Combination of neoantigen DNA plasmid vaccine VB10.NEO and bempegaldesleukin (NKTR-214) induces strong neoantigen-specific T cell responses and sustained tumor regression in pre-clinical models

Abstract #2256

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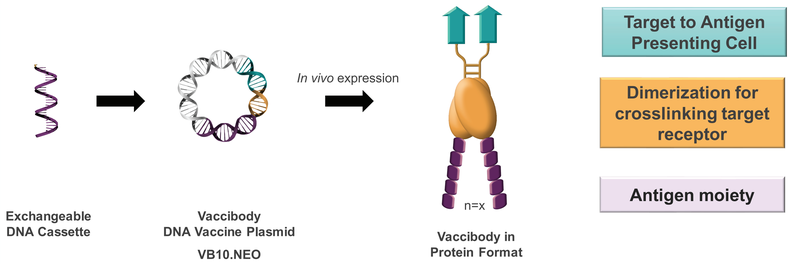
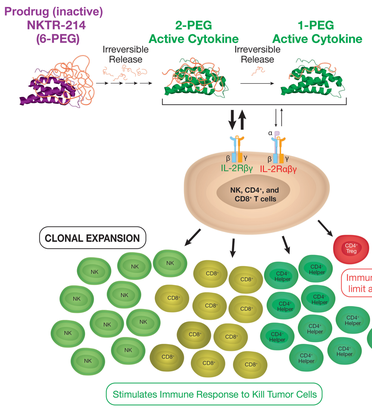
BACKGROUND



VB10.NEO is a potent DNA plasmid vaccine with intrinsic adjuvant effect designed for efficient delivery of personalized neoepitopes and is currently being tested in combination with checkpoint inhibitors in patients with advanced solid tumors.

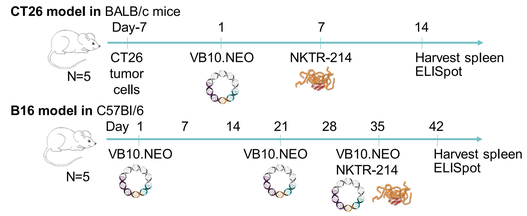


Bempegaldesleukin (NKTR-214), a CD122-preferential IL-2 pathway agonist, provides sustained signaling through the heterodimeric IL-2 receptor pathway (IL-2Rβγ) to preferentially activate and expand NK and effector CD8+ T cells over T-regulatory cells. Bempegaldesleukin is currently in multiple clinical trials in combination with checkpoint inhibitors.

CONCLUSIONS

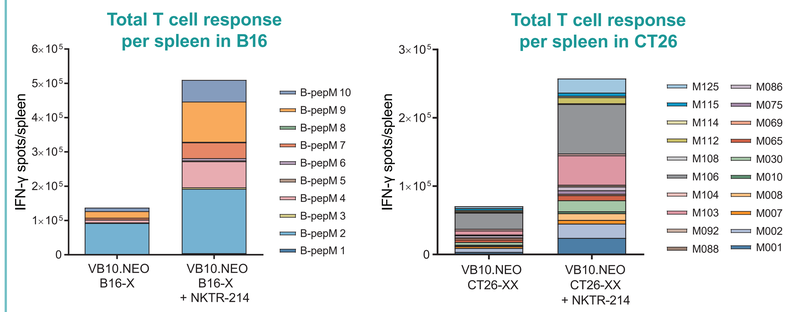
- Combination of VB10.NEO and bempegaldesleukin (NKTR-214) synergizes to elicit greater breadth and depth of neoantigen-specific T cell responses than each individual treatment.
- The synergistic effect was observed in both CD4 and CD8 T cells, and most pronounced on CD8 T cell responses, further supporting the combination's potential to induce strong immunogenic CD8+ T cell responses.
- VB10.NEO in combination with bempegaldesleukin (NKTR-214) and anti-PD-1 induce rapid, complete and durable tumor regression of small tumors and long-lasting stabilization of large tumors supporting the rationale for examining the combination clinically.
- A phase I clinical trial in squamous cell carcinoma of the head and neck (SCCHN) patients is planned to start 2019.

VACCINATIONS – ELISPOT

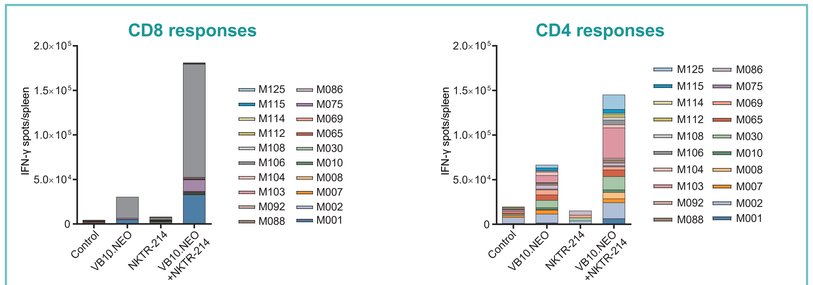


IFN-γ ELISpot: Mice were vaccinated with 20 µg VB10.NEO (i.m.) in combination with electroporation with or without 0.8 mg/kg NKTR-214 (i.v) before spleens were harvested and pooled to analyze CD8 and CD4 neoantigen-specific T cell responses when re-stimulated with peptides corresponding to each neoepitope inserted in the VB10.NEO vaccine construct.

