PRECLINICAL PHARMACODYNAMIC CHARACTERIZATION OF STK-026: A NOVEL IL-12 PARTIAL AGONIST FOR CANCER WITH MAINTAINED CD8 T CELL ACTIVITY, REDUCED NK-MEDIATED TOXICITY AND AN IMPROVED THERAPEUTIC WINDOW

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Background Interleukin-12 (IL-12) is a pro-inflammatory cytokine composed of p35 and p40 subunits produced by antigen-presenting cells to stimulate Th1 cells, cytotoxic CD8 T cells, and NK cells. IL-12 has potent anti-tumor properties in multiple preclinical models, however clinical applications of wild type IL-12 (IL-12wt) or IL-12wt-Fc fusions are hampered by severe dose-limiting toxicities. Preclinically, IL-12 toxicity is mediated by NK cell activation.

Here we report on a novel human IL-12 partial agonist (STK-026) with diminished binding to IL-12Rb1. STK-026 was designed to increase selectivity towards antigen activated T cells, which strongly upregulate IL-12Rb1 upon activation, and to reduce stimulation of NK cells or resting T cells, which express modest levels of IL-12Rb1.

Methods To understand the preclinical pharmacology of STK-026, we generated a half-life extended mouse surrogate of the IL-12 partial agonist (mSTK-026) for pharmacokinetic (PK) and pharmacodynamic (PD) assessment in healthy and tumor-bearing mice. Further, PK and PD parameters of human STK-026 were analyzed in healthy cynomolgus macaques.

Results At efficacious doses, systemic administration of a half-life extended version of wild type mouse IL-12 (mIL-12wt-Fc) induced significant weight loss and lethality with early proinflammatory cytokine release and systemic NK cell activation. Conversely, mSTK-026 was well tolerated, and avoided rapid NK cell activation seen with mIL-12wt-Fc. Both mSTK-026 and mIL-12wt-Fc showed robust single-agent anti-tumor efficacy in syngeneic tumor models however mSTK-026 demonstrated a >10-fold higher therapeutic index than mIL-12wt-Fc. Depletion of NK cells did not diminish anti-tumor efficacy of either IL-12 and efficacy of mSTK-026 was associated with intratumoral CD8 T cell activation and myeloid cell activation. In cynomolgus macaques, human STK-026 demonstrated antibody like PK, was well-tolerated at all doses tested (highest: 5mg/kg), and induced no detectable systemic IL-6 or TNFα. Compared to hIL-12wt-Fc, STK-026 avoided early spikes in NK cell activity and systemic chemokine levels, reduced lymphocyte activation in peripheral tissues, and reduced ALT/AST induction at doses activating effector and memory CD8 T cells.

Conclusions Overall, mSTK-026 retained anti-tumor efficacy without spikes of early NK activation and induction of severe toxicities seen with mIL-12wt-Fc. Similarly, human STK-026 avoided early spikes of NK activity in cynomolgus macaques and showed reduced signs of systemic toxicities compared to hIL-12wt-Fc. These data suggest that STK-026 is a novel immunotherapy approach with the potential to maintain anti-tumor efficacy while avoiding dose limiting toxicities classically associated with IL-12 therapy.