ULTRA-PH SENSITIVE NANOPARTICLES INCREASE THERAPEUTIC INDEX OF IL-2-Fc

Background Aldesleukin (IL-2) is clinically approved for the treatment of melanoma and renal cancer, but its use is restricted by short half-life and dose limiting toxicities. Protein engineering and prodrug approaches are under extensive investigation but with limited success. Fusion of bivalent IL-2 (IL-2-Fc) increases the half-life and efficacy of IL-2 when administered intravenously, but also elevates toxicity compared to IL-2. We developed ON-BOARD, an ultra-pH sensitive nanoparticle technology for tumor-targeted delivery of drug payloads, including biologics to acidic tumor microenvironment (TME).

The clinical safety and feasibility of ON-BOARD has been demonstrated by the effective delivery of fluorophores to solid tumors for imaging of multiple cancer types in Phase I/II clinical trials by pegsitacianine. Herein we report ONM-405, an ON-BOARD-encapsulated IL-2-Fc, which is designed to mask toxicity in normal tissues after systemic administration, while achieving pH-activatable release of IL-2-Fc at the tumor site against solid cancers.

Methods ONM-405 was formulated through non-covalent self-assembly, pH-dependent protein release was analyzed by fast protein liquid chromatography. Anti-tumor efficacy was evaluated by tumor growth inhibition and survival in murine cancer models. Toxicity was evaluated through bodyweight loss, cytokine release syndrome, lung edema and major organ histology in mice and cynomolgus macaques.

Results ONM-405 shows pH-dependent protection and release of IL-2-Fc. Intravenous injection of ONM-405 in mice demonstrates dramatically reduced toxicity and similar antitumor efficacy compared to IL-2-Fc (figure 1). The maximum tolerated dose (MTD) of IL-2-Fc was determined as 2.1 mg/kg, 5Q2D×3. Using the same IL-2-Fc equivalent dose, mice treated with ONM-405 show no bodyweight loss, >100-fold reduction in systemic IFN-γ compared to unencapsulated IL-2-Fc, and undetectable lung edema. At 9-fold higher doses over the MTD of IL-2-Fc (i.e., equivalent IL-2-Fc dose of 18.9 mg/kg), ONM-405 only displayed minor, reversible adverse responses such as temporary bodyweight loss. In tumor-bearing mice, ONM-405 inhibited tumor growth at 0.14 mg/kg in immune hot MC38 tumors and 0.7 mg/kg in cold B16F10 tumors, which are comparable to IL-2-Fc. At a dose of 6.3 mg/kg (3-fold higher than MTD of IL-2-Fc), ONM-405 achieved complete response in 5/7 MC38-bearing mice. ONM-405 has significantly widened therapeutic window (>135-fold, 0.14-18.9 mg/kg) compared to IL-2-Fc (15-fold, 0.14-2.1 mg/kg). The enhanced safety profile of ONM-405 is further validated in non-human primates.

Conclusions ON-BOARD technology offers an effective tumor-directed on/off switch achieving antitumor efficacy in solid tumors in response to the acidic TME, while minimizing systemic toxicity of IL-2-Fc in normal tissues.

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