Checkpoint inhibitors synergize with therapeutic platforms, ZVex™ and GLAAS™, by enhancing lentiviral vector-induced tumor-specific immunity and adjuvant-mediated anti-tumor efficacy

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Abstract

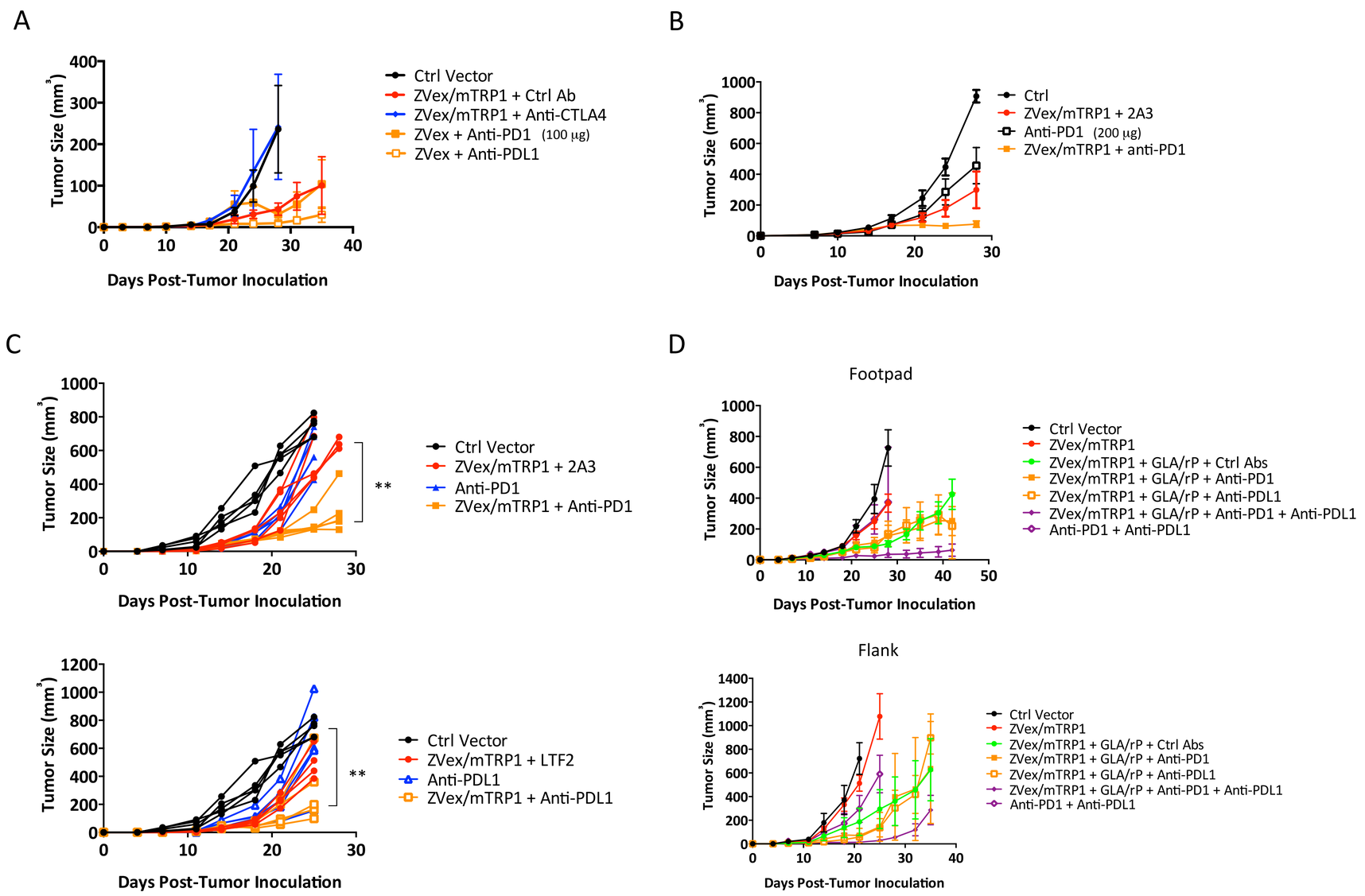
While the administration of checkpoint inhibitors has resulted in impressive clinical responses in patients with late-stage cancers, a subset of patients exhibits insufficient or no clinical response presumably due to the absence of tumor-specific cytotoxic T lymphocytes (CTLs), supporting the rationale to combine checkpoint inhibitors with therapeutic platforms that generate effector T cells.

Here, we evaluated whether checkpoint blockade could further enhance anti-tumor immunity induced by ZVex and/or GLAAS in mouse tumor models. ZVex (a lentiviral vector platform that generates high levels of tumor antigen-specific CTLs) and GLAAS (with formulated glucopyranosyl lipid A, a synthetic TLR4 agonist, as its central component) are complementary platforms capable of generating tumor-specific immunity through the *in vivo* induction of antigen-specific T cells.

