CD40 represents a unique target for immunotherapy due to its powerful effect on multiple relevant cell types:
- CD40 activation on dendritic cells (DCs) promotes their conversion to antigen-presenting cells (APCs) that are efficient for the stimulation of T cell responses.
- CD40 activation on macrophages promotes their ability to mediate effector functions such as phagocytosis.
- CD40 activation on B cells promotes proliferation and antigen presentation.
- CD40 activation on malignant B cells leads to tumor growth inhibition and rejection in xenograft models.

Functional aspects of CD40 agonist antibodies will substantially influence its activity profile:
- Block/not block natural ligand (CD40L) interaction,
- Promote/lack Fc receptor interaction,
- Require/not require FcR binding for agonistic function,
- Potency of agonistic activity.

CDX-1140 represents a novel fully human CD40 agonist antibody with unique properties. Comparisons are presented with CP-870,893, also known as clone 21.4.1 (US patent 8388971).

### IND-Enabling Studies
- **CDX-1140 in vitro Cytokine Response Assays**
  - CDX-1140 was tested for cytokine production in whole human blood assays in plate-bound and solution format. No significant increases of cytokines (TNFα, IL6, IL1β, IFNγ, IL8, IL-12p40, and IL2) were observed above isotype control.

- **Tissue Cross-reactivity Studies**
  - Membrane staining was present only in epithelium in a number of tissues and mononuclear cells in GLP-compliant tissue cross-reactivity study.

- **CDX-1140 stained human and monkey tissues similarly.**

- **Study Design:**
  - Serum level of IL-12p40 (NOAEL) was determined to be the high dose level of 10 mg/kg.

**Pharmacological Effects Show Dose-dependent CD40 Activation**

- **CDX-1140 has Dose-dependent and Fc-independent Agonist Activity**

- **CDX-1140 has Similar Binding but Lower Agonist Activity**
  - CDX-1140 was tested for cytokine production in whole human blood assays in plate-bound and solution format. No significant increases of cytokines (TNFα, IL6, IL1β, IFNγ, IL8, IL-12p40, and IL2) were observed above isotype control.

- **Study Design:**
  - Serum level of IL-12p40 (NOAEL) was determined to be the high dose level of 10 mg/kg.

**Pharmacological Effects are Maintained Over the Course of the Study**

- The serum IL-12p40 levels and B cells were determined as above. Of note dose levels lower than 10 mg/kg all had significant ADA responses that likely impact the evaluation of their potential pharmacological effects.

### CDX-1140: Phase 1 Clinical Trial

- **Study in Patients with Advanced Solid Tumors**
  - Dose(s) of CDX-1140 was administered at different dose levels to assess safety and pharmacodynamics.
  - Pharmacodynamic endpoints included changes in lymphocyte counts, B cells, and serum levels of IL-12p40.

**Pharmacokinetic Parameters**

- **CDX-1140: Anti-lymphoma Activity**
  - CDX-1140 has Direct and Indirect Anti-lymphoma Activity

**Conclusions and Next Steps**

- CDX-1140 represents a novel CD40 agonist antibody with a unique profile relative to other CD40 agonist antibodies:
  - Designed to achieve systemic doses with good tissue penetration,
  - Synergy with CD40L at low doses may promote local agonist activity.

- A Phase 1 Study with CDX-1140 in advanced cancer patients is planned to initiate in 2017.

- Following dose escalation of CDX-1140, combinations will be explored with immunotherapy and conventional therapies.