ANV419, a selective IL-2Rβ/γ agonist in patients with relapsed/refractory advanced solid tumors

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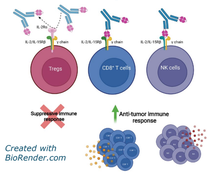
Background

- ANV419 is a potent, selective, IL-2Rβγ targeted antibody IL-2 fusion protein, designed to enable the clinical delivery of high dose IL-2 to stimulate anti-tumor response while minimizing toxicities
- ANV419 is engineered to preferentially stimulate tumor-killing CD8⁺ effector T cells (T effs) and NK cells, with minimal activation of immunosuppressive regulatory T cells (T regs) by hindered binding of IL-2 to the IL-2Rα subunit
- ANV419 showed high effector selectivity and a favorable safety profile in pre-clinical models, with preferentially enhanced signaling and expansion of T effs / NK cells over T regs, and enhanced NK cell killing of human tumor cell lines [1,2]

Cell activation by ANV419



Study design

- ANV419-001 is an open-label, multi-center Phase 1 study (NCT04855929) consisting of four parts
- The primary objectives are to evaluate the safety, tolerability, and the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D). Secondary objectives include pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary anti-tumor activity

Key eligibility

- Age ≥ 18 years
- Advanced solid tumors with disease progression 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
- No symptomatic CNS metastases

Part A Single-patient dose-escalation

- 3 µg/kg (n=1)
- 6 µg/kg (n=1)
- 12 µg/kg (n=1)

Part B 3+3 design

- 24 µg/kg Q2W (n=5)
- 48 µg/kg Q2W (n=3)
- 72 µg/kg Q2W (n=3)
- 108 µg/kg Q2W (n=6)
- 162 µg/kg Q2W (n=3)
- 243 µg/kg Q2W (n=6)
- 364 µg/kg Q2W (n=5)
- 243 µg/kg Q3W (n=6)

MTD / RP2D

Part C ANV419 dose intensification in NSCLC

ANV419 162 µg/kg Q1W × 4 followed by 243 µg/kg Q2W

Part D ANV419 in combination with ipilimumab 3+3 cohort

ANV419 starting dose 72 µg/kg + ipilimumab 1 mg/kg Q3W × 4

ANV419 treatment for 12 months or until intolerable toxicity

- 40 patients were enrolled at data cut-off (22 March 2023) at five sites in Spain, the UK, and Switzerland (median age 59.5 years [range 30–79]; 27 [67.5%] were male). Patients had a median 3 (range 1–8) prior lines of systemic therapy. Melanoma (13 [32.5%]; 6 [15.0%] cutaneous), colorectal cancer (7 [17.5%]), and renal cell carcinoma (5 [12.5%]) were the most common tumor types

Safety

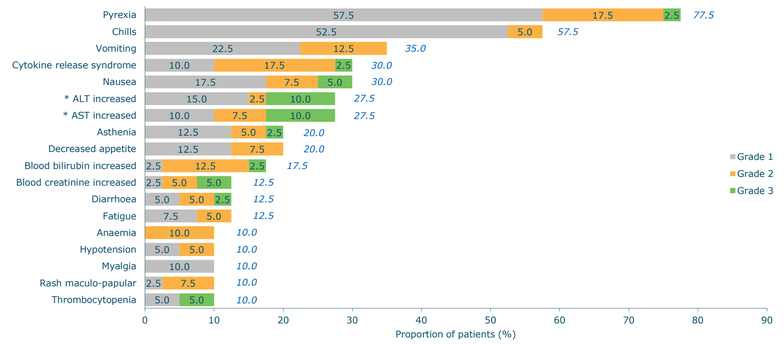
Summary of safety

Events, n (%)	Total (N=40)
Any TEAE	40 (100)
Any related TEAE	39 (97.5)
Any Grade ≥ 3 TEAE	27 (67.5)
Any related Grade ≥ 3 TEAE	14 (35)
Any serious TEAE	22 (55)
Any related serious TEAE	10 (25)
Any Grade 5 TEAE	0 (0)

TEAE, treatment-emergent adverse event.

- ANV419 was generally well tolerated
- All drug-related events were reversible and responded to standard supportive therapy
- Two patients treated at 364 µg/kg experienced DLTs (Grade 3 cytokine release syndrome [CRS] and Grade 3 pemphigoid); the MTD was thus 243 µg/kg)
- Three (7.5%) patients had a Grade 4 event (all lymphopenia and treatment related); no Grade 5 events occurred
- No AE led to discontinuation; two (5.0%) patients required dose interruptions and six (15.0%) required dose reductions

Drug-related TEAEs in ≥10% patients by preferred term (CTCAE v5)

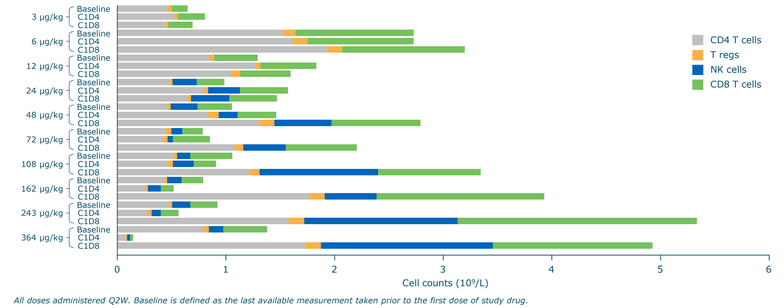


** 13 patients experience ALT (alanine aminotransferase) elevation [11 drug related] and 13 patients experience AST (aspartate aminotransferase) elevation [11 drug related]. ALT and AST elevation occurred simultaneously in 12 patients [10 drug related].*

