ANV419 is a novel CD122-biased IL-2/anti-IL-2 fusion protein showing increased efficacy in combination with checkpoint inhibitors and treatments acting through antibody dependent cellular cytotoxicity

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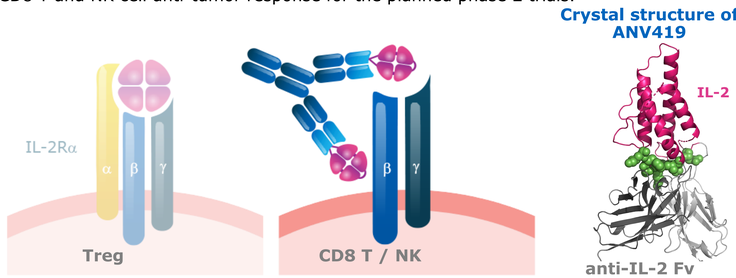
Background

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

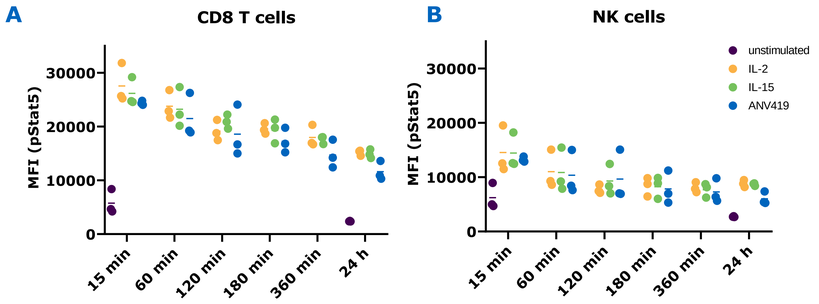
ANV419 is an IL-2/anti-IL-2 fusion protein with natural affinity to the heterodimeric IL-2Rβ/γ, but no affinity for IL-2Rα. As a result, ANV419 induces selective proliferation of CD8 T cells and NK cells over Tregs and is currently tested in a phase 1/2 trial for the treatment of solid tumors.
Goal of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



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

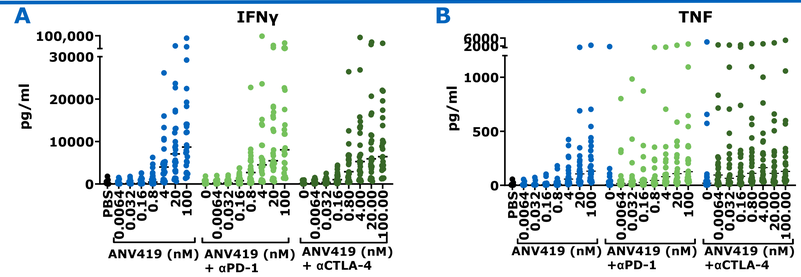
ANV419 induces Stat5 phosphorylation with kinetics and magnitude comparable to IL-2 and IL-15



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

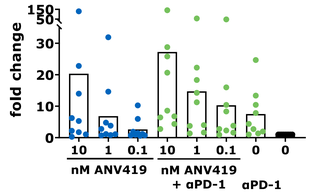
Results

ANV419 enhances T cell cytokine response in combination with checkpoint inhibitors in whole blood assay



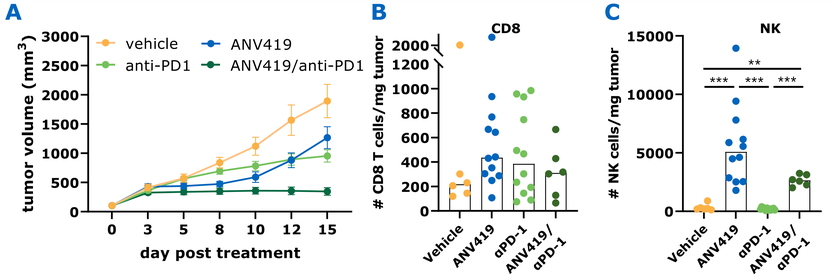
Whole blood from 25 healthy donors was incubated with ANV419 at the indicated concentration alone and in combination with 10 µg/ml pembrolizumab (anti-PD-1) or 10 µg/ml ipilimumab (anti-CTLA-4). After 24 hours at 37°C IFNγ (A) and TNF (B) were measured in the supernatants.

