Combining CD27 costimulation and PD-1 blockade into a bispecific antibody improves T cell activation and anti-tumor activity over combination of individual antibodies

Laura A. Vitale, Lawrence J. Thomas, Thomas O’Neill, Jennifer Widger, Laura Mills-Chen, Andrea Crocker, Colleen Patterson, Anna Wasiau, Eric Forberg, James Boyer, Crystal Sisson, Jeffrey Weidlick, Shannon Renn-Bingham, Russ Hammond, Joel Goldstein, Henry C. Marsh, Jr., Li-Zhen He, Michael Yellin, Torl Keeler, Celldex Therapeutics, Inc., Hampton, N.J. 08827, Needham, MA 02494, and Fall River, MA 02723

BACKGROUND

- This program builds from our experience with full-length CD27 agonist mAbs in combination with novel mAbs that demonstrated:
  - No additive toxicity concerns
  - Enhancement of tumor PD-1 expression and CD8 T cells
  - Durable responses in patient populations unlikely to respond to PD-1 monotherapy
  - Best clinical activity observed with regimens that used similar doses (3 mg/kg) of each antibody administered on the same schedule

- CDX-527 is a bispecific antibody (BsAb) that combines blocking the PD-1 checkpoint pathway with CD27 costimulation of T cells
  - Designed from novel PD-1 and CD27 antibodies
  - Advantages of the BsAb include:
    - Cost and development advantages relative to 2 mAbs
    - Better CD27 agonist activity via PD-L1 cross-linking especially in tumor microenvironment

CDX-527 Surrogate BsAb

- Full length PD-L1 mAb binds human IgG1s genetically linked to single chain variable domains of uCD27 mAbs 2B3
  - Includes human Fc region as part of the BsAb construct
  - Retaining Fc receptor cross-linking for CD27 agonist activity
  - Retaining FcYr binding activity for antibody-like half-life (PK)
  - Repeated antigen binding
  - Bispecific for CD27 and PD-L1

- T Cell Co-Stimulation

  - Efficient T cell co-stimulation by CDX-527 through CD27 and TCR Signaling

Inhibition of PD-1 and CD80

- CDX-527 Potently Inhibits PD-L1 binding to PD-1 or CD80

Mixed Lymphocyte Reaction

- CDX-527 is More Effective Than Parental Antibodies in MLR Activity

T Cell Activation with CDX-527 Requires Both PD-L1 and OKT3

- The CDX-527 surrogate construct replaces the PD-1 mAb (CR12) with sequences from the PD-L1 mAb, antihuman (4D9). Anti-L1 binds to both human and mouse PD-L1.

Combination of Parental Antibodies Does Not Provide Efficient T Cell Activation

- Bivalent for CD27 and PD-L1
- Enabling Protein A purification
- Retaining FcRn binding activity for antibody-like half-life (PK)
- Retaining Fc receptor cross-linking for CD27 agonist activity

CDX-527 Surrogate BsAb

- Downstream effects of CD27 activation
- Efficient T cell stimulation
- Potent expansion of Vaccine Induced CD8 T cell responses

CDX-527 Surrogate is More Effective Than Parental Antibodies in BCL-1 Lymphoma Model

CDX-527 Surrogate has Direct Anti-Lymphoma Activity in Xenograft Model

Dose-escalation Study Portion

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CDX-527 Surrogate BSA

- Efficient T cell activation
- Integrated cost and development advantages
- Best clinical activity observed with regimen

Anti-Tumor Activity

Summary and Next Steps

- Bispecific antibodies redirect immune pathways involved in controlling immune responses to tumors. Are rapidly growing area for the development of next generation PD-1 therapies

- Our prior clinical experience with combining CD27 activation and PD-1 blockade provide the rationale for linking these two pathways into one molecule

- The preclinical studies demonstrate that CDX-527 is more potent at T cell activation and anti-tumor immunity than the combination of parental monoclonal antibodies

- Next steps for CDX-527 include:
  - Completion of CDX-527 GMP manufacturing activities
  - Completion of IND enabling studies
  - IND planned for H1 2020
  - Phase 1 dose escalation trial