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Synergistic anti-tumor activity of PD-1 signaling blockade and CD27 costimulation correlates with enhanced ratio of effector to regulatory T cells at the tumor site

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CD27 as a Target for Immunotherapy

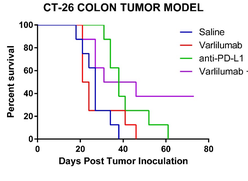
Antibodies that recognize immune cell surface molecules can be used to enhance or target immune responses against tumors. These include antibodies that activate antigen presenting cells (*e.g.* anti-CD40), antibodies that block immune checkpoints (*e.g.* anti-CTLA-4, anti-PD-1), and T cell co-stimulatory antibodies (*e.g.* anti-4-1BB). The costimulatory molecule CD27 is a member of the tumor necrosis factor (TNF) receptor superfamily, and is constitutively expressed on the majority of mature T cells, memory B cells, and a portion of natural killer (NK) cells. The interaction of CD27 with its ligand CD70 plays key roles in the following processes:

- Costimulation through CD27 on T cells causes activation, proliferation, survival, and maturation of effector capacity and memory;
- Costimulation through CD27 on human B cells activates and promotes the generation of plasma cells, proliferation, and the production of immunoglobulin;
- Costimulation through CD27 on NK cells induces cytolytic activity.

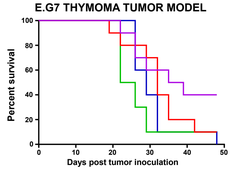
Varlilumab (CDX-1127)

- Varlilumab (CDX-1127) is a fully human IgG1 monoclonal antibody to CD27
- Varlilumab induces activation and proliferation of human T cells when combined with T cell receptor stimulation.
- In huCD27 transgenic mice, varlilumab enhances antigen-specific CD8$^+$ T cell responses when combined with vaccines, and has shown potent anti-tumor activity in syngeneic tumor models.
- Varlilumab has shown promising results in a Phase 1 clinical trial of patients with advanced malignancies.
  - Good safety profile with no MTD through 10 mg/kg,
  - Expected PK profile for human IgG and no significant anti-drug antibodies detected,
  - Clear biological effects consistent with the expected mechanism of action,
  - Evidence of clinical activity seen with durable stable disease and clinical responses.

Synergistic Anti-Tumor Activity of α-PD-L1 and Varlilumab: CT-26 and E.G7 models

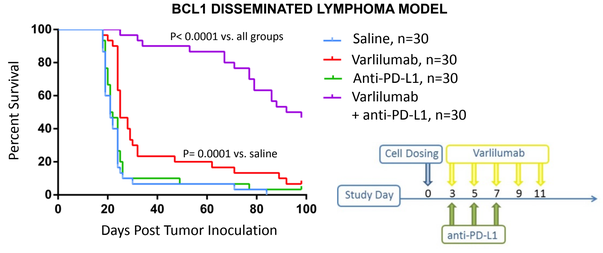


hCD27-Tg mice were inoculated with 1.5x10^4 of CT-26 cells on day 0, 10 mice per group. Anti-PD-L1 (clone 10F9G2) 0.1 mg was administered on day 15, 17 and 19; varlilumab 0.6 mg on day 9, 11, 13, 15 and 17.



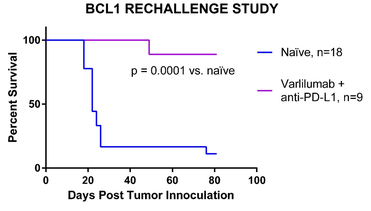
hCD27-Tg mice were inoculated with 0.5x10^6 of E.G7 cells on day 0, 10 mice per group. Anti-PD-L1 (clone 10F9G2) 0.2 mg was administered on day 5, 8, 12, 15, 19; varlilumab 0.2 mg on day 5, 12, 19.

Synergistic Anti-Tumor Activity of α-PD-L1 and Varlilumab: BCL1 model



Groups of 10 female huCD27 Tg mice (Balb/c background) were challenged with 10^7 BCL1 B-lymphoma cells administered intravenously on Day 0. Animals were then treated with 5 doses of varlilumab (200μg), 3 doses of anti-PD-L1(100μg), a combination of the two treatments, or saline, starting on day 4.

Combination Treatment of α-PD-L1 and Varlilumab Induces Protective Immuniity

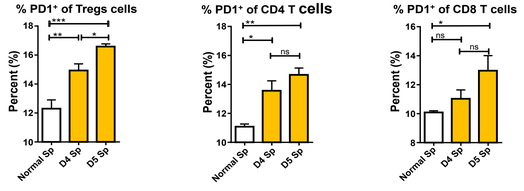


Mice that were long-term survivors from previous BCL1 combination treatment were re-challenged with 10^7 BCL1 tumor cells, and compared to naïve mice.

