a manageable safety profile, with most adverse events related to LD.[2] Importantly, there have been no events of immune effector cell associated neurotoxicity syndrome (ICANS) or grade > 3 cytokine release syndrome (CRS).

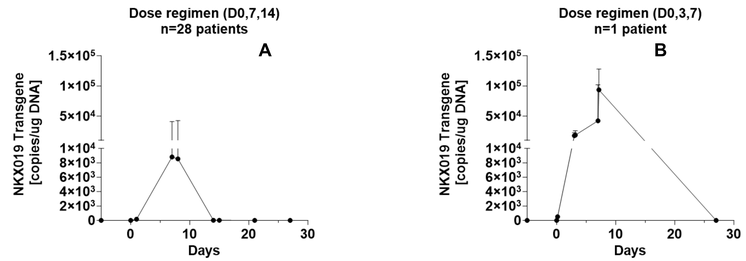
Four subjects received retreatment after initial CR and subsequent PD (Figure 2). All four subjects had at least 4 months of CR prior to PD. Time from PD to LD start for retreatment was < 4 weeks. All 4 subjects achieved CR after one cycle and received one cycle as consolidation. After retreatment, minimal duration of response was 5 months with follow up ongoing. Two subjects remain in CR. One subject had allogeneic stem cell transplant in CR, and one had PET scan findings of indeterminate significance and has received no additional therapy. There were no new safety signals during retreatment, including no cases of CRS or ICANS.

Figure 2. Swimlane plot of subjects who received retreatment with NKX019



Preliminary pharmacokinetic (PK) data (available in May 2024) showed minimal persistence of NKX019 after dosing with total clearance within 28 days. There was significantly lower exposure for NKX019 with the day 14 dose compared to the doses given on days 0 and 7 (Figure 3A), presumably secondary to host immune recovery. PK data from a patient dosed with alternate dosing on days 0, 3, and 7 showed extended overall exposure and sequentially increased Cmax levels compared to dosing on days 0, 7, and 14 (Figure 3B). There was no change in the safety profile observed in the subjects dosed to date, with only low-grade CRS and no ICANS.

Figure 3. NKX019 CAR NK+ Pharmacokinetics



(A) PK data represents current NKX019 monotherapy-treated patient PK data (all doses, indications and cycles included) (B) Preliminary PK data from one patient with 2 cycles of treatment

CONCLUSIONS

NKX019 showed better exposure with an alternative dosing strategy in which doses were given more proximal to LD.

In addition, retreatment after initial CR and subsequent PD was safe and effective, suggesting that relapse occurred due to initial insufficient depth of response, not inherent resistance to NK cell killing.

These findings support an alternate strategy for NKX019. Dosing within 10 days of LD takes advantage of temporary host immune suppression afforded by LD which may drive deeper responses and longer duration of response, while maintaining a manageable AE profile. This dosing strategy could have implications beyond hematologic malignancies to autoimmune diseases.

1. Brudno, Jennifer N., and James N. Kochenderfer. "Limited utility of chimeric antigen receptor (CAR) T-cell retreatment: experience with a human anti-CD19 CAR." *Bone Marrow Transplantation* 58.10 (2023): 1157-1159.
2. Dickinson, Michael, et al. "First in human data of NKX019, an allogeneic CAR NK for the treatment of relapsed/refractory (R/R) B-cell malignancies." *Hematol Oncol* 41.S2 (2023): 526-527.