ANV600, a *cis*-signaling αPD-1/IL-2Rβ/γ agonist, expands both CD4⁺ and CD8⁺ tumor specific T cells by acting in the tumor microenvironment and draining lymph nodes

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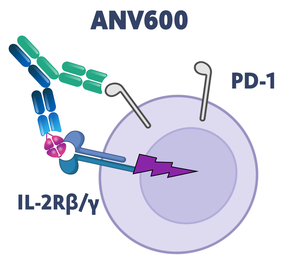
Background

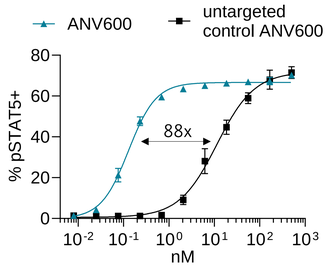
ANV600 combines a unique non-blocking PD-1 targeting approach with an IL-2Rβ/γ selective agonistic principle

The cytokine bearing arm (blue) of the bispecific antibody is composed of IL-2 fused to an anti-IL-2 antibody, which sterically prevents IL-2Rα from binding to the fusion protein. It therefore selectively signals through IL-2Rβ/γ. The targeting arm (green) consists of a high affinity αPD-1 antibody to selectively deliver ANV600 to tumor antigen experienced PD-1⁺ T cells. The anti-PD-1 arm binds to a unique epitope on PD-1 that enables combination of ANV600 with PD-1 checkpoint inhibitors.



ANV600 anchoring to PD-1 increases IL-2R signaling potency on PD-1⁺ cells

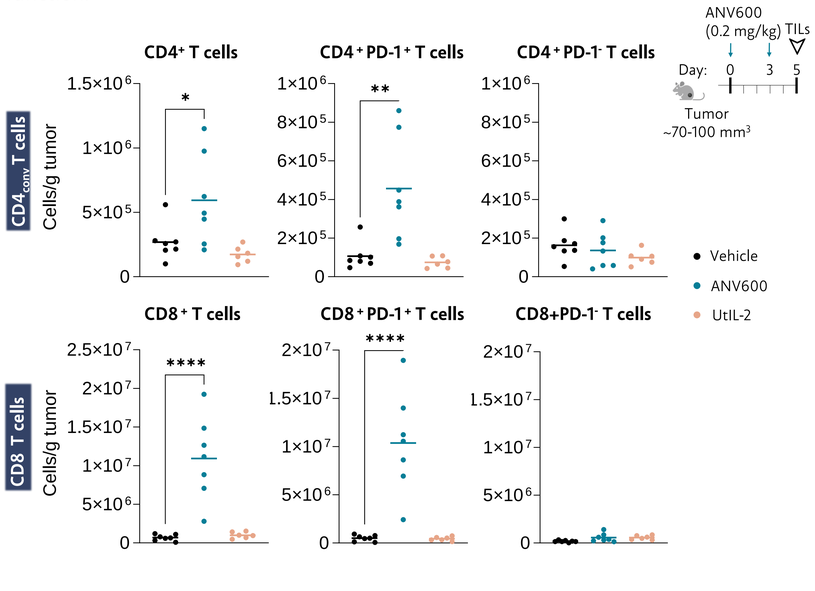
Potency measurements of STAT5 phosphorylation in PD-1⁺ Jurkat T cells demonstrate a strong PD-1 targeting effect of ANV600. Compared to a non-targeted IL-2Rβ/γ agonist control molecule, ANV600 has an 88-fold increased IL-2R signaling potency on PD-1 expressing cells.



