Functional characterization of CDX-1140, a novel CD40 antibody agonist for cancer immunotherapy
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Introduction
CD40 represents a unique target for immunotherapy due to its powerful effect on multiple relevant cell types:
- CD40 activation on DCs promotes their conversion to APCs that are efficient for stimulation of T cell responses
- CD40 activation on macrophages promotes their ability to mediate effector function 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/facilitate Fc receptor interaction
- Require/not require FcR binding for agonistic function
- Potency of agonistic activity

CDX-1140 represents a novel CD40 agonist antibody with unique properties

Comparisons are presented with CP-870,893 also known as clone 21.4.1 (US patent 8388971)

Making and Characterization of CDX-1140

Anti-CD40 monoclonal antibodies (mAbs) were generated by immunization of human Ig transgenic mice (H2L2 strain of HarboFF® transgenic mice) with recombinant and cell surface expressed human CD40. Hybridomas were selected using a reporter cell assay engineered to express CD40 and Fnfβ-responsive luciferase. The variable regions of lead antibodies were cloned in human IgG1 or IgG2 constant domains and expressed in CHO cells. From this panel, CDX-1140, a human IgG2 antibody, was selected for further development.

CDX-1140: Agonist Activity

CDX-1140 represents a novel CD40 agonist antibody with unique profile:
- Agonist activity is independent of Fc

CD40L enhances CDX-1140 agonist activity

CDX-1140: Activity in Lymphoma Model

CDX-1140 does not block CD40L binding

CDX-1140: Non-human Primate Pilot Study

Study Design

Clinical chemistry

Hematology

Circulating B cells

Serum IL-12

Anti-KLH titers

Administration of CDX-1140 in this study was well tolerated in cynomolgous monkeys without any toxicity parameter being significantly outside of control levels. Pharmacologic decreases in white blood cells, lymphocytes and neutrophils were seen in CDX-1140 dosed animals, with most significantly a transient decrease in B cells. Increase in KLH-specific IgG was observed with CDX-1140, but not significant due to few animals and significant variability.

Conclusions and Next Steps

- CDX-1140 represents a novel CD40 agonist antibody with a unique profile:
  - Potent agonist that functions independent of FcR interactions
  - Strong cooperation with CD40L for enhanced activity
  - Direct anti-lymphoma activity in vivo
  - Pharmacologic activity in monkeys minimal evidence of toxicity

- CDX-1140 manufacturing and IND-enabling studies are ongoing

- 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

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