NOVEL CEAXCD47 (NILK-2401) AND CEAXCD3 (NILK-2301) KL BISPECIFIC ANTIBODIES FOR MULTIMODAL IMMUNOTHERAPY OF CEA-EXPRESSING SOLID CANCER

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Background We present here our novel macrophage-directed CEAXCD47 bispecific antibody (bsAb) NILK-2401 alone and in combination with the CEAXCD3 T-cell retargeting bsAb NILK-2301 for multimodal treatment of CEA-expressing solid malignancies, e.g., gastrointestinal or lung carcinomas.

Methods BsAbs are generated using LCB’s fully human κλ body platform based on a common heavy chain and on one κ and one λ light chain, determining specificity and affinity. Binding, inhibition of CD47-SIRPα interaction, antibody-dependent cellular phagocytosis (ADCP) and antibody-dependent cellular cytotoxicity (ADCC) were assessed in vitro using colorectal (n=3), lung (n=2), and gastric (n=2) cancer cell lines. Human monocyte-derived macrophages (MDMs) or peripheral blood mononuclear cells (PBMCs) were used as effector cells. Combination activity (“mixed killing assay”) of NILK-2401 and NILK-2301 was assessed by flow cytometry, incubating both effector cell populations with tumor cells. In vitro safety data include binding to other CEACAM-members, ADCP of CEA-negative cells (n=3), cytokine release in whole blood, erythrophagocytosis, and platelet activation. In vivo, NSG-mice were co-engrafted SC with PBMCs, MDMs, and LS-174T tumor cells, and exposed to 10 mg/kg NILK-2401 IV once weekly vs. control. Pharmacokinetics and tolerability were assessed in cynomolgus monkeys and Tg32 human FcRn mice.

Results NILK-2401 has a functional IgG1 Fc part and shows low nM binding-affinity to CEA and high nM binding-affinity to CD47, enabling tumor specific blockade of the CD47-SIRPα interaction. Elimination of CEA-expressing cell lines by ADCP and ADCC is induced, including CEA-high (e.g., MKN-45) and low expressing cell lines (e.g., LS-174T). Killing activity was CEA-dependent as no phagocytosis of CD47-positive but CEA-negative cells, including red blood cells, was observed. Likewise, no platelet activation occurred. In the mixed killing assay, NILK-2301 plus NILK-2401 combination showed an additive effect, both increasing maximum activity (Emax) and necessitating lower doses of the T-cell bsAb to reach Emax. E.g., Emax of 30% killing (NILK-2301 alone) was increased in combination with NILK-2401 at 0.1/1/10 μg/mL to 40%, 80%, and 80%, respectively. In vivo, NILK-2401 delayed tumor growth vs. mean of control in 100% (15/15) of mice and prevented establishment of detectable tumors (i.e., >50mm³, d23 post co-engraftment) in 53% (8/15). In cynomolgus and Tg32 mice, doses of 0.5 and 20 mg/kg NILK-2401 (single IV dose) were well tolerated.

Conclusions NILK-2401 bsAb is active as single agent with limited potential side effects due to the tumor-targeted blockade of CD47. NILK-2401 plus NILK-2301 combination treatment significantly increases activity, without overlapping safety profiles. GMP drug substance has been produced for both molecules.

Ethics Approval Animal experiments were approved by the animal research committee of Geneva canton and experiments performed in accordance with the Swiss Federal Veterinary Office guidelines. This included submission and approval of the project by the Commission Cantonale d’Expérimentation Animale (CCEA; GE83 and GE134).