Abstract #5100

Combination of κλ bispecific antibodies targeting innate (CEAxCD47, NILK-2401) and adaptive immunity (CEAxCD3, NILK-2301 and CEAxCD28, NILK-3301) for next generation immunotherapy of CEA-expressing cancers

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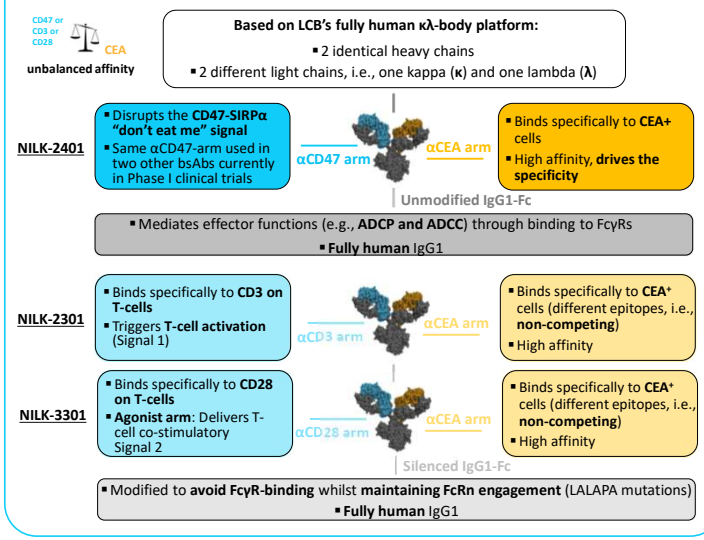
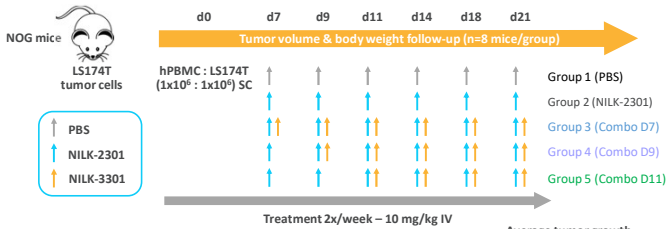
BACKGROUND

- The CEAxCD3 bispecific antibody (bsAb) NILK-2301 couples CEA (CEACAM5) on cancer cells and CD3 on T-cells inducing T-cell activation (signal 1) and tumor cell killing (TDCC). T-cell activation can be boosted by CEA-targeted CD28-costimulation (NILK-3301; signal 2).
- NILK-2401, carrying a fully effective IgG1 Fc, induces antibody-dependent phagocytosis (ADCP) and antibody-dependent cytotoxicity (ADCC) of tumor cells by co-targeting CEA and the innate immune checkpoint CD47.

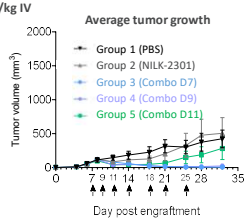
NILK-2301 & NILK-2401 & NILK-3301 BsAbs

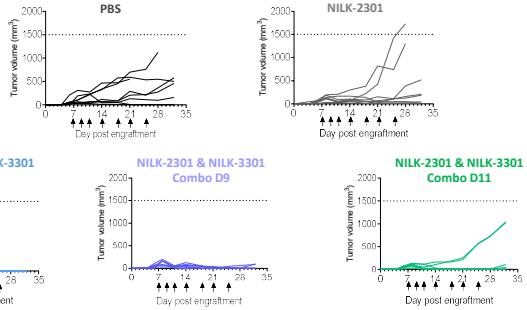


NILK-2301 + NILK-3301 *IN VIVO* COMBINATION ACTIVITY



- Simultaneous (Combo D7) and sequential (d+2 [Combo D9] or d+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.

