First-in-human phase 1 study of the CD40 agonist monoclonal antibody (mAb) CDX-1140 alone and in combination with CDX-301 (rhFLT3L) in patients with advanced cancers: Interim results

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BACKGROUND

- CD40 plays key roles in dendritic cell, macrophage, and B cell functions[1]
  - Critical for adaptive immune responses, including "licensing" CD8+ T cell cytotoxic activity and T cell dependent-B cell functions
  - Directly induces macrophage tumoricidal activity
- In contrast to normal cells, CD40 agonism can lead to direct growth inhibition/killing of CD40-expressing tumor cells[2,3]

- CDX-1140: fully human IgG2 agonist anti-CD40 mAb[4]
  - Potently activates cells in an FcR-independent manner
  - Directly kills CD40-expressing cancer cells
  - Selected based on linear dose-dependent activity in vitro and in vivo
  - Hypothesized to achieve good systemic exposure and tumor penetration, without dose limiting toxicity observed with other potent agonist anti-CD40 mAbs
  - Does not block CD154 (CD40L)-CD40 interactions and shown to synergize with sCD154 in vitro

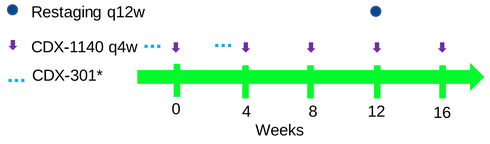
- CDX-301 (rFLT3L): potent DC growth factor[5]
  - FLT3L increases key DC subset, CD103+ subset in mice and CD141+ subset in humans, critical for "cross-presentation" of tumor antigens and licensing CD8+ T cell cytolytic activity[5,6,7,8]
  - CD103+ DC subset critical for activity of immunotherapy and adoptive T cell therapy in murine models and presence of intratumoral CD141+ DC signature correlates with better clinical outcome in patients with cancer[6,7,8]
  - CD40 ligation and FLT3L are synergistic in murine tumor models[9]

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

CDX-1140 monotherapy
- Patients with advanced solid tumors and non-Hodgkin lymphoma
- Dose escalation from 0.01 to 3.0 mg/kg IV q4w
  - 1+5 design for 1st two dose levels, then 3+3 design thereafter
- DLT evaluation period: 28 days after the 1st infusion

CDX-1140 + CDX-301
- Patients with advanced solid tumors
- CDX-1140 dose escalation from 0.09 to 3.0 mg/kg IV q4w
  - 3+3 design for all cohorts
- CDX-301 (75 μg/kg sc) x 5 days prior to 1st two CDX-1140 doses
- DLT evaluation period: 7 days after the 2nd CDX-1140 infusion (i.e., about 35 days after the 1st CDX-1140)



*CDX-301 is administered for patients in the combination portion only

ClinicalTrials.gov: NCT03329950

Dose-Escalation Status

Monotherapy (n=22)

- 0.01 mg/kg (n=2) Pancreatic, CRC
- 0.03 mg/kg (n=1) Bladder
- 0.09 mg/kg (n=3) HN, Ovarian, Cholangiocarcinoma
- 0.18 mg/kg (n=7) Pancreatic, CRC, Gastric, RCC (x2), HN, Ovarian
- 0.36 mg/kg (n=3) Pancreatic (x2), Ovarian
- 0.72 mg/kg (n=3) Ovarian (x2), DLBCL
- 1.5 mg/kg (n=3) Ovarian, HN, Melanoma

Combination (n=8)

- 0.09 mg/kg (n=5) Pancreatic, CRC, Mesothelioma, NSCLC (x2)
- 0.18 mg/kg (n=3) Melanoma (x2), HN

Currently enrolling in 0.36 mg/kg cohort

One DLT (pneumonitis & hypoxia)

If MTD not reached, patients will be enrolled into 3.0 mg/kg cohort

Baseline Patient Characteristics

	Monotherapy (n=22)	Combination (n=8)
Age, years (median, [range])	66.2 (44, 87)	62 (51, 83)
Male	12 (55%)	5 (63%)
ECOG		
0	8 (36%)	2 (25%)
1	14 (64%)	6 (75%)
No. prior treatment regimens (mean [range])	4.4 (1, 9)	4.4 (1, 8)
Prior checkpoint inhibitor	9 (41%)	5 (63%)
Prior chemotherapy	18 (82%)	6 (75%)

References
1. Vonderheide, et al. CCR 2013
2. Wang, et al. Leuk. Lymph. 2008
3. Zhou et al. CII 2012
4. Vitale, et al. CII 2018
5. Anandasabapathy, et al. BMT 2015
6. Salmon, et al. Imm. 2016
7. Spranger, et al. Can Cell 2017
8. Broz, et al. Can Cell 2014
9. Borges, et al. JI 1999

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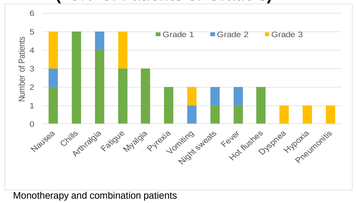
Abbreviations: ADA, antidrug antibody; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRC, colorectal cancer; DC, dendritic cells; DLBCL, diffuse large B-cell lymphoma; DLT, dose limiting toxicity; ECOG, Eastern Cooperative Oncology Group; HN, head and neck; LOQ, limit of quantitation; NSCLC, non-small cell lung cancer; PD, pharmacodynamic; PK, pharmacokinetic; PBMC, peripheral blood mononuclear cell; RCC, renal cell cancer; SD, standard deviation; WBC, white blood count