In C57BL/6 mice, anti-PD1 or anti-PDL1 – but not anti-CTLA4 – enhanced ZVex/mTRP1-induced CD8 T cell response. Mirroring the immunogenicity results, ZVex/mTRP1-induced anti-tumor protection in B16F10-tumor bearing mice was enhanced by the addition of anti-PD1 or anti-PDL1, but not anti-CTLA4. Additionally, compared to either anti-PD1 or anti-PDL1 alone, the combined administration of both checkpoint inhibitors best improved anti-tumor efficacy induced by ZVex/mTRP1, or G100 (GLA-SE alone), or the combination of ZVex/mTRP1 and GLAAS (in this case, GLA-SE)/TRP1 protein.

Our findings support the combination of checkpoint inhibitors with ZVex and/or GLAAS-based product candidates in clinical trials.

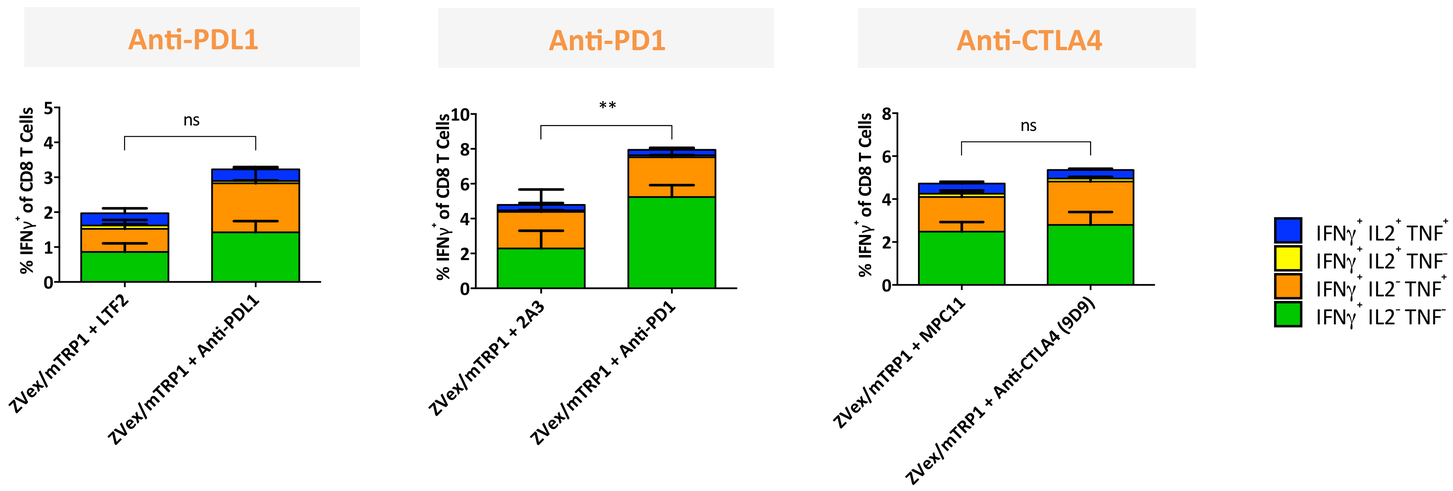
Anti-PD1 or anti-PDL1 enhances anti-tumor efficacy induced by ZVex and/or GLAAS platforms



Methods

C57BL/6J mice (5-10 females/group) were inoculated with 1 x 10^6 B16F10 cells in the footpad, SC, (A-D, top panel) or 1 x 10^5 B16F10 cells in the flank, SC, (D, bottom panel). Mice with palpable tumors were immunized with 2 x 10^{10} vector genomes of ZVex/mTRP1-A463M, SC, and 5 μg TRP1 SLPs formulated with 5 μg GLA in 2% SE, IM, and 100-200 μg control antibodies or checkpoint inhibitors (as detailed in the figure), IP. Control antibodies or checkpoint inhibitors were administered every 3-4 days until the end of study. (D) ZVex (Z) and GLA/rP (G) were administered sequentially, Z-Z-G-Z-G-Z-G, with a week in-between each treatment. Error bars represent Mean ± SEM. ** $p < 0.005$.

Anti-PD1 or anti-PDL1 enhances ZVex-induced antigen-specific CD8 T cell response



Methods

C57BL/6J mice (5 females/group) were immunized with 2 x 10^{10} vector genomes of ZVex/mTRP1-A463M, SC, and 100 μg control antibodies or checkpoint inhibitors (as detailed in the figure), IP on Day 0. Control antibodies or checkpoint inhibitors were administered every 3-4 days until the end of study. On Day 14, splenocytes harvested from mice were stimulated with H-2^b-restricted peptide $TRP1_{455/9M}$ for 5 h at 37°C to evaluate CD8 T cell responses via intracellular cytokine staining and flow cytometry. Error bars represent Mean ± SEM. ** $p < 0.005$; ns = not significant.

Conclusions

- Combining checkpoint inhibitors with ZVex and/or GLAAS-based product candidates capitalizes on the strength of each therapeutic platform: ZVex and GLAAS efficiently generate the effector T cells needed for an effective anti-tumor response. By blocking active immune checkpoints, checkpoint inhibitors further enhance ZVex- and/or GLAAS-induced anti-tumor immunity.
- As PDL1 is not the only ligand for PD1 and PD1 is not the only receptor for PDL1, inhibition of signaling through either PD1 or PDL1 alone may not be sufficient to completely block the PD1/PDL1 checkpoint, at least in the model used.

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