ANV419 is a novel CD122-biased IL-2/anti-IL-2 fusion protein with potent CD8 T cell and NK cell stimulating capacity that shows additive efficacy in combination with checkpoint inhibitors and treatments acting through antibody dependent cellular cytotoxicity

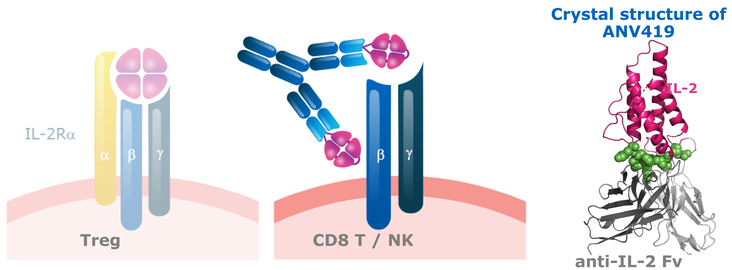
Kirsten Richter[1], Nicole Egli[1], Laetitia Petersen[1], Patrizia Murer[1], Andreas Katopodis[1], Christoph Huber[1]

[1]Anaveon, Basel Switzerland

Background

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

ANV419 is an IL-2/anti-IL-2 fusion protein with natural affinity to the heterodimeric IL-2Rβ/γ, but no affinity for IL-2Rα. As a result, ANV419 induces selective proliferation of CD8 T cells and NK cells over Tregs and is currently tested in a phase 1/2 trial for the treatment of solid tumors.
Goal of the presented study was the evaluation of the activity of ANV419 on NK and CD8 T cells and its potential synergy with complementary immune-oncology mechanisms that can strengthen its NK or CD8 T cell anti-tumor response for the planned phase 2 trials.

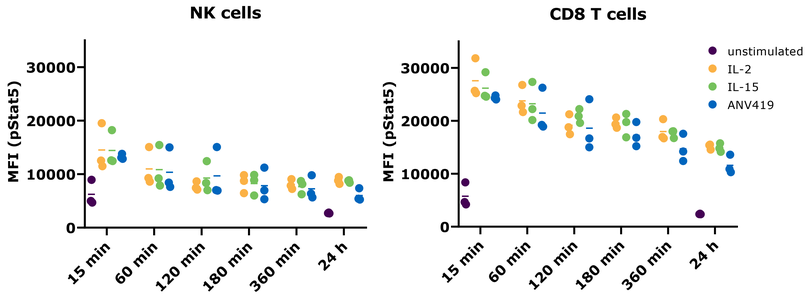


Crystal structure of ANV419

IL-2 is fused to an IL-2 specific antibody that binds with high affinity to the IL-2Rα binding domain of IL-2. IL-2 is linked to the light chain of the antibody, allowing ANV419 to present IL-2 to the dimeric IL-2Rβ/γ while sterically excluding binding to the trimeric IL-2R.
Marked in green in the ANV419 crystal structure are the amino-acids of IL-2 that interact with the IL-2Rα chain and are sterically blocked by the anti-IL-2 antibody.

Results

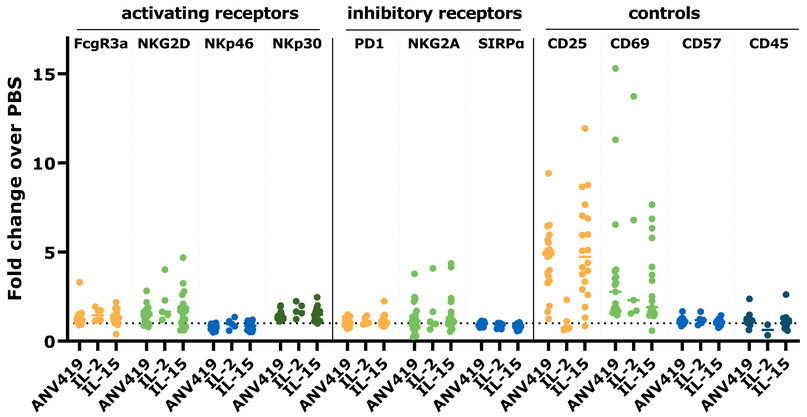
ANV419 induces Stat5 phosphorylation at comparable kinetics and magnitude as IL-2 and IL-15



PBMCs were stimulated with 10 nM ANV419, IL-2, IL-15 or left unstimulated. Stat5 phosphorylation in NK and CD8 T cells was measured by flow cytometry at the indicated time points.

