Preliminary results from a first-in-human phase 1 study of the CD40 agonist monoclonal antibody (mAb) CDX-1140

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Preliminary results from a first-in-human phase 1 study of the CD40 agonist monoclonal antibody (mAb) CDX-1140

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BACKGROUND

- Agonist CD40 mAbs can mediate antitumor immunity1
  - Enhance tumor antigen presentation by dendritic cells (DCs)
  - Activate tumoricidal macrophages
  - Direct growth inhibition/killing of CD40-expressing tumor cells

- CDX-1140: fully human IgG2 agonist anti-CD40 mAb2
  - Activates DCs and B cells in an FcR-independent manner
  - Potent antitumor activity against CD40-expressing cancer cells
  - Unique and linear dose-dependent in vitro and in vivo activity; should allow for significant tumor and tissue penetration without dose limiting-toxicities (DLT) from systemic CD40 activation

- CDX-301 (rFLT3L): DC growth factor3, 4
- CDX-1140: fully human IgG2 agonist anti-CD40 mAb2
- Agonist CD40 mAbs can mediate antitumor immunity1
  - Activates DCs and B cells in an FcR-independent manner
  - Activates tumoricidal macrophages
  - Festival body immune response

Study Design

- Phase 1 dose-escalation and cohort expansion study evaluating safety, PK, PD, and preliminary clinical activity of CDX-1140 as monotherapy and in combination with CDX-301
- Patients with advanced solid tumors who have exhausted standard-of-care treatment options, with measurable disease
- CDX-1140 & CDX-301 are synergistic in murine tumor models6, 7

CDX-1140 monotherapy

- Dose escalated from 0.09 to 3.0 mg/kg IV q4w
- Patients with advanced solid tumors who have exhausted Phase 1 dose-escalation and cohort expansion study

CDX-301 (rFLT3L): DC growth factor3, 4

- Increases multiple DC subsets in blood and tissues
- May mediate antitumor immunity through promotion of CD141+ DCs, tumor antigen uptake and cross presentation to CD8+ T cells5
- CD40 ligation and FLT3L are synergistic in murine tumor models6, 7

CONCLUSIONS AND FUTURE DIRECTIONS

- CDX-1140 monotherapy to date (at doses ≤ 0.18 mg/kg):
  - Well-tolerated with minimal drug-related toxicity
  - No safety concerns to date with initial patients
  - Neither dose limiting toxicity (DLT) nor significant drug-related toxicity
  - No other treatment related SAEs or treatment related deaths
  - No treatment related symptoms at doses ≤ 0.18 mg/kg (n=22)

References
2. Viale, et al. CIR 2018
3. Anandasabapathy, et al. BMt 2015
4. Breton, et al. JEM 2015
7. Thomas, et al. AACR, 2018

CDX-1140 + CDX-301:

- Further dose-escalation will define recommended dose for evaluation of clinical activity in expansion cohorts
- Study amended to include non-Hodgkin’s lymphoma (NHL) in monotherapy portion
  - CDX-1140 has direct killing effect on CD40-expressing NHL cells
- Future opportunities include combinations with varilumab (in lymphomas), radiation therapy, and/or checkpoint blockade
  - Several B cell lymphomas including DLBCL and follicular lymphoma express CD40 and CD27
  - Varilumab is a potent anti-CD27 agonist
  - CDX-1140 synergizes with varilumab in NHL models

Liver Function Tests or Platelets

- Mean I L-12p40 (pg/mL)
- Mean I L-1R A (pg/mL)
- Mean TNF-alpha (pg/mL)
- Mean IL-6 (pg/mL)
- Mean MIP-1 beta (pg/mL)
- Mean IL-12p40 (pg/mL)
- Mean IL-1RA (pg/mL)
- Mean TNF-alpha (pg/mL)
- Mean MIP-1 beta (pg/mL)
- Mean IL-6 (pg/mL)
- Mean CD141+ DCs, tumor antigen uptake and cross presentation to CD8+ T cells

Pharmacokinetic Analysis

- CDX-1140 is quantifiable at doses ≥ 0.09 mg/kg
- Exposure appears dose proportional

Dose-Dependent Induction of Pro-Inflammatory Cytokines and Chemokines

- IL-12p40
- IL-1RA
- IP-10
- MIP-1 beta
- IL-6
- TNF-alpha

Enhanced cytokine production

Monocytes

Liver Function Tests or Platelets

Cytokines and Chemokines

References

ClinicalTrials.gov: NCT03329950