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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 immunity[1]
  - 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 mAb[2]
  - 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 factor[3, 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 cells[5]
- CD40 ligation and FLT3L are synergistic in murine tumor models[6, 7]

Study Design

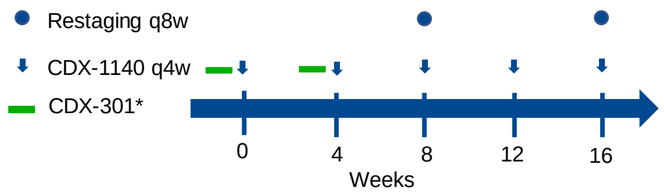
- Phase 1 dose-escalation and cohort expansion study evaluating safety, PK, PD, and preliminary clinical activity of CDX-1140 as monotherapy and in combination with CDX-301
- Patients with advanced solid tumors who have exhausted standard-of-care treatment options, with measurable disease and documented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

CDX-1140 monotherapy

- 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 in combination with CDX-301

- 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: 35 days after the 1st CDX-1140 infusion (i.e., 7 days after the 2nd infusion)



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

Dose-Escalation Status

Monotherapy (n=13)

- 0.01 mg/kg (n=2) Pancreatic, CRC
- 0.03 mg/kg (n=1) Bladder
- 0.09 mg/kg (n=3) HNSCC, Ovarian, Cholangiocarcinoma
- 0.18 mg/kg (n=7) Pancreatic, CRC, Gastric, RCC (x2), HNSCC, Ovarian

Combination (n=4)

- 0.09 mg/kg (n=4) Pancreatic, CRC, Mesothelioma, NSCLC

Observation for DLT ongoing

One DLT (pneumonitis & hypoxia) DLT evaluation complete; dose-escalation proceeding

References
1. Vonderheide, et al. CCR 2013
2. Vitale, et al. CII 2018
3. Anandasabapathy, et al. BMT 2015
4. Breton, et al. JEM 2015
5. Salmon, et al. Imm. 2016
6. Borges, et al JI 1999
7. Thomas, et al. AACR, 2018
8. Li-zhen, et al ASH 2016

Abbreviations: CRC, colorectal cancer; RCC, renal cell cancer; NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; WBC, white blood count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PK, pharmacokinetic; PD, pharmacodynamic; SD, standard deviation; DLBCL, diffuse large B-cell lymphoma

ClinicalTrials.gov: NCT03329950

INITIAL RESULTS

Baseline Patient Characteristics

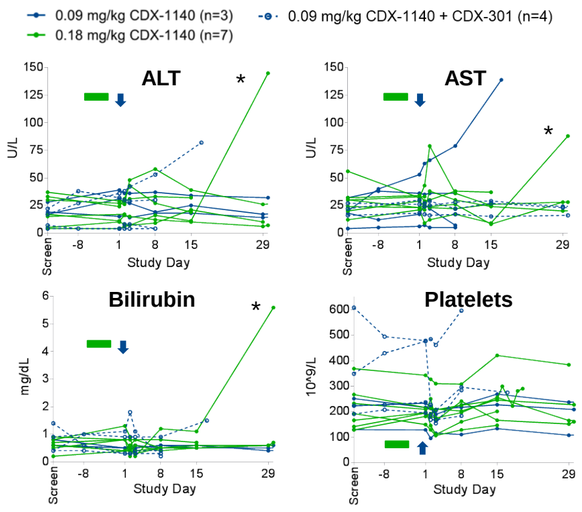
	Monotherapy (n=13)	Combination (n=4)
Age, years (median, [range])	64.5 (44-81)	60.5 (53-83)
Male	9 (69%)	2 (50%)
ECOG		
0	5 (38%)	0
1	8 (62%)	4 (100%)
No. prior treatment regimens (mean [range])	4 (1-9)	3 (2-5)
Prior checkpoint inhibitor	7 (54%)	1 (25%)
Prior chemotherapy	12 (92%)	4 (100%)

Data shown as n (%) unless otherwise specified.

