ANV419, an IL-2R-beta-gamma targeted antibody-IL-2 fusion protein, induces selective effector cell proliferation in patients with progressed cancer

Poster # CT140

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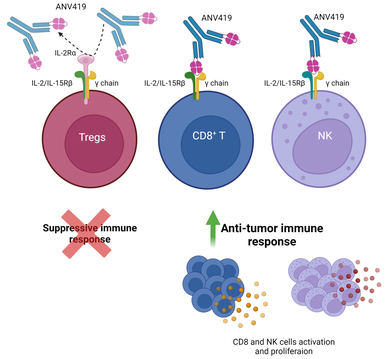
ANV419 Background

- Developing a safe and effective non alpha IL-2R agonist to selectively stimulate immune effector cells remains an important therapeutic goal for the treatment of patients with cancer
- ANV419 is a potent, highly selective IL-2Rβγ binding agonist, consisting of an antibody specific for the IL-2Rα-binding domain of IL-2, fused to native hIL-2
- ANV419 promotes signaling through the dimeric IL-2 receptor (IL-2Rβγ, CD122/CD132) expressed on CD8⁺ T and NK cells but not through the trimeric receptor (IL-2Rα/β/γ, CD25/CD122/CD132) expressed on Treg cells (Fig. 1)
- In pre-clinical models, ANV419 has shown high effector selectivity and a favourable safety profile and the FIH phase I/II dose finding study is ongoing (ANV419-001; NCT04855929)

Fig. 1 Cell activation by ANV419



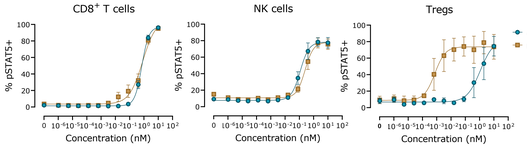
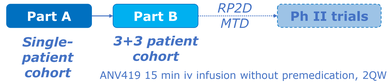


Fig. 2 STAT5 phosphorylation in human PBMCs
In vitro ANV419 has a reduced potency for STAT5 phosphorylation in Tregs while maintaining full potency in CD8⁺ T cells and NK cells

Study Design and Patient Characteristics



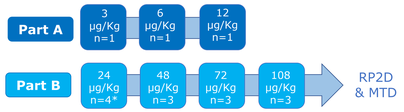
ANV419 15 min iv infusion without premedication, 2QW

Inclusion Criteria
- Adults aged ≥ 18 years.
- Advanced solid tumors with evidence of progressive disease as within last 3 months
- Relapsed/refractory advanced solid tumor, progressing after at least one line of treatment for advanced or metastatic disease
- ECOG PS 0-1

Primary objectives
- Safety and tolerability of ANV419
- Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) of ANV419

Secondary objectives (main)
- Objective Response Rate (RECIST v1.1)
- Pharmacokinetics of ANV419
- Pharmacodynamic markers of immune cell activation: immunophenotyping and ki67 proliferation

Patient Recruitment



* One patient not DLT evaluable

Demographics/Performance Status	TOTAL n=16
Age (mean; yrs)	61.9
Male	69% (11)
Female	31% (5)
ECOG PS 0	50%(8)
ECOG PS 1	50%(8)
Primary cancer diagnosis	
Cutaneous Melanoma	19% (3)
Non cutaneous melanoma (uveal, mucosal)	31% (5)
Oesophageal adenocarcinoma	6% (1)
Colorectal adenocarcinoma	6% (1)
Hepatocellular carcinoma	6% (1)
Renal carcinoma	13% (2)
Pancreatic adenocarcinoma	6% (1)
Adenoid cystic carcinoma maxillary sinus	6% (1)
NSCLC	6% (1)
Number of lines of prior systemic therapy	
Lines of prior systemic therapy, range	1-8
Prior use of immunotherapy	88%(14)
Prior use of targeted therapy	56% (9)
Prior use of chemotherapy	44%(7)

Cut-off date March 8th

Safety

- All ANV419 related AEs are Grade 1 or Grade 2; no ANV419 related AEs ≥Grade 3
- Safety profile has been consistent across all cycles and dose levels of ANV419
- Most patients experienced chills (G1), with or without low-grade fever (G1), uniformly starting 2-4 hours post infusion, which resolved with antipyretic treatment
- One patient experienced transient, self-limiting Grade 2 LFT increase post ANV419
- 8 patients experienced low-grade infusion related reaction within the first 24 hours manifesting as chills with low grade-fever, sometimes with asthenia and fatigue
- G2 CRS was reported in one patient (hypotension G2, fever G1 and chills G1), which resolved with 500ml iv fluid
- Four SAEs were reported in three patients, none of which were ANV419 related
- No patients required ANV419 interruption or discontinuation due to AE
- 63 doses of ANV419 have been administered over 6 dose levels
- ANV419 dosing continues at 108 µg/kg with no DLTs observed to date