Results

ANV600 preferentially expands tumor infiltrating CD8⁺ PD-1⁺ and CD4⁺ PD-1⁺ T cells

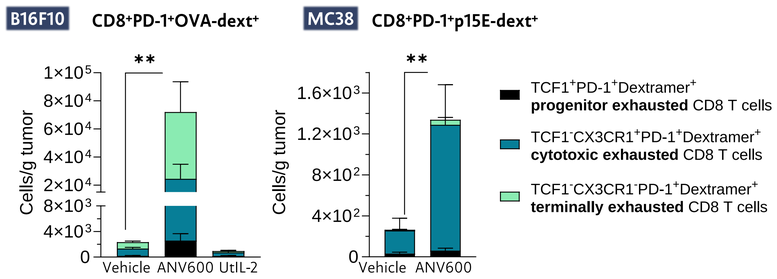
Compared to an untargeted IL-2Rβ/γ agonist (UtIL-2), treatment of subcutaneous (s.c.) B16F10 tumor bearing human PD-1 (hPD-1) transgenic mice with ANV600 induces expansion of intratumoral CD8⁺ and CD4⁺Foxp3⁻ ($CD4_{conv}$) T cells, which is mainly driven by the effect on the PD-1⁺ subsets. The increase in $CD4_{conv}$ PD-1⁺ T cells suggests that ANV600 not only enhances cytotoxic T cell activity but also promotes helper T cell function.



Results

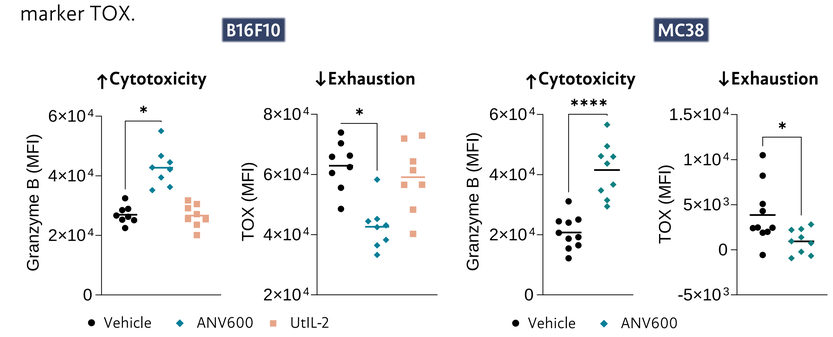
ANV600 increases tumor antigen-specific CD8⁺PD-1⁺ tumor infiltrating lymphocytes

TILs analysis from tumor bearing hPD-1 transgenic mice reveals that ANV600 significantly expands CD8⁺PD-1⁺OVA-dextramer⁺ cells in B16F10-OVA tumors and CD8⁺PD-1⁺p15E-dextramer⁺ cells in MC38 tumors compared to vehicle or untargeted IL-2Rβ/γ agonist (UtIL-2) treatment. This expansion is particularly pronounced in the cytotoxic exhausted T cell subset (T_{cex}), critical for potent anti-tumor responses.



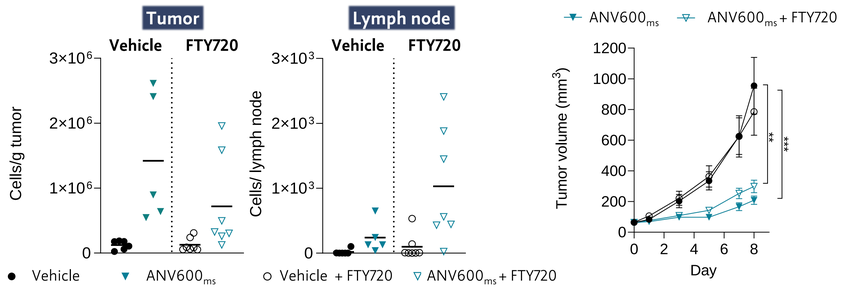
Intratumoral T_{cex} cells are more functional and less exhausted after ANV600 therapy

Upon treatment with ANV600, cytotoxic exhausted (T_{cex}) CD8⁺ T cells in B16F10-OVA and MC38 tumors from hPD-1 transgenic mice exhibit higher Granzyme B expression, reflecting enhanced effector functionality, along with a reduction in the exhaustion marker TOX.