Toxicity

- 1 DLT (CDX-1140 monotherapy, 0.18 mg/kg): grade 3 pneumonitis and hypoxia. Patient subsequently died due to Enterobacter pneumonia/bacteremia deemed unrelated to CDX-1140
- No other treatment related SAEs or treatment related deaths
- All additional treatment-related toxicity grade 1-2: nausea, fatigue, anorexia, arthralgia, myalgia, fever, chills, generalized muscle weakness, hot flash, dizziness

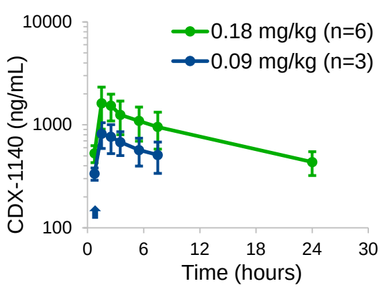
No Significant Drug-related Changes in Liver Function Tests or Platelets



* Patient with common bile duct obstruction unrelated to CDX-1140.

Expected dose-dependent, transient decrease in lymphocytes also observed (see flow cytometry)

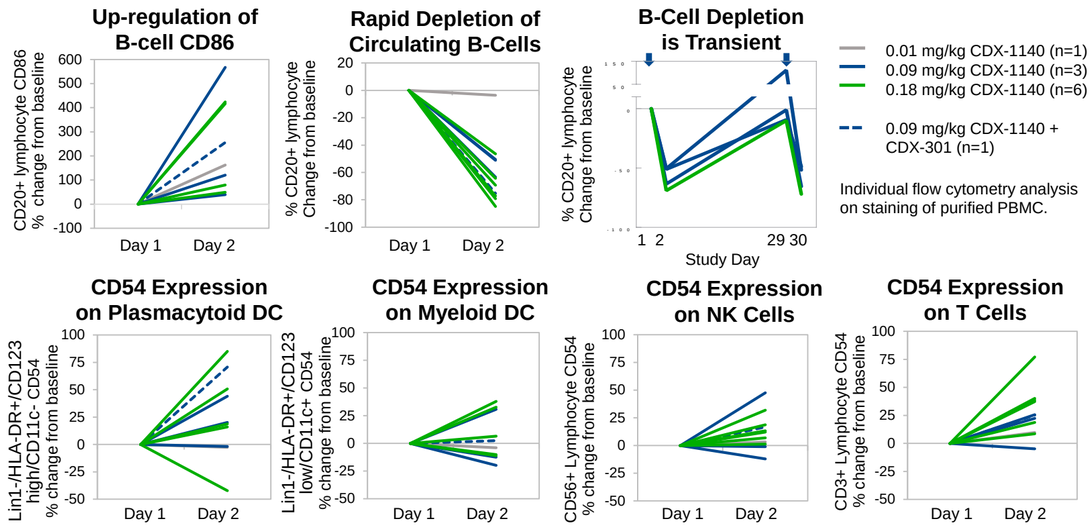
Pharmacokinetic Analysis



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

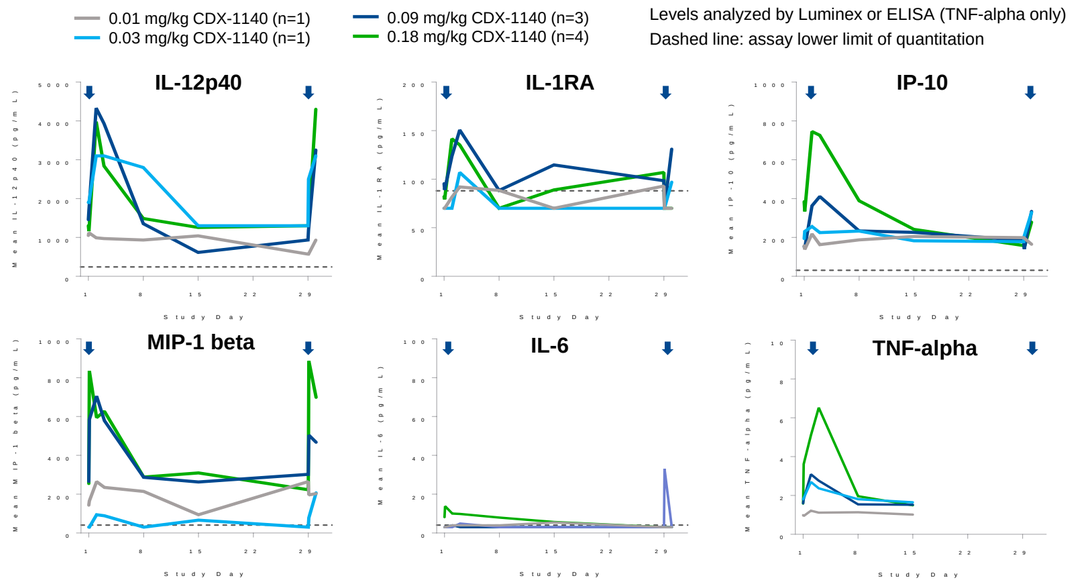
Mean (± SD) serum levels of CDX-1140 (monotherapy) following first 90 minute infusion