EX VIVO T CELL RESPONSES

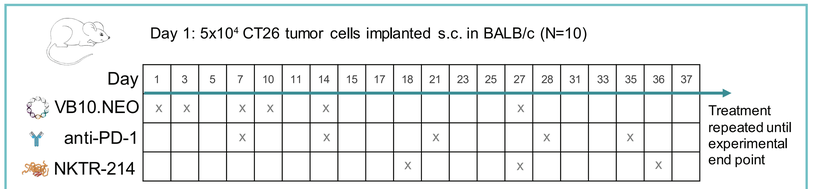


The combination of VB10.NEO and NKTR-214 greatly synergizes, resulting in up to 5-fold increase in the number of neoantigen-specific T cell responses compared to VB10.NEO alone in two different tumor models. A stronger response to each neoantigen was observed, but also to increased numbers of neoantigens, showing that both the breadth and depth of the immune responses were elevated. The stacked IFN-γ + T cells response for all neoepitopes are shown for each tumor model.



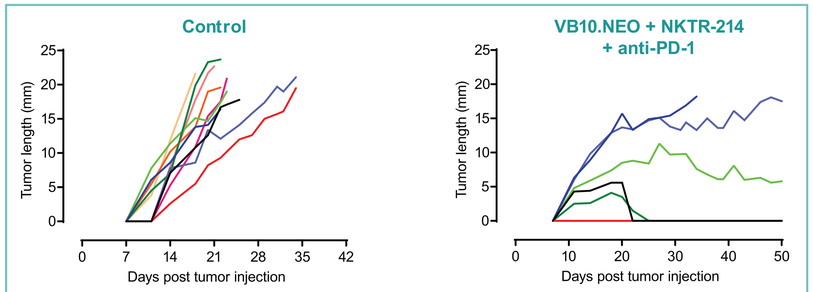
The VB10.NEO and NKTR-214 combination showed an even more evident effect on CD8 T cell responses as the combination elicited a stronger neoantigen-specific CD8 T cell response (6-fold) versus CD4 T cell response (2.5-fold) compared with VB10.NEO alone. Enhanced breadth and depth of the immune response was evident for both CD4 and CD8 T cells.

THERAPEUTIC TUMOR CHALLENGE

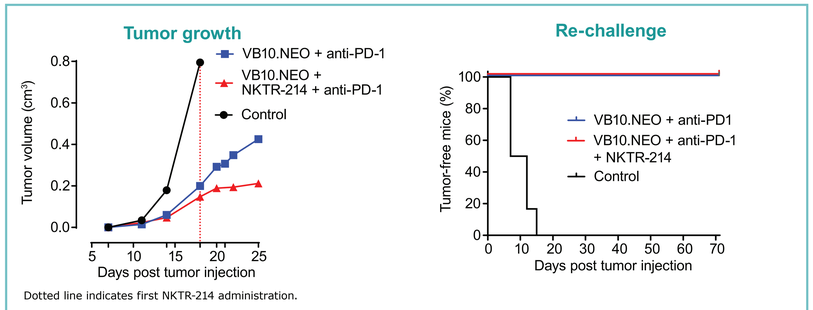


CT26 colon carcinoma cells were implanted s.c. at day 0, prior to i.m. injection + electroporation with 50 µg VB10.NEO at day 1, 3, 7, 10, 14, 27 and 64. 200 µg anti-PD-1 was injected i.p. q7d starting at day 7 and 0.8 mg/kg NKTR-214 was injected i.v. q9d starting day 18. Tumor growth was monitored until experimental end point.

TUMOR PROTECTIVE IMMUNE RESPONSES



Adding NKTR-214 (from day 18) to a therapeutic treatment regimen with VB10.NEO and anti-PD-1 in the CT26 colon carcinoma model resulted in rapid, complete and long-lasting tumor regression in mice with relatively small tumors and long-lasting stabilization of larger tumors. Each line represents individual mice (n=10).



The immediate effect of adding NKTR-214 at day 18 (red line, left) is striking as the tumor growth reduced immediately. Tumor-free re-challenged mice were fully protected (right). The data demonstrate the strong rationale for bringing these unique and non-overlapping mechanisms together to create an effective treatment of established tumors.

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