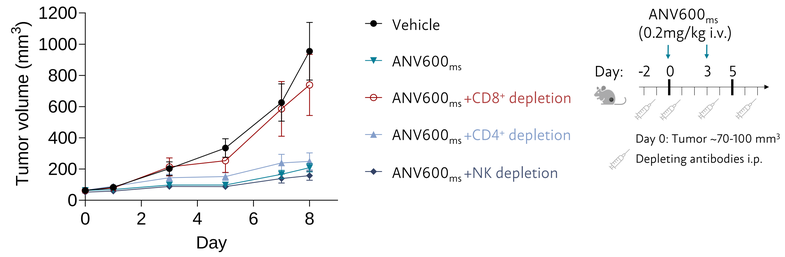
ANV600 primarily amplifies cytotoxic exhausted CD8⁺ T cells locally within the tumor

In B16F10 tumor-bearing mice treated with ANV600 mouse surrogate ($ANV600_{ms}$), blockade of T cell egress from lymph nodes with FTY720 partially reduces the number of cytotoxic exhausted (T_{cex}) CD8⁺ T cells in the tumor and increases their retention in the draining lymph nodes. Despite FTY720 treatment, $ANV600_{ms}$ maintains anti-tumor efficacy, suggesting that its therapeutic effects are primarily driven by localized action in the tumor rather than systemic lymphocyte trafficking.



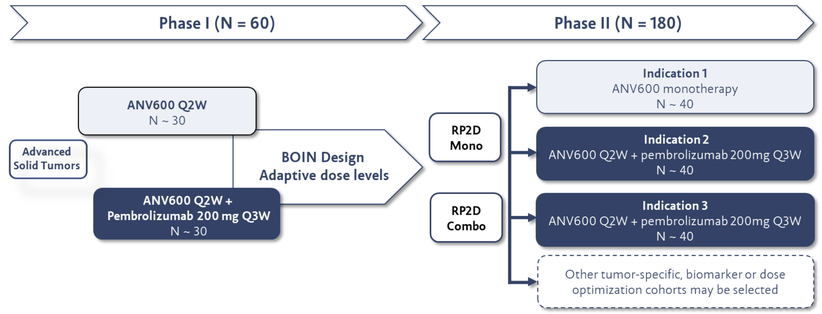
Anti-tumor activity of ANV600 relies on CD8 T cells

In the B16F10 tumor model, depletion of CD8⁺ T cells abolishes the tumor growth inhibition induced by $ANV600_{ms}$, leading to significant tumor progression. In contrast, depletion of CD4⁺ T cells or NK cells has a minor impact on the therapeutic efficacy of $ANV600_{ms}$, as tumor growth remains suppressed in these groups. These results further highlight that CD8⁺ T cells are the primary mediators of ANV600 anti-tumor efficacy.



ANV600 is currently tested in the Phase I/II clinical trial EXPAND-1 (NCT06470763)

The purpose of study ANV600-001 is to characterize the safety, tolerability, pharmacokinetics, pharmacodynamics, immunogenicity and antitumor activity of ANV600 administered as a single agent or in combination with pembrolizumab in adult participants with advanced solid tumors.



Conclusions

- ANV600 is a PD-1 targeted IL-2Rβ/γ agonist combinable with PD-1 blocking checkpoint inhibitors.
- ANV600 preferentially expands tumor-infiltrating PD-1⁺ CD8⁺ and CD4⁺ T cells, supporting both cytotoxic T cell activity and helper T cell function, crucial for effective long-term anti-tumor immunity.
- ANV600 amplifies tumor antigen-specific T cells in the B16F10-Ova and MC38 s.c. tumor models, especially within the cytotoxic exhausted CD8⁺ T cell (T_{cex}) subset.
- The anti-tumor efficacy of ANV600 is primarily driven by localized action in the tumor and depends on the CD8⁺ T cell immune response.
- A Phase I/II clinical trial (NCT06470763) has been initiated to evaluate the safety and efficacy of ANV600 in cancer patients as monotherapy and in combination with pembrolizumab.