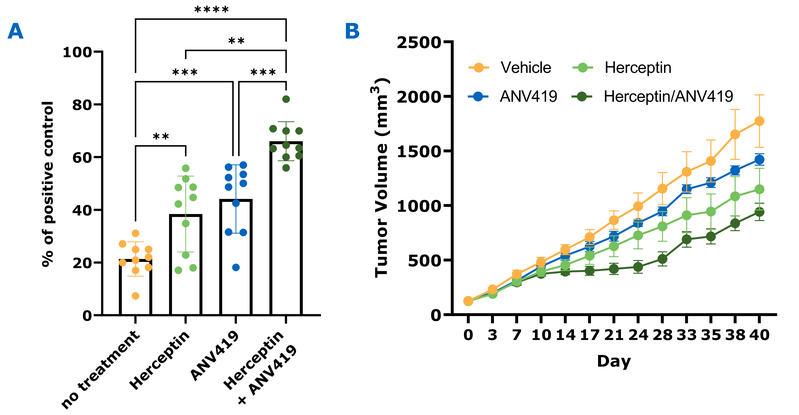
Results

ANV419 treatment leads to similar regulation of NK receptors compared to IL-2 and IL-15



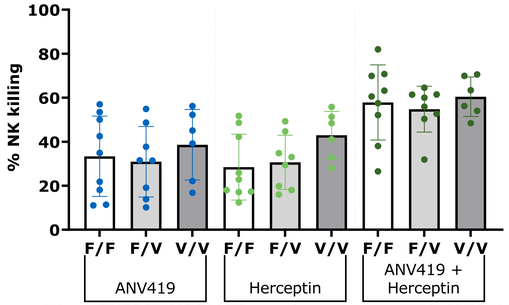
Isolated human NK cells were treated with 8nM ANV419, IL-2 or IL-15 for 18h and analyzed for expression of the indicated cell surface molecules by flow cytometry. The unchanged levels of CD25 upon IL-2 treatment most likely reflect CD25 internalization.

ANV419 improves NK cell mediated killing and potentiates antibody dependent cellular cytotoxicity (ADCC)



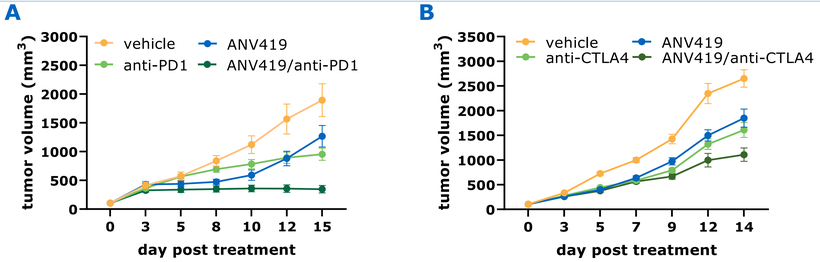
A) *In vitro* NK cell killing of HER2 expressing HCC1954 cells in presence of 10nM ANV419 and/or 0.07 nM Herceptin (trastuzumab).
B) Tumor growth using BALB/c Nude mice in a Her2-expressing NCI-N87 xenograft mouse model. The mice (n=10) were treated with 7.5 mg/kg Herceptin 2QW and/or 220 µg/kg ANV419 QW.

ANV419 amplifies NK cell mediated killing independent of FcγR3a SNP F158V



Primary human NK cell killing of HER2+ HCC1954 cells in presence of 10nM ANV419 and/or 0.07 nM Herceptin was measured by live cell imaging and correlated with FcγR3a SNP F158V. Killing was normalized to Staurosporine control treated target cells.

ANV419 enhances tumor growth inhibition in combination with PD1 or CTLA4 blockade in the syngeneic H22 mouse model



BALB/c mice (n=12) were injected s.c. with H22 hepatic carcinoma cells on day 0 and treated with
A) vehicle, 0.2 mg/kg ANV419 i.v. 2QW, 10 mg/kg anti-PD1 (clone RMP1-14) i.p. 2QW or a combination of ANV419 and anti-PD1.
B) vehicle, 3 doses of 0.2 mg/kg ANV419 i.v. 2QW, 3 doses of 1 mg/kg anti-CTLA4 (clone 9D9) i.p. 2QW or a combination of ANV419 and anti-CTLA4.

Conclusions

- The data presented here support the initiation of clinical phase 2 studies assessing ANV419 treatment in indications in which NK and CD8 T cells are involved in tumor resolution as monotherapy and in combination with ADCC inducing treatments or checkpoint inhibitors
- Please visit poster 749P for more information on our phase 1 data

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