First in Human Data of NKX019, an Allogeneic CAR NK for the Treatment of Relapsed/Refractory (R/R) B-cell Malignancies

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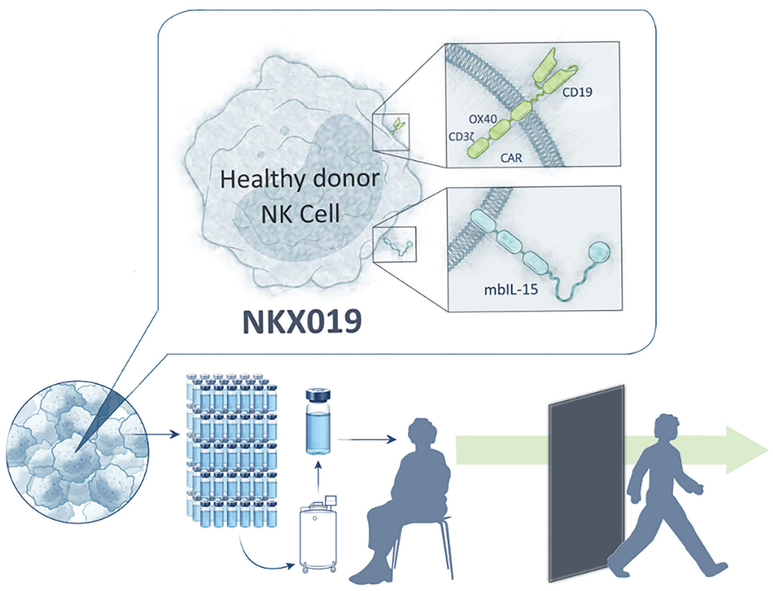
Background

Autologous CAR T-cell therapies have altered the treatment landscape for many patients (pts) with advanced B-cell malignancies, however custom manufacturing precludes prompt treatment and can result in manufacturing failure. T-cell mediated toxicities are common and can be severe, thereby limiting the population of eligible pts. These challenges limit CAR T-cell therapy administration to certified treatment centers, further restricting patient access.

NKX019 is a cryopreserved, allogeneic CD19-targeting CAR NK-cell therapy, derived from healthy donor NK cells, with CD3 zeta and OX40 costimulatory domains and a separate membrane bound IL-15 for activation. NKX019 has shown encouraging *in vitro* and *in vivo* cytotoxicity. Development of an on demand allogeneic NK-cell therapy may address challenges associated with CAR-T therapy.



Cryopreserved and ready for outpatient treatment

Methods

This is an open label, phase 1 trial (**NCT05020678**) for adults with r/r B-cell malignancies with ≥2 prior lines of therapy excluding prior auto CD19 CAR T-cell therapy. Following 3 days of lymphodepletion (LD) with fludarabine and cyclophosphamide, pts received NKX019 at 3 dose levels (3×10^8, 1×10^9, or 1.5×10^9 CAR+ NK cells/dose on days 0, 7, and 14 of a 28-day cycle). Additional cycles were allowed to deepen response. Tolerability, anti-tumor activity, cellular kinetics, and immune responses were evaluated.

