**BACKGROUND**

- Coupling carcinoembryonic antigen-related cell adhesion molecule 5 (CEA or CEACAMS) on tumor cells and CD3 on T-cells by CEAxCD3 bispecific antibodies (bsAbs) activates the latter to destroy CEA-positive cancer cells.
- Clinical activity is, however, limited, in part by insufficient T-cell activation, dose-limiting toxicities (e.g., cytokine release syndrome (CRS), or immunogenicity).

**AIMS & MECHANISM OF ACTION**

**Strategy & aims**
Combination of CEAxCD3 bsAb with CEA-targeted CD28-costimulation shall
- T-cell activity & tumor cell killing ↑
- Duration of response ↑
- Better controllable dose response (CRS risk ↓)

**Mechanism of action (MoA):**
1) Mediates co-engagement of CEA on tumor cells and CD3 & CD28 on T-cells.
2) TCR/CD3 cross-linking leading to T-cell activation (Signal 1) & co-stimulation via CD28 engagement (Signal 2).
3) Release of cytokines & cytolytic enzymes.
4) Redirected killing of CEA+ tumor cells by effector T-cells.

**NILK-2301 & NILK-3301 BsAbs**

- CEA is (over-) expressed in tumors of epithelial origin, including but not limited to colorectal, gastric, lung, and pancreatic carcinomas.

**NILK-3001 IS NOT SUPERAGONISTIC**

- Superagonistic activity of NILK-3001 was excluded in in vitro T-cell proliferation, for both CD3+ (left panel) and CD8+ (not shown) T-cells, as well as activation assays (right panel).
- The superagonistic mononuclear anti-human CD28 antibody (IgG4κ) TGN1412 (Theralizumab) was used as comparator.
- NILK-3001 activates T-cells only in the presence of primary T-cell stimulation (Signal 1; left panel) and CEA-expressing target cells (right panel).

**IN VIVO ACTIVITY**

- Simultaneous (Combo D7) and sequential (d2+2 [Combo D9] or d4+4 [Combo D11]) combination treatment of NILK-2301 plus NILK-3301 induces markedly improved activity and tumor regression in 8/8 (Combo D7), 8/8 (Combo D9), and 6/8 (Combo D11) mice, respectively.
- No signs of toxicity were observed in any of the groups.
- Activity was also seen in CD34+ humanized BREGSF mice (genOway).

**CONCLUSIONS**

- NILK-3001 is active as single agent.
- NILK-3001 + NILK-3301 combination treatment significantly increases activity already at low NILK-3001 doses with reduced cytokine release when given sequentially.
- IND-filing for NILK-2301 is expected in Q1/2023.

**CONTACT**

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