Activation of Peripheral Blood Immune Cells



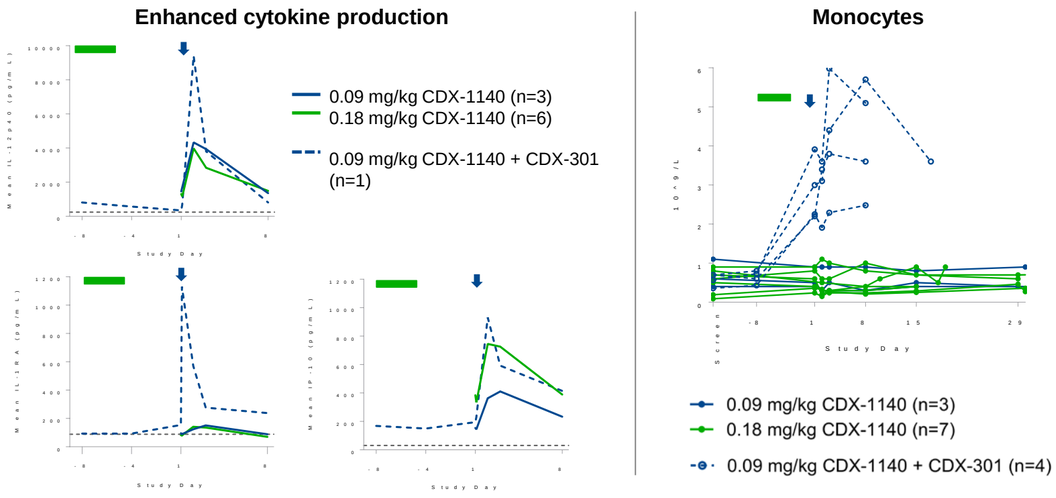
Individual flow cytometry analysis on staining of purified PBMC.

Dose-Dependent Induction of Pro-Inflammatory Cytokines and Chemokines



Levels analyzed by Luminex or ELISA (TNF-alpha only)
Dashed line: assay lower limit of quantitation

Preliminary Evidence of Increased Immune Activity with Combination of CDX-1140 and CDX-301



CONCLUSIONS AND FUTURE DIRECTIONS

- CDX-1140 monotherapy to date (at doses ≤ 0.18 mg/kg):
  - Well-tolerated with minimal drug-related toxicity
  - Transient, dose-dependent pharmacodynamic effects
  - Results consistent with CD40-mediated immune cell activation and the hypothesis that CDX-1140 may achieve dose levels optimal for systemic exposure
- CDX-1140 (at 0.09 mg/kg) in combination with CDX-301:
  - No safety concerns to date with initial patients
  - Preliminary evidence of enhanced immune activation
- 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[2]
- Future opportunities include combinations with varlilumab (in lymphomas), radiation therapy, and/or checkpoint blockade
  - Several B cell lymphomas including DLBCL and follicular lymphoma express CD40 and CD27
  - Varlilumab is a potent anti-CD27 agonist
  - CDX-1140 synergizes with varlilumab in NHL models[8]

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