TNB-486, a Novel Fully Human Bispecific CD19 x CD3 Antibody That Kills CD19-Positive Tumor Cells with Minimal Cytokine Secretion

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Abstract # 4070

Background:
• CD19 is a well-established target in B-cell malignancies.
• Existing therapies elicit significant immune-mediated toxicity.
• The Tenebio antibody platform uses fully human VH domains and an NGS-based discovery pipeline.
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Results and Methods

Figure 2: TNB-486 lyses CD19+ NALM-6, RI-1, and Raji cells in a dose-dependent manner but not CD19- K562 cells, while inducing minimal cytokine secretion. Dose response curves for cytoxicity (A) and cytokine secretion (B) induced by TNB-486 (purple), a positive control (red) and a negative control (gray) are shown. The positive control incorporates a strongly activating CD3 similar to that used in blinatumomab. Resting human T cells were used as effector cells for all experiments.

Figure 3: TNB-486 induces T cell activation and proliferation. TNB-486 induces activation (A) and proliferation (B) of primary human CD4+ and CD8+ T cells as shown by increased %CD69+ and %CFSE+ cells respectively. Dose response curves for TNB-486 (purple), a positive control (red) or a negative control (gray) are shown.

Figure 4: TNB-486 shows favorable pharmacokinetic features. BALB/c mice were administered a single dose of TNB-486 at either 1 mg/kg or 10 mg/kg. Concentration vs time plot of TNB-486 in serum is shown. Group mean terminal half-life (t1/2) ranged from 2.6 – 4.1 days.

Figure 5: TNB-486 mediates clearance of CD19+ Burkitt Lymphoma tumor cells in mice. CIEA-NOG mice were administered Raji-luc tumor cells on day 0, human PBMCs on day 5, and TNB-486 on days 6, 11 and 16. Bioluminescent imaging over the course of 14 days shows TNB-486 mediated clearance of tumor cells at all doses except at 10 ng.

Figure 6: TNB-486 mediates clearance of CD19+ DLBLCL tumor cells in mice. CIEA-NOG mice were administered SUDHL-10 tumor cells on day 0, human PBMCs on day 19 followed by TNB-486 every 4 days. Tumor volume of all mice from day 19 (before treatment) and days after treatments are shown. TNB-486 mediated clearance of tumor cells at all doses except at 1 ug.

Conclusions:
• TNB-486 induces less cytokine secretion than a conventional T-cell engaging bispecific in vitro, without reduction in tumor cytokoty in vitro and in vivo.
• A Phase 1 clinical trial of TNB-486 in Non-Hodgkin Lymphoma will begin in Q4 2020.

Figure 1: TNB-486 Development

TNB-486 is a fully human T-BSab combining fixed-light-chain (FLC) and heavy-chain-only (HCO) arms paired using knobs-in-holes. The FLC arm weakly activates CD3. The HCO arm has a high-affinity anti-CD19 moiety.