ANV600 IS A NOVEL PD-1 TARGETED IL-2Rβγ AGONIST THAT IS COMBINABLE WITH THERAPEUTIC PD-1 INHIBITORS

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Background Targeting of stimulatory cytokines to PD-1 expressing tumor infiltrating lymphocytes (TILs) is a promising approach to reinvigorate antitumor immune responses. Currently, PD-1 checkpoint inhibitors (CPIs) have been established as the standard of care for many cancer indications. Here we present ANV600, a bispecific IL-2Rβγ agonist that employs a unique non-blocking PD-1 targeting arm. This is a first example that demonstrates the therapeutic combination of existing PD-1 inhibitors with novel PD-1 directed stimulatory cytokines.

Methods A fully human non-blocking anti-PD-1 antibody was identified and used to generate a PD-1 targeted IL-2Rβγ selective anti-IL-2 antibody/IL-2 fusion protein (ANV600). The ANV600 binding site on PD-1 was modelled using the Protean 3D software. Simultaneous binding of ANV600 and multiple existing PD-1 blocking antibodies was tested by surface plasmon resonance analysis and on PD-1 expressing cells by flow cytometry. For efficacy studies transgenic human PD-1 mice were implanted subcutaneously with B16F10 or MC38 mouse tumor cells and were treated with ANV600 monotherapy or combination with pembrolizumab or nivolumab. Tumor growth was monitored, and TILs analyses were performed by flow cytometry.

Results Modelling of the binding site of ANV600 to PD-1 revealed that the epitope does not overlap with the PD-L1 binding domain and does not compete with a range of established PD-1 CPIs. This was confirmed in plate- and cell-based binding assays, where simultaneous binding of ANV600 and PD-1 CPIs to recombinant or cell surface PD-1 was demonstrated. Furthermore, ANV600 induced full STAT5 phosphorylation in a PD-1 expressing T cell line in the presence of saturating concentrations of pembrolizumab or nivolumab.

In transgenic human PD-1 mice, ANV600 monotherapy led to marked tumor growth retardation in the B16F10 and MC38 subcutaneous tumor models, which are poorly responsive to PD-1 inhibitor therapy. In both models the pronounced antitumor effect was further increased when ANV600 was combined with pembrolizumab or nivolumab. Consistent with the antitumor efficacy, analysis of TILs revealed strong increases of PD-1+ pre-exhausted and cytotoxic CD8 T cells in tumors of ANV600 treated mice.

Conclusions Separating PD-1 blockade from cytokine targeting allows precision dosage of the potent ANV600 cytokine therapeutic while maintaining sustained PD-1 blockade with established anti-PD-1 CPIs. Our data demonstrate proof of concept in mouse tumor models. ANV600 is currently in late preclinical development and the promising combination therapy data presented here warrants its clinical development as co-treatment with established PD-1 CPIs.

Ethics Approval All animal experiments were approved by the Cantonal Veterinary Office Basel, Switzerland, and performed in accordance with the Swiss laws for animal welfare and protection and the ‘Ethical Principles and Guidelines for Experiments on Animals by the Swiss Academies of Arts and Sciences’.

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