Favorable pre-clinical safety profile of the novel not-alpha IL-2 agonist ANV419 supports first in human clinical development

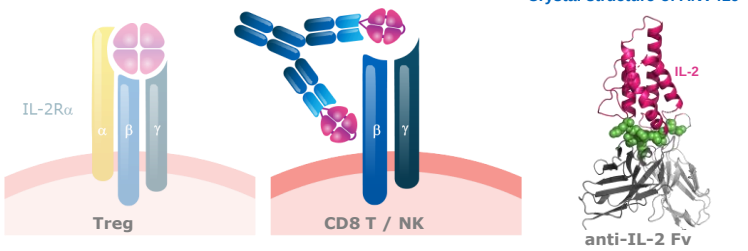
Alonso Guzman[2], Elena Garralda[2], Christoph Bucher[1], Silvio Costanzo[1], Philippe Jacqmin[3], Andreas Katopodis[1], Jennifer Sims[4], Christoph Huber[1]
[1]Anaveon, Basel Switzerland; [2]Vall d' Hebron Institute of Oncology (VHIO), Barcelona Spain; [3]MnS, Dinant Belgium; [4]Integrated Biologix, Basel Switzerland

Background

ANV419 is an IL-2/anti-IL2 antibody fusion protein for expansion of CD8 T cells and NK cells

ANV419 is a novel interleukin-2/anti-IL-2 fusion protein with preferential signaling through the IL-2 βγ receptor that induces selective proliferation of CD8 T cells and NK cells in vivo. ANV419 has the potential to substantially separate CD8 T cell and NK cell mediated anti-tumor responses from the dose limiting toxicities observed with recombinant IL-2 (aldesleukin). The safety and pharmacodynamic effects of ANV419 were studied in a 4-week cynomolgus monkey GLP study to support the ongoing PhI dose finding clinical study to establish the recommended PhII dose (RP2D) in cancer patients.

Crystal structure of ANV419



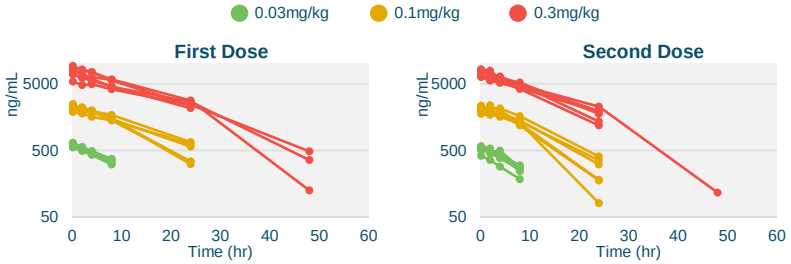
IL-2 is fused to an IL-2 specific antibody that binds with high affinity to the IL-2Rα binding domain of IL-2. The IL-2 is linked to the light chain of the antibody, allowing ANV419 to present IL-2 to the dimeric βγ IL-2 receptor while sterically excluding binding to the trimeric αβγ IL-2 receptor.
Marked in green in the ANV419 crystal structure are the IL-2 amino-acids that make contact with the IL-2 receptor α and are sterically blocked by the anti-IL-2 antibody.

Methods

ANV419 was administered to cynomolgus monkeys (3 males and 3 females per dose) 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.

