ANV419, a selective IL-2Rβ/y agonist in patients with relapsed/refractory advanced solid tumors

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Background

- ANV419 is a potent, selective, IL-2Rβ/y-targeted antibody–Fc fusion protein, designed to enable the clinical delivery of high dose IL-2 to stimulate anti-tumor response while minimizing toxicity.
- ANV419 is engineered to preferentially stimulate tumor-killing CD8+ effector T cells (T effs) and NK cells, with minimal activation of immunosuppressive regulatory T cells (T regs) by hindering binding of IL-2 to the IL-2Rα subunit.
- ANV419 showed high effector selectivity and a favorable safety profile in preclinical models, with preferentially enhanced signaling and expansion of T effs / NK cells over T regs, and enhanced NK cell killing of human tumor cell lines.

Study design

- ANV419 is an open-label, multi-center Phase 1 study (NCT04895926) consisting of four parts:
- The primary objectives are to evaluate the safety, tolerability, and the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D).
- Secondary objectives include pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary anti-tumor activity.

Key eligibility

- Age ≥ 18 years
- Advanced solid tumor with documented progression or refractory/relapsed advanced disease or at least one line of treatment has been exhausted
- ECOG PS 0–1
- Baseline Ki67+ of CD8+ T cells ≥ 15% for eligible patients (not required in case of CRC metastases)

Efficacy

- At doses ≥ 108 μg/kg, 15 evaluable patients had SD and one patient with metastatic NSCLC (post-pemetrexed chemotherapy) had a durable PR of ~7 months.

Pharmacokinetics and pharmacodynamics

- ANV419 exhibited a long half-life (~12 hours at 243 µg/kg), good tissue distribution (Vi: 1.1–4.2 L), and ANV419 induced a dose-dependent preferential expansion of proliferating CD8+ T/NK cells over T reg cells.

Conclusions

- Treatment with ANV419 was generally well tolerated; the safety profile was characterized by pyrexia, chills, headache, AST/ALT elevations, vomiting, and CRS in some patients.
- Adverse events were manageable with standard supportive care. CRS was managed with anti-pyretics, intravenous fluids, and occasionally steroids; IL-6 antagonists were not required at the MTD and below.
- ANV419 led to a dose-dependent preferential expansion of CD8+ T cells and NK cells over T regulatory cells.
- Dose-dependent anti-tumor activity was observed at doses ≥ 108 μg/kg, with a durable partial response in NSCLC.
- Based on the totality of data, 243 µg/kg Q2W was declared as the RP2D.
- The B-2 major coagulant delivered by one dose of ANV419 at the RP2D of 243 µg/kg was comparable to those from one cycle of aldesleukin (14 doses), with prolonged exposure due to its longer half-life.

References:


Poster 1031P