NKX019, AN OFF-THE-SHELF CD19 CAR-NK CELL, MEDIATES IMPROVED ANTI-TUMOR ACTIVITY AND PERSISTENCE IN COMBINATION WITH CD20-DIRECTED THERAPEUTIC MABS

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Background
NKX019 is an investigational CD19-targeting chimeric antigen receptor (CAR) natural killer (NK) cell therapy with engineered persistence for treating B cell malignancies. NKX019 exhibits more rapid cytotoxic kinetics than CD19-directed CAR T cells, and lower production of cytokines associated with cytokine release syndrome (CRS).1 The safety and clinical activity of NKX019 are currently being evaluated in a phase I [GM1] clinical study [NCT05020678]. Recent studies2,3 have shown that combining NK cell therapies with monoclonal antibodies (mAbs) may improve targeted NK cell activation and overcome some of the disadvantages associated with the stand-alone use of therapeutic mAbs. CD20-targeted mAbs such as rituximab (RTX) and obinutuzumab (OBI), can mediate antibody-dependent cellular cytotoxicity (ADCC), a key effector mechanism of NK cells. RTX also activates some levels of caspase-dependent direct cell death (DCD). OBI is engineered to induce improved DCD and ADCC mechanisms.4 Antigen escape is reported in 30–95% of relapses after CD19-directed CAR T cell therapy in B cell–acute lymphoblastic leukemia (B-ALL).5 Here, we describe the potential advantage of using NKX019 in combination with [GM2] RTX or OBI to reduce relapse following monotherapy with either agent alone by targeting both CD19+ and CD20+ malignant B cells.

Methods
NK cells, isolated from healthy PBMCs, were expanded and engineered to express a CD19-targeted CAR and membrane-bound interleukin 15 to generate NKX019. NKX019 cells were cryopreserved and freshly thawed for experimental use. NKX019-mediated cytotoxicity was assessed in both 4-Hour (4H) and extended assays in the presence or absence of anti-CD20 mAbs, RTX or OBI, using CD19+ and CD20+ expressing tumor B cell lines: Raji (lymphoblast-like), DOHH-2 (follicular lymphoma) and EHEB (B-Lymphoblastoid) cells. A non-glycosylated version of RTX (RTX mutant) with compromised ADCC function was used to evaluate ADCC-mediated vs ADCC-independent activity of NKX019.

Results
NKX019 in combination with RTX or OBI demonstrated increased activity and persistence against tumor B cell lines in a 4H kill assay and in tumor rechallenge experiments. NKX019 in combination with RTX demonstrated an enhanced cytotoxicity against EHEB lymphoblastoid cell line in a manner consistent with ADCC. OBI demonstrated increased activity in comparison to RTX, as a single agent and in combination with NKX019 cells.

Conclusions
This study demonstrates increased activity and persistence of NKX019 when used in combination with approved CD20-targeted mAbs, RTX and OBI, against B cell malignancies. A first-in-human Phase I clinical trial of NKX019 in combination with RTX is planned.

REFERENCES