INTERIM RESULTS

Safety

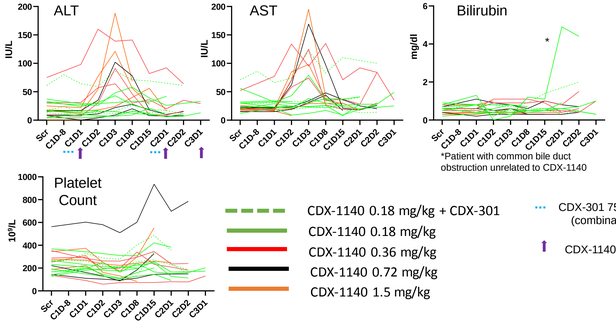
Incidence of Treatment Related AEs (>5% of Patients or Grade 3)



Monotherapy and combination patients

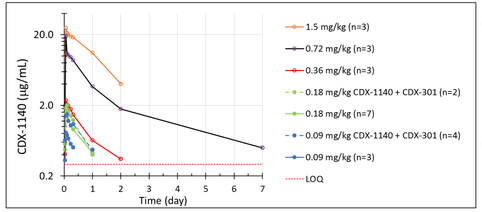
- Among all patients, only 3 monotherapy patients with treatment related SAEs
  - 0.18 mg/kg: grade 3 pneumonitis and hypoxia (DLTs) and grade 3 dyspnea. Patient subsequently died due to Enterobacter pneumonia/bacteremia deemed unrelated to CDX-1140
  - 0.72 mg/kg: grade 2 possible cytokine release, grade 3 fatigue and grade 1 fever
  - 0.72 mg/kg: grade 3 fatigue and nausea

Liver Function Tests & Platelets (up to Cycle 3)



- Dose-dependent, transient, low-grade changes in liver transaminases without effects on bilirubin
- Minimal changes in platelet count
- No significant changes observed in lower dose cohorts (not shown)

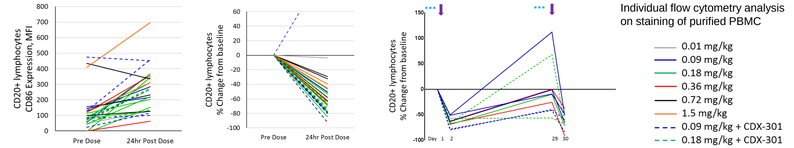
Pharmacokinetic and Antidrug Antibody Analysis



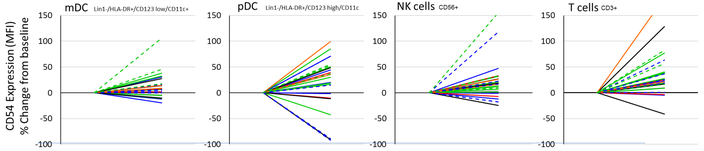
- Interim analysis: CDX-1140 mean C_{max} values are 19.1 and 25.5 μg /ml for 0.72 and 1.5 mg/kg CDX-1140 cohorts, respectively
- To date no significant ADA responses to CDX-1140 or CDX-301 observed

Activation of Peripheral Blood Immune Cells

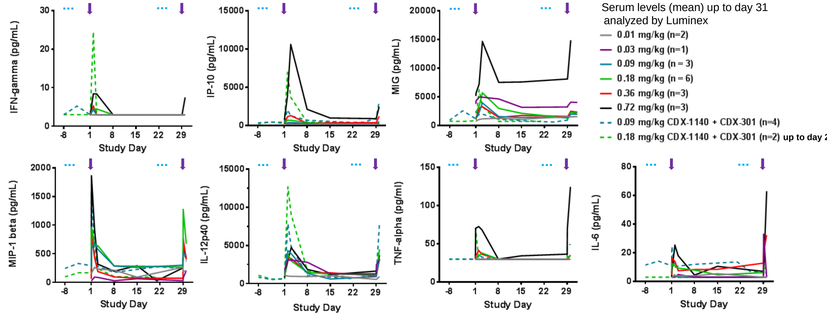
Activation and transient decrease of B cells



Activation of DCs, NK, and T cells



Dose-Dependent Induction of Pro-Inflammatory Cytokines and Chemokines



CONCLUSIONS AND FUTURE DIRECTIONS

- Consistent with our preclinical studies, the clinical data support that CDX-1140 is a potent CD40 activator that is generally well tolerated at systemic drug concentrations expected to engage CD40 expressing cells in the tumor microenvironment
  - MTD not yet reached, currently at dose level of 1.5 mg/kg with C_{max} values of 25 μg/ml
  - CDX-1140 activates peripheral immune cells and increases relevant pro-inflammatory cytokines and chemokines
- Addition of CDX-301 has not affected the tolerability at the dose levels of CDX-1140 tested to date (0.18 mg/kg) and enhances the cytokine response
- Among patients who have been restaged, the best response to date has been SD (recent dose levels still under evaluation)
- Additional patient enrollment (backfill) has been initiated at the 0.72 mg/kg CDX-1140 dose level, and tumor specific expansion cohorts are planned
- Future combination opportunities being considered include varlilumab, PD-1/PD-L1 inhibitors and radiation therapy