FAVORABLE PRE-CLINICAL SAFETY PROFILE OF THE NOVEL NOT-ALPHA IL-2 AGONIST ANV419 SUPPORTS FIRST IN HUMAN CLINICAL DEVELOPMENT

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Background ANV419 is a novel interleukin-2 (IL-2)/anti-IL-2 fusion protein with preferential signaling through the IL-2 beta/gamma receptor that induces selective proliferation of CD8 T cells and NK cells in vivo for the treatment of cancer. The safety and pharmacodynamic effects of ANV419 were studied in a 4-week cynomolgus monkey GLP study to support the ongoing PhI dose escalation clinical trial.

Methods ANV419 was administered by i.v. injection over 1 min at doses of 0.03, 0.1, 0.3 mg/kg, or vehicle control on days 1 and 15 of the 29-day study. Assessments included body weight, blood pressure, hematology, clinical pathology, serum cytokines, immunophenotyping, histopathology, and pharmacokinetics.

Results The pharmacokinetics of ANV419 were characterized by target mediated disposition, with a half-life of approximately 24h at concentrations not affected by target mediated clearance. Dose-dependent increases in WBC were observed after each injection, driven by preferential expansion of CD8 T cells and NK cells over Tregs. NK cells were more sensitive to ANV419 than CD8 T cells reaching maximal proliferation in blood at 0.03 mg/kg vs. 0.3 mg/kg for CD8 T cells. Hematological changes included: transient dose-dependent increase in basophils; elevation in eosinophils, up to 2.2-fold above control animals at > 0.03 mg/kg, remaining within the normal range for cynomolgus monkeys (<1.94 G/L); minor decrease in platelets at day 4 after each injection. There were no relevant treatment-related changes in inflammatory serum cytokines (IL-1b, IL-5, IL-6, IL-8, IFNg, TNFa, GM-CSF). A mild systemic inflammatory response was observed at 0.3 mg/kg evidenced by a transient increase of CRP on days 4 and 19, preceded after the first injection by a slight dose dependent increase in IL-1RA at 4h post injection, and an increase in IL-10 at 24h post treatment at 0.3mg/kg. No significant changes in body weights or blood pressure and no signs of capillary leak were observed during the entire study. A multi-part PhI dose-escalation study of ANV419 has been initiated in cancer patients. In the part A single patient escalation cohort, two patients have been dosed Q2W multiple times with 0.003mg/kg and 0.006mg/kg respectively with the expected PD profile and no DLT observed.

Conclusions Consistent findings, relating to expected effects of ANV419 as a not-alpha IL-2 agonist, demonstrated a favorable tolerability and safety profile at pharmacodynamically relevant doses that strongly support its translational development in cancer patients to identify clinical benefits.

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