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

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ANV419 is a potent, selective, IL-2Rβ/y agonist engineered to preferentially stimulate tumor-killing CD8+ effector T cells (T eff) and NK cells, with minimal activation of immunosuppressive regulatory T cells (Tregs) or bystander toxicity. ANV419 showed high effector selectivity and a favorable safety profile in preclinical models, with preferentially enhanced signaling and expansion of T eff / NK cells over Tregs, and enhanced NK cell killing of human tumor cell lines.

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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 tumor with documented measurable disease
- Relapsing/refractory advanced solid tumor
- ECOG PS 0–1
- Tumor type: RCC, colorectal cancer (CRC), non-CRC CA, Cervical cancer (CervCA), CUP, cancer of unknown primary (CUP), cutaneous melanoma (Cut Mel), hepatocellular carcinoma (HCC), head and neck cancer (HNC), NSCLC, OesCA, PDAC
- Disease status: Relapsed/refractory advanced or metastatic disease
- Target lesion diameter ≥ 1 cm
- ≤ 50% overlap with prior radiation therapy
- ≤ 60% overlap with prior surgery
- Baseline target lesion not treated at start of study
- ≤ 2 times of normal range (TNR) of creatinine and liver enzymes
- ≤ 2.5 times TNR of total bilirubin
- ≤ 3 times TNR of AST (≤ 5× for baseline ≥ 5×)
- No prior nivolumab, ipilimumab, or anti-CTLA-4 therapy
- No prior checkpoint inhibitors (anti-PD-1/PD-L1/anti-CTLA-4) in the 12 months before start of study
- No prior ANV419 treatment for 12 months or until radiotherapy/laboratory recovery

Mean absolute cell counts (safety population)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>0</th>
<th>6 μg/kg</th>
<th>12 μg/kg</th>
<th>24 μg/kg</th>
<th>364 μg/kg</th>
<th>72 μg/kg Q2W</th>
<th>48 μg/kg Q2W</th>
<th>243 μg/kg Q2W</th>
<th>108 μg/kg Q2W</th>
<th>162 μg/kg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki67+ of CD8+ T cells (%)</td>
<td>100</td>
<td>50.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Ki67+ of NK cells (%)</td>
<td>100</td>
<td>50.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
<td>40.0</td>
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</tbody>
</table>

Pharmacokinetics and pharmacodynamics

- ANV419 exhibited a long half-life (~12 hours at 243 µg/kg), good tissue distribution (Vss: 1.1–4.2 L), and sustained plasma concentrations (AUC0-71 173,100 ± 143 µg.h/mL).
- ANV419 induced a dose-dependent preferential expansion of proliferating CD8+ T / NK cells over T reg cells.

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

<table>
<thead>
<tr>
<th>Drug-related TEAEs in ≥10% patients by preferred term (CTCAE v5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Grade 3 anemia</td>
</tr>
<tr>
<td>Blood cell count abnormality (%)</td>
</tr>
</tbody>
</table>

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-IL-6, anti-IL-1, anti-IL-12/23a, anti-IL-18, and anti-IL-35.
- 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 / IL-2Rβ/y agonists 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 larger half-life.

Acknowledgements: Thank you to the patients, families, and sites for participating in the ANV419-001 study. Study sponsored by Anaveon AG.

Poster 1031P

ANV419 dose: 243 µg/kg Q2W (n=5), 108 µg/kg Q2W (n=6), 72 µg/kg Q2W (n=3), 48 µg/kg Q2W (n=3), 12 µg/kg (n=1)