Antibodies that recognize immune cell surface molecules can be used to enhance or , and has shown potent anti-tumor activity in .

Varilumab (CDX-1127) is a fully human IgG1 monoclonal antibody to CD27 constitutively expressed on the majority of mature T cells, memory B cells, and a portion of natural killer (NK) cells. The interaction of varilumab with its ligand CD27 plays key roles in the following processes:

- Costimulation through CD27 on NK cells induces cytolytic activity.
- 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.

Varilumab (CDX-1127)

- Is currently engaged in the following combination clinical trials:
  - PD-L1 signaling blockade and CD27 costimulation in syngeneic tumor models.
  - Varilumab is a fully human monoclonal antibody to CD27.
  - Varilumab enhances antigen-specific CD8 T cell responses when combined with vaccines, and has shown potent anti-tumor activity in syngeneic tumor models.
  - Varilumab has shown promising results in a Phase I clinical trial of patients with advanced malignancies.

Synergistic Anti-Tumor Activity of CD27 and CD27 Costimulation Correlates with Enhanced Ratio of Effector to Regulatory T Cells at the Tumor Site

2. Increases in myeloid cells, particularly neutrophils.
3. Increases in the ratio of CD8 T cells to Tregs.
4. Increased functional capacity of CD4+ and CD8+ T cells.

In huCD27 Tg mice (n=3) treated with anti-PD-L1 and varilumab, long-term protective immunity to BCL1 was observed. Splenocytes from normal or BCL1 inoculated mice were stained for T cell markers and PD-1 (n=3), and compared to naïve mice.

- Increased functional capacity of CD4+ and CD8+ T cells.
- Increases in myeloid cells, particularly neutrophils.
- Increases in the ratio of CD8+ T cells to Tregs.
- Increased functional capacity of CD4+ and CD8+ T cells.

These results support the clinical development of combinations of varilumab 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 varilumab and Anti-PD-1 (mAbsX). Currently enrolling.
B) Phase 1/2 study of varilumab and MPDL3280A (anti-PD-1) in renal cell carcinoma- To be initiated in 2015.