BCL1 Tumor Characterization

BCL1 DISSEMINATED LYMPHOMA MODEL

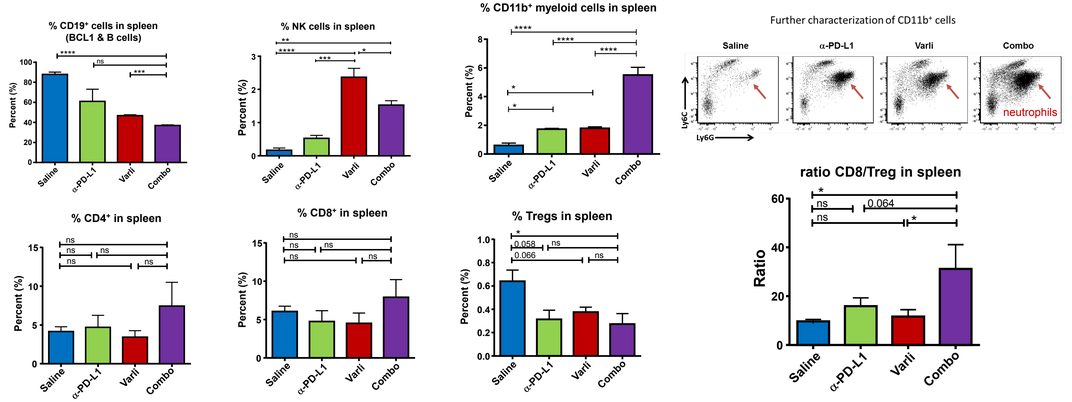
- **The BCL1 i.v. inoculation results in the spleen as the primary site of tumor growth.**
- **BCL1 tumor is CD19$^+$ and PD-L1$^+$.**
- **The BCL1 tumor model shows an increase in PD-1$^+$ T cells.**



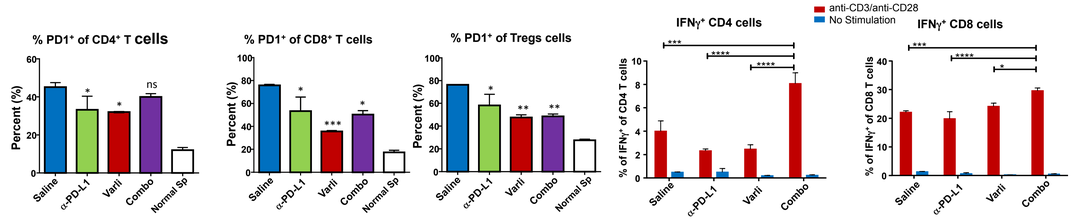
Spleen cells from normal or BCL1 inoculated mice were stained for T cell markers and PD-1 (n=3), * = p<.05, ** = p<.01, *** = p<.001

Investigation of the Mechanism of Synergy

Treatment effect on cell populations in tumor bearing spleens



Characterization of T cells from tumor bearing spleens



huCD27 Tg mice (n=3) were treated as indicated in the tumor survival study. Spleens were harvested on day 12 and analyzed by flow cytometry to distinguish cell populations. Intracellular cytokine staining (IFNγ) was performed after incubation for 5 hours in the presence or absence of anti-CD3ε/anti-CD28 mAbs, and analyzed by flow cytometry in gated CD4$^+$ T cells and CD8$^+$ T cells. * p<0.05, **p<0.01, ***p<0.001.

Summary and Combinations In Clinical Trials

- Varlilumab (CDX-1127) is a fully human agonist antibody to CD27 in Phase 1/2 clinical development in patients with advanced malignancies.
- The combination of varlilumab and anti-PD-L1 resulted in a significant improvement in survival over monotherapy in multiple tumor models.
- In the BCL1 model, mice treated with varlilumab plus anti-PD-L1 showed long term protective immunity to BCL1.
- Investigation of the mechanism of synergy in the BCL1 lymphoma model resulted in the following observations in the tumor bearing spleens:
  1. Greater reduction in tumor cells
  2. Increase in myeloid cells, particularly neutrophils
  3. Increase in the ratio of CD8$^+$ T cells to Treg
  4. Increased functional capacity of CD4$^+$ and CD8$^+$ T cells

- These results support the clinical development of combinations of varlilumab with PD-1 signaling blockade. Celldex is currently engaged in the following combination clinical trials:

  A Phase 1/2 dose escalation and cohort expansion study of varlilumab and Anti-PD-1 (nivolumab) in refractory solid tumors- Currently enrolling

  A Phase 1/2 study of varlilumab and MPDL3280A (anti-PD-L1) in renal cell carcinoma- To be initiated in 2015