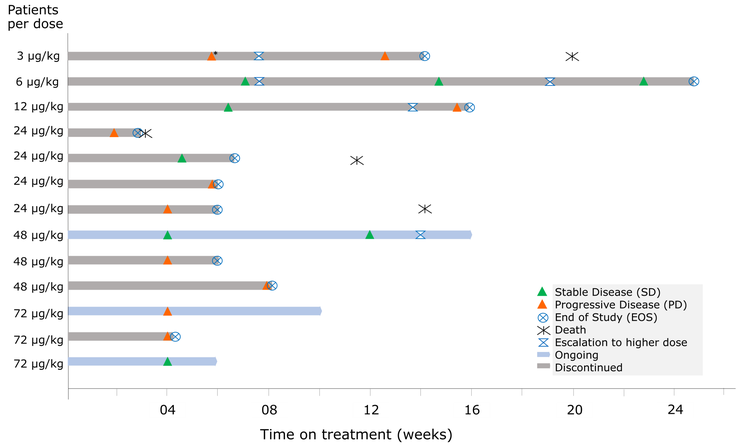
Number and Grade of Adverse Events by Preferred Term	3µg/kg n=1	6µg/kg n=2[a]	12µg/kg n=2[a]	24µg/kg n=6[a]	48µg/kg n=3	72µg/kg n=4[a]	TOTAL n=13
Chills	3 (G1)	2 (G1)	12 (G1)	13 (G1)	3 (G1)		33
Pyrexia		1 (G1)	10 (G1)	13 (G1)	3 (G1)	5 (G1)	32
Fatigue			4 (G1)	2 (G1)	2 (G1)		8
Vomiting				1 (G1)	1 (G1)	2 (G1)	4
AST increased					1 (G2) 2 (G1)		3
ALT increased					1 (G2) 1 (G1)		2
Cytokine release syndrome (CRS)				1 (G2) 1 (G1)			2
Nausea					1 (G1)	1 (G1)	2
Alkaline phosphatase increased					1 (G1)		1
CRP increased				1 (G1)			1
Dyspnoea						1 (G1)	1
Hot flush					1 (G1)		1
Temperature regulation disorder					1 (G1)		1
Abdominal discomfort				1 (G1)			1

Cut-off date March 14th

AEs (CTCAE v5.0) reported as definitely related, probably related and possibly related to ANV419 in the EDC
a: Includes all patients escalated to this dose

Clinical Response

On-study patients' duration & responses by RECIST

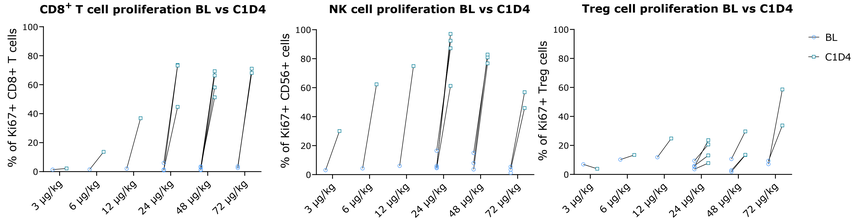


*Continued ANV419 as patient was deriving clinical benefit despite PD

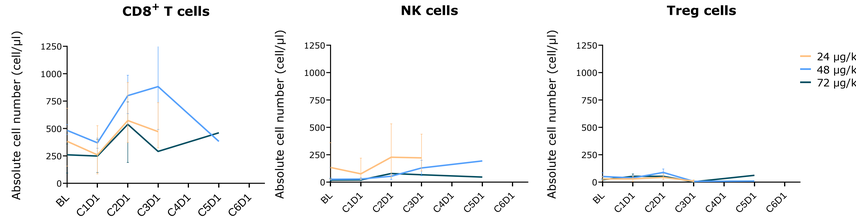
Pharmacodynamics and Pharmacokinetics

ANV419 selectively induces dose dependent proliferation of CD8⁺ T cells and NK cells but not Treg cells

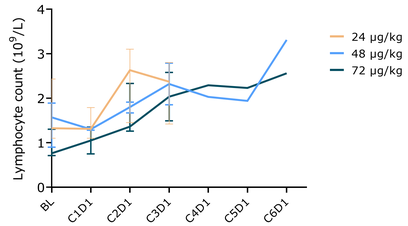
Pharmacodynamic evaluation showed a dose dependent increase of Ki-67 positivity in CD8⁺ T cells and NK cells but not regulatory T cells at of 3, 6, 12 (one patient per cohort) and 24 and 48 (average of 4 and 3 patients respectively) µg/kg doses on day 4 (C1D4) of the study compared to baseline (BL). At 72µg/kg mean CD8⁺ T cell and NK proliferation was 70% and 51% respectively, while the mean Treg proliferation increased to 48%



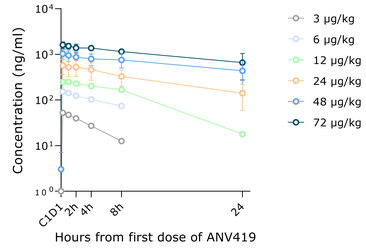
ANV419 increase the absolute counts of CD8⁺ and NK cells



Blood Lymphocyte Counts increase across cycles



Serum C_{max} increases with increasing ANV419 doses



Conclusions

- ANV419 is well tolerated, with only G1 and G2 drug related AEs, Chills
- No patients required ANV419 interruption or discontinuation due to AEs
- ANV419 selectively induces proliferation of immune effector cells and not Tregs in patients
- PK/PD are dose dependent
- In this heavily pre-treated population, 2 patients achieved SD beyond 10 weeks on ANV419 treatment
- On the basis of the encouraging data from the ANV419-001 study, a phase II program investigating efficacy of ANV419 in multiple tumor types, including melanoma, has been initiated