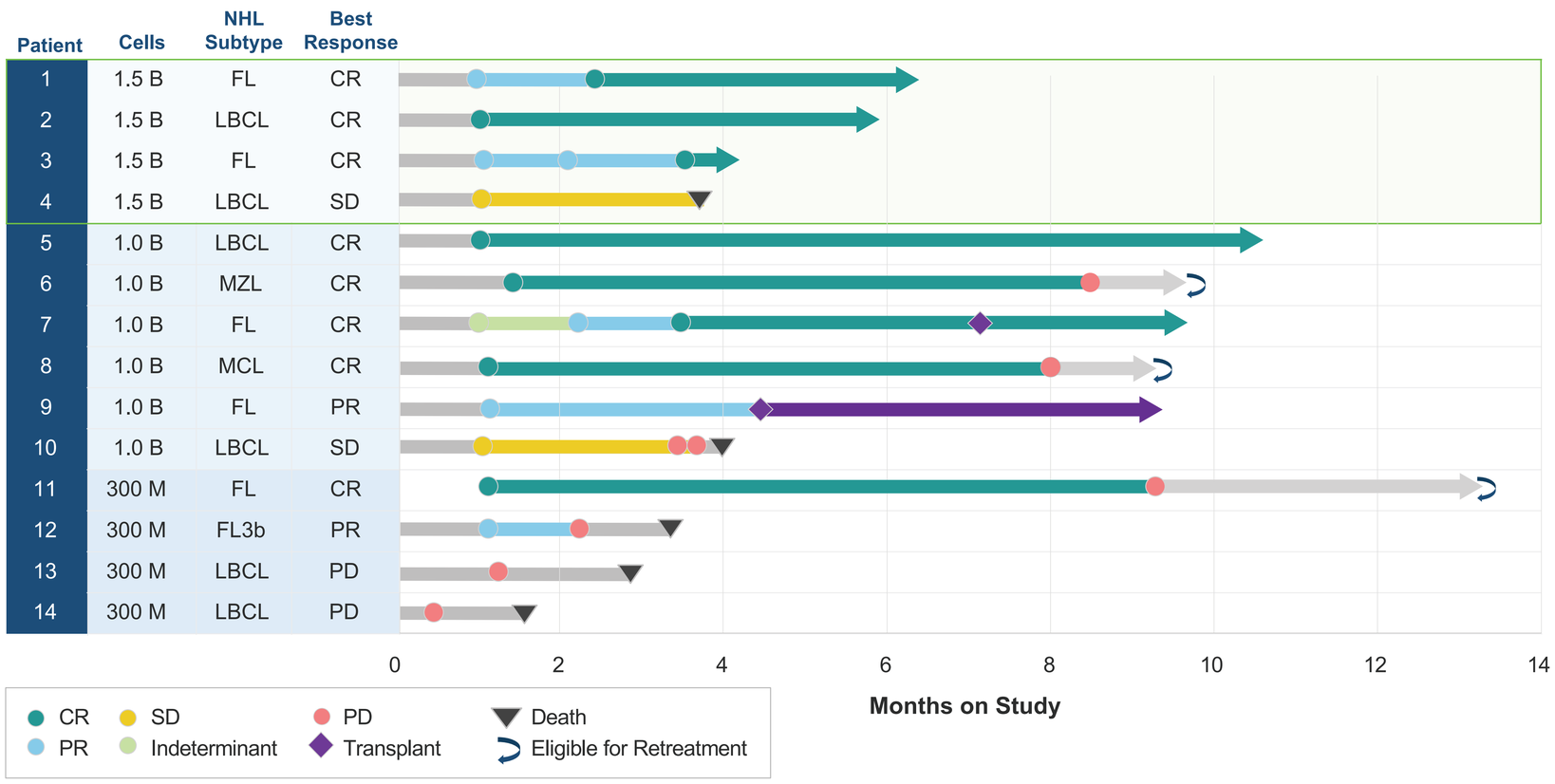
Results

As of November 2022, 19 pts in the US and Australia with r/r B-cell malignancies (14 with non-Hodgkin lymphoma (NHL) (LBCL, FL, MZL, or MCL) and 5 with leukemia (ALL or CLL) received NKX019. Median age was 59 years (range 21-82), with median 4 prior lines of therapy.

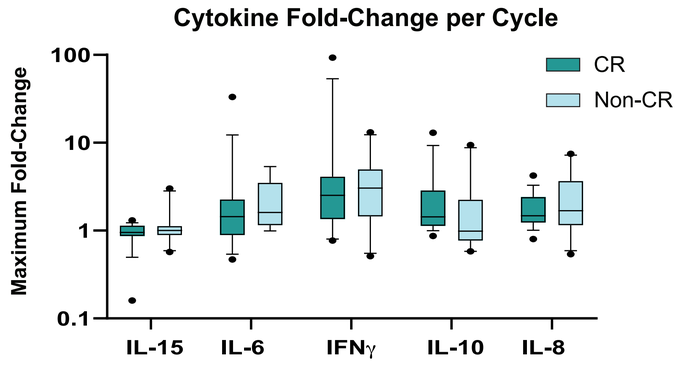
Grade 3/4 hematologic toxicity was 84%, consistent with expected myelosuppression related to LD. There was one grade 3 infection. No treatment related AEs leading to discontinuation of NKX019 were observed. No dose limiting toxicities, neurotoxicity, or GvHD were reported. Five of 19 pts (26%) developed transient fever within 8 hours of NKX019 dosing, but no pts developed signs of cytokine release syndrome beyond 24 hours after cell infusion.

Efficacy was shown across histologies, with 8 pts achieving CR, including 5 after a single treatment cycle. Three pts deepened from PR to CR with additional cycles. Three of the 4 pts with NHL treated at the 1.5 billion cell dose also achieved CR. In the 2 higher dose cohorts, there was an 80% ORR and 70% CR rate in NHL, including a 50% CR rate in LBCL. With regards to durability, 5 pts had CR that exceeded 6 months, including one pt with LBCL, who had CR for over 9 months.

Three pts have had presumed disease recurrence, each after at least 6 months of CR and none at the highest dose level. These pts are eligible for retreatment. Pharmacokinetic data showed a correlation between higher cell doses and higher peak concentration (C_{max}), with a trend toward higher C_{max} in pts achieving CR. No association was observed between clinical response and elevation of serum cytokines.



Dose Level	C_{max}	All subjects	CR	Non-CR
300 M cells	n	5	1	4
	Median (range)	**< 6.7** (< 6.7-393)	**393** (393)	**< 6.7** (< 6.7-234)
1 B/1.5 B cells	n	14	7	7
	Median (range)	**156.9** (< 6.7-567.0)	**298** (< 6.7-567.0)	**< 6.7** (< 6.7-481)



Conclusion

- **Initial data with NKX019 shows durable efficacy across multiple NHL histologies and the option for retreatment in the setting of relapse.**
- **On demand dosing and a manageable safety profile allow for increased patient access, including in the outpatient setting.**
- **Expansion cohorts are now enrolling and will include both LBCL patients who are CAR naïve and CAR experienced.**

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