Pharmacokinetics and pharmacodynamics

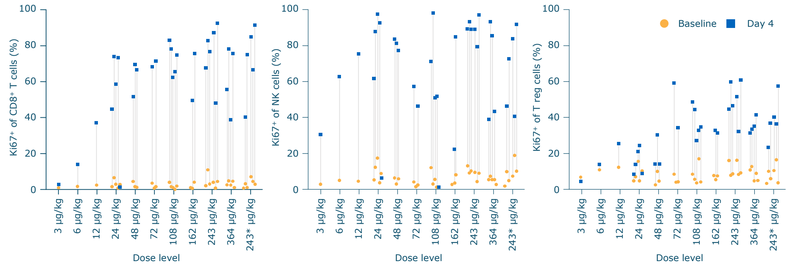
- ANV419 exhibited a long half-life (~12 hours at 243 µg/kg), good tissue distribution (V_{ss}: 1.1–4.2 L), and sustained plasma concentrations (AUC_{last} 173,100 h*µg/L at 243 µg/kg)
- ANV419 induced a dose-dependent preferential expansion of proliferating CD8⁺ T / NK cells over T reg cells

Mean absolute cell counts (safety population)



All doses administered Q2W. Baseline is defined as the last available measurement taken prior to the first dose of study drug.

Proliferation of CD8⁺ T cells, NK cells, and T regs (Day 4 compared to Baseline)

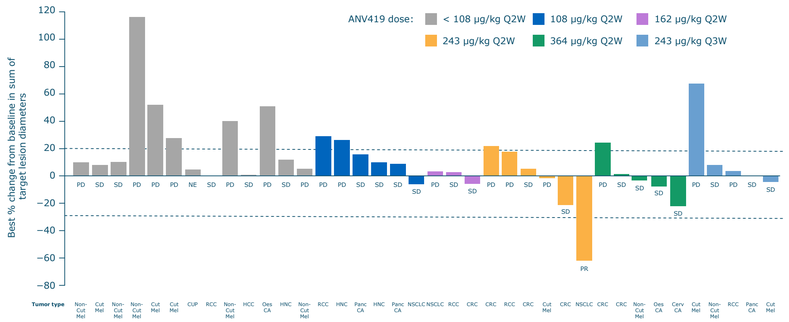


** indicates Q3W dosing, all other doses are administered Q2W.*

Efficacy

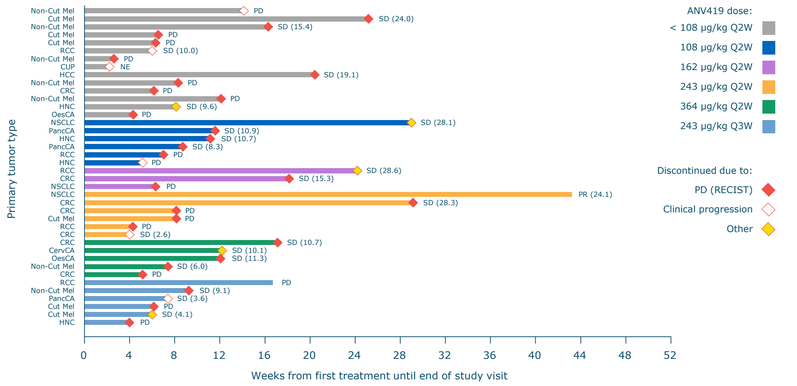
- At doses ≥ 108 µg/kg, 15 evaluable patients had SD and one patient with metastatic NSCLC (post-chemoimmunotherapy) had a durable PR of almost 7 months

Best percentage change from baseline in target lesion sum of diameters and RECIST v1.1 assessment



Response evaluable population. Two patients are excluded who had no target sum of diameters recorded due to not all target lesions being assessed.
CRC, colorectal cancer; CervCA, cervical cancer; CUP, cancer of unknown primary; Cut Mel, cutaneous melanoma; HCC, hepatocellular carcinoma; HNC, head and neck cancer; NE, not evaluable; Non-Cut Mel, non-cutaneous melanoma; NSCLC, non-small cell lung cancer; OesCA, oesophagus carcinoma; PancCA, pancreatic carcinoma; PD, progressive disease; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.

Time on study and best overall response



Response evaluable population. Two patients remained on treatment at data cut-off (22 March 2023). Duration of response/SD is shown in parentheses). See waterfall figure for abbreviations.

Conclusions

- Treatment with ANV419 was generally well tolerated; the safety profile was characterized by pyrexia, chills, nausea, AST/ALT elevations, vomiting, and CRS in some patients
- Adverse events were manageable with standard supportive care. CRS was managed with anti-pyretics, intravenous fluids, and occasionally steroids; IL-6 antagonists were not required at the MTD and below
- ANV419 led to a dose-dependent preferential expansion of CD8⁺ T cells and NK cells over T regulatory cells
- Dose-dependent anti-tumor activity was observed at doses ≥ 108 µg/kg, with a durable partial response in NSCLC
- Based on the totality of data, 243 µg/kg Q2W was declared as the RP2D and is being studied in ongoing studies
- The IL-2 molar equivalents delivered by one dose of ANV419 at the RP2D of 243 µg/kg are comparable to those from one cycle of aldesleukin (14 doses), with prolonged exposure due to its longer half-life

References: 1. Huber C, et al. *JITC* 2020;8 (Supplement 3):571 (abstract); 2. Richter K, et al. *Ann Oncol* 2022;33 (Supplement 7):S558 (abstract).

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