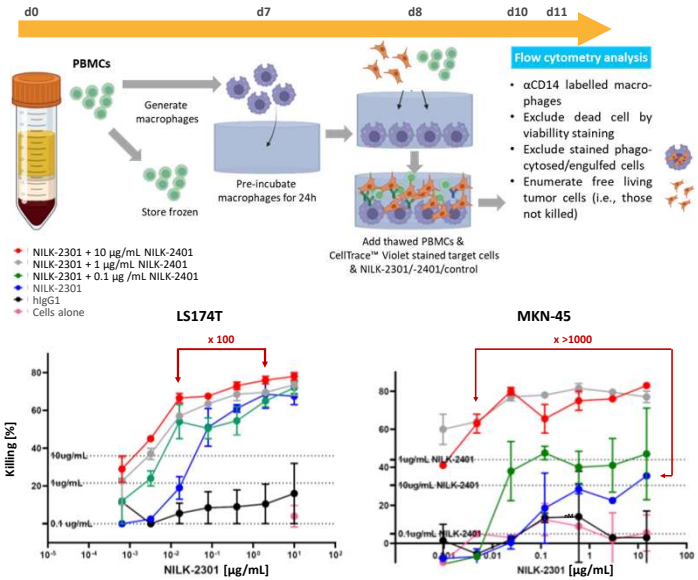




- No signs of toxicity were observed in any of the groups.

NILK-2401 + NILK-2301 COMBINATION ACTIVITY

"Mixed killing assay": NILK-2401 boosts activity of NILK-2301

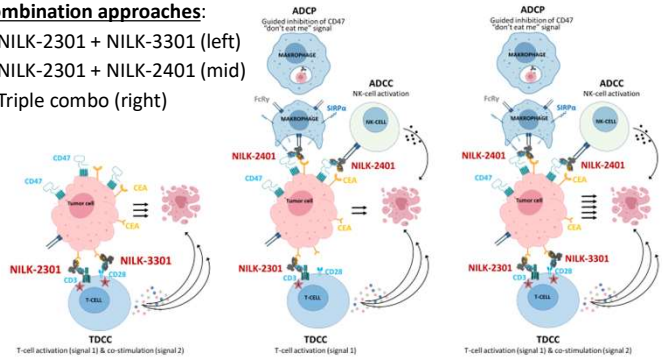


- Equivalent activity of NILK-2401 plus NILK-2301 combination therapy at 100-fold (LS174T; left panel) to >1000-fold MKN-45; right panel) lower doses compared to NILK-2301 monotherapy [i.e., ≈ 0.02 vs. 2 / 20 µg/mL].
- Combination treatment boosts NILK-2301 activity (Emax) by 15 to 250%.
- Simultaneous reduction of necessary T-cell engager dose (i.e., side effects ↓↓) and increase in activity ↑↑, i.e., EC50 reduced by a factor of 10 - 100.

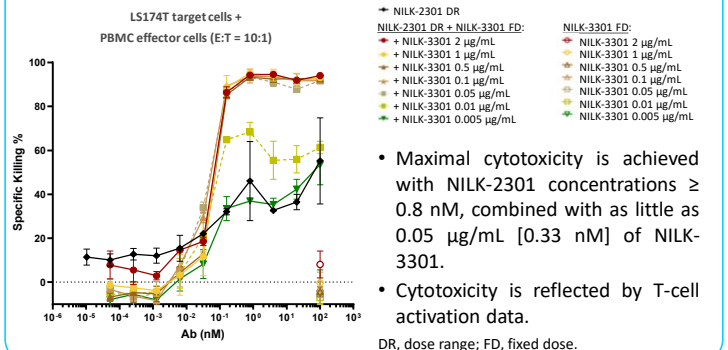
MECHANISM OF ACTION & COMBO STRATEGY

Combination approaches:

- NILK-2301 + NILK-3301 (left)
- NILK-2301 + NILK-2401 (mid)
- Triple combo (right)



NILK-2301 + NILK-3301 *IN VITRO* COMBINATION ACTIVITY



- Maximal cytotoxicity is achieved with NILK-2301 concentrations ≥ 0.8 nM, combined with as little as 0.05 µg/mL [0.33 nM] of NILK-3301.
- Cytotoxicity is reflected by T-cell activation data.

DR, dose range; FD, fixed dose.

CONCLUSIONS

- NILK-2301 and NILK-2401 are active as single agents.
- Addition of NILK-2401 or NILK-3301 to NILK-2301 significantly increases activity, already at 10 -100x lower CEAxCD3 doses.
- GMP drug substance has been produced for NILK-2301 and NILK-2401.
- Generation of the clonal cell line for NILK-3301 clinical material production is ongoing.

CONTACT

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