ANV419 enhances IFNγ production by T cells in combination with checkpoint inhibitors in a mixed lymphocyte reaction



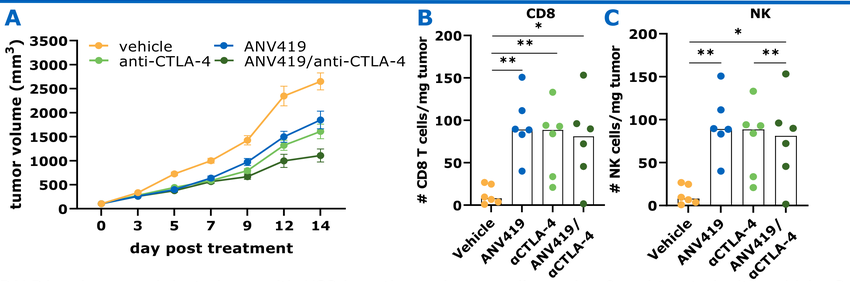
PMBCs from two healthy donors were mixed in the presence of the indicated concentrations of ANV419 or a combination of ANV419 with 10 µg/ml anti-PD-1 (pembrolizumab) for two days. IFNγ was measured in the supernatants.

ANV419 enhances tumor growth inhibition in combination with PD-1 blockade in the syngeneic H22 mouse model



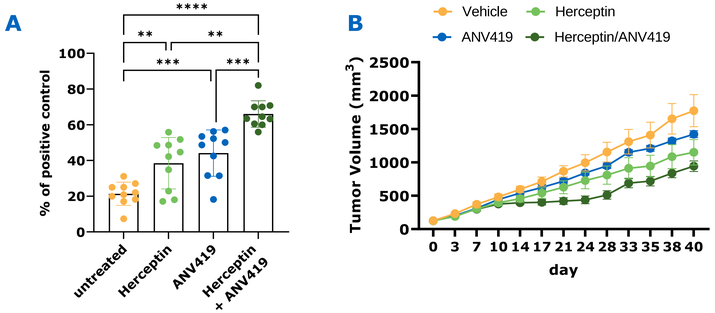
BALB/c mice were injected s.c. with H22 hepatic carcinoma cells on day 0 and treated with vehicle, 0.2 mg/kg ANV419 i.v. 2QW, 10 mg/kg anti-PD-1 (clone RMP1-14) i.p. 2QW or a combination of ANV419 and anti-PD-1. (A) Tumor volume over time (n=12). (B/C) Tumor infiltrating lymphocytes (TILs) were analyzed on day 5 (n=6-12/group).

ANV419 enhances tumor growth inhibition in combination with CTLA-4 blockade in the syngeneic H22 mouse model



BALB/c mice were injected s.c. with H22 hepatic carcinoma cells on day 0 and treated with vehicle, 3 doses of 0.2 mg/kg ANV419 i.v. 2QW, 3 doses of 1 mg/kg anti-CTLA-4 (clone 9D9) i.p. 2QW or a combination of ANV419 and anti-CTLA-4. (A) Tumor volume (n=12). (B/C) TILs were analyzed on day 4 (n=6).

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.

Conclusions

- ANV419 increases T cell functionality
- ANV419 shows activity as monotherapy and in combination with checkpoint inhibitors as well as ADCC inducing treatments
- These data support phase 2 studies assessing ANV419 treatment in indications in which CD8 T and NK cells are involved in tumor resolution
- Please visit poster 631 for more information on our phase 1 data

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Poster 1099