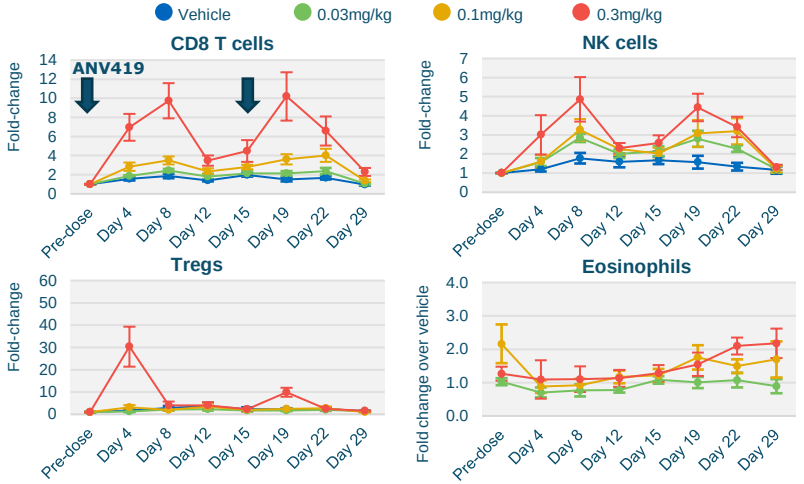
Results

ANV419 demonstrates an extended half-life



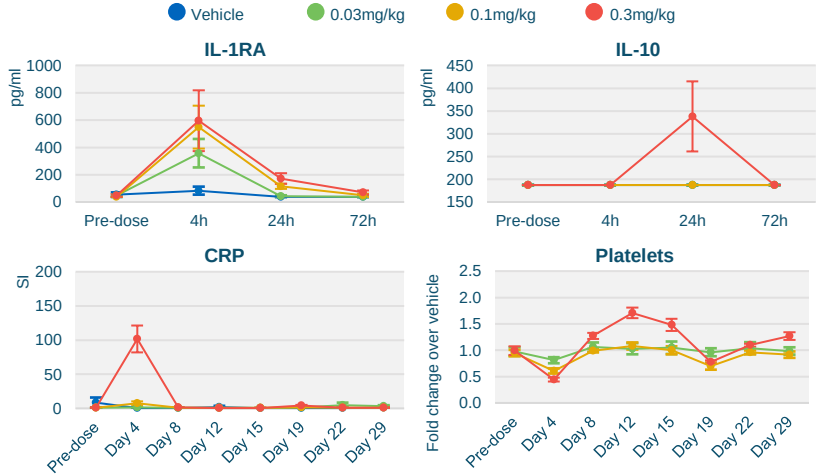
- The pharmacokinetics of ANV419 were characterized by target mediated disposition, with a half-life of approximately 24h at concentrations not affected by target mediated clearance.

Dose-dependent preferential expansion of CD8 T cells and NK cells



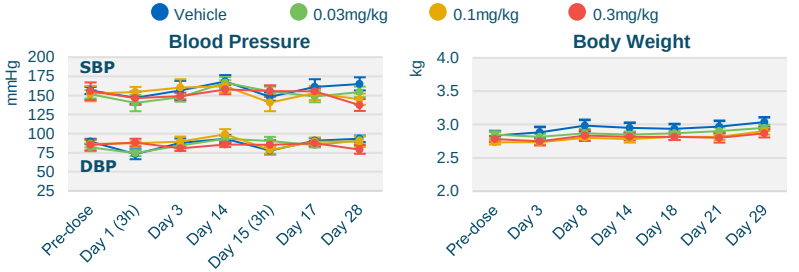
- Dose-dependent expansion of CD8 T cells and NK cells in peripheral blood with transient mobilization of Treg into the blood at the highest ANV419 dose of 0.3mg/kg. Sensitivity to ANV419 follows the sequence NK cells > CD8 T cells > Treg.
- Minimal expansion of eosinophils in the normal range for NHPs and likely unrelated to ANV149 dosing was observed after the second ANV419 dose by hematology measurements.

Absence of pro-inflammatory cytokine release but MOA-related transient inflammatory signature



- ANV419 did not induce release of pro-inflammatory cytokines associated with cytokine release syndrome (IFNγ, TNFα, GM-CSF, IL-1β, IL-5, IL-6) at 4, 24, or 72h post injection.
- Dose-dependent release of anti-inflammatory cytokines IL-1RA and IL-10 between 4h and 24h post ANV419 injection followed by a MOA-related inflammatory signature (CRP release, platelet reduction) that coincides with the peak pharmacological response.

No signs of vascular leak syndrome

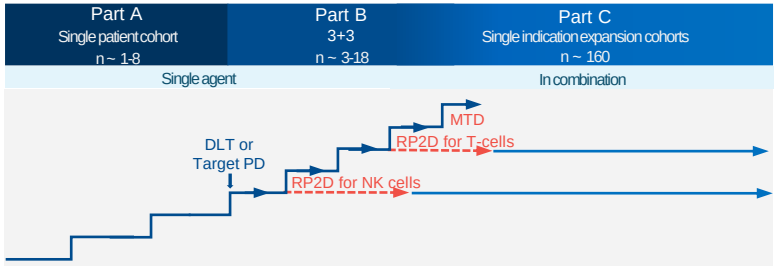


- Dosing of NHPs with ANV419 did not lead to changes in parameters indicative of vascular leak syndrome such as reduced blood pressure, breathing difficulties or increase in body weight.

NOAEL of 0.3mg/kg supports intended FIH starting dose of 3µg/kg and escalation to therapeutically relevant doses

- Based on its toxicology profile the highest tested dose of 0.3mg/kg was considered as the No Observed Adverse Effect Level (NOAEL).
- Applying a conservative toxicological algorithm (based on NHP to human body surface scaling) to the NOAEL and including a 10-fold safety factor supports a maximum recommended safe FIH starting dose of 10µg/kg.
- The NOAEL of 0.3mg/kg allows dose escalation to therapeutically relevant levels of CD8 T cell and NK cell expansion.

ANV419-001, an adaptive, three part open-label dose finding, and combination drug evaluation clinical study has been initiated



- Part A of the trial has been completed without observing a DLT.
- Part B has been initiated based on the level of PD response and is ongoing.

Conclusions

- ANV419 is a novel not-alpha IL-2 agonist with antibody-like properties that preferentially expands CD8 T cells and NK cells for cancer immunotherapy.
- The GLP toxicity study in NHPs demonstrated excellent safety and tolerability of ANV419 despite rapid i.v. injection over 1min with the highest tested dose of 0.3mg/kg considered as the NOAEL.
  - No signs of vascular leak syndrome, cytokine release syndrome or eosinophilia that are normally associated with recombinant IL-2 (aldesleukin) treatment were observed up to 0.3mg/kg.
  - The PK/PD and safety profile of ANV419 observed in NHPs supports a clinical dosing interval of every two weeks or greater at therapeutically relevant doses.
- Initial clinical data of ANV419 suggest a favorable safety/PD relationship, warranting further development in patients with malignancies.