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

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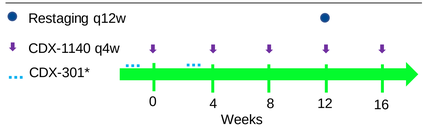
BACKGROUND

- Agonist CD40 mAbs can mediate antitumor immunity[1]
- CDX-1140: fully human IgG2 agonist anti-CD40 mAb[2]
  - Activates DCs and B cells in an FcR-independent manner
  - Antitumor activity against CD40-expressing cancer cells
  - Unique and linear dose-dependent *in vitro* and *in vivo* activity; may allow for significant tumor and tissue penetration without dose limiting-toxicities from systemic CD40 activation
- CDX-301 (rhFLT3L): DC growth factor[3]
  - May augment antitumor immunity through expansion of CD141+ DCs, with subsequent tumor antigen uptake and cross presentation to CD8+ T cells[4]
- CD40 ligation and FLT3L are synergistic in murine tumor models[5]
- Interim data is presented in this ongoing Phase 1 study

Study Design & Study Status

- 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
- Primary efficacy endpoint: ORR as determined by iRECIST (solid tumors) and LYRIC (lymphoma; monotherapy only)



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

Monotherapy Arm

Study Portion	Cohort	CDX-1140 Dose Level (mg/kg q4w)	Patients (n)
Dose-Escalation	1	0.01	2
	2	0.03	1
	3	0.09	3
	4	0.18	7
	5	0.36	3
	6	0.72	9
	7	1.5	10
	8	3.0	7
Expansion Cohorts	9 (SCCHN)	1.5	Up to 15
	10-13		Up to 15 per cohort

CDX-301 Combination Arm

Study Portion	Cohort	CDX-1140 Dose Level (mg/kg q4w)	Patients (n)
Dose-Escalation	1A		
	2A		
	3A	0.09	5
	4A	0.18	3
	5A	0.36	3
	6A	0.72	6
	7A	1.5	3-6
	8A		
Expansion Cohorts	9A-10A	Dose chosen during escalation	≈12 patients per cohort

Patient in the combination arm receive CDX-301 (75 µg/kg sc) x 5 days prior to 1st two CDX-1140 doses

MTD | Above the MTD | Cohort currently under evaluation | Not studied

- CDX-1140 monotherapy dose escalation completed to 3.0 mg/kg, with MTD and RP2D determined to be 1.5 mg/kg
- Monotherapy SCCHN cohort expansion initiated at 1.5 mg/kg
- Enrollment in CDX-1140 1.5 mg/kg + CDX-301 cohort is ongoing
- 62 patients enrolled and 12 patients are still ongoing

RESULTS

Baseline Patient Characteristics

	Monotherapy (n=42)	Combination (n=20)
Age, years (median, [range])	66.5 (41-87)	62.6 (50-83)
Male	20 (48%)	8 (40%)
ECOG		
0	16 (38%)	6 (30%)
1	26 (62%)	14 (70%)
No. prior treatment regimens (mean [range])	4.2 (1-9)	3.7 (1-9)
Prior checkpoint inhibitor	19 (45%)	11 (55%)
Prior chemotherapy	32 (76%)	15 (75%)
Tumor type		
Ovarian	15 (36%)	2 (10%)
SCCHN	6 (14%)	1 (5%)
Melanoma	5 (12%)	3 (15%)
NSCLC	0 (0%)	6 (30%)
NHL	2 (5%)	N/A
Gastric	1 (2%)	1 (5%)
Other	13 (31%)	7 (35%)

Data shown as n (%) unless otherwise specified.

Safety

- CDX-1140 monotherapy and in combination with CDX-301 has been generally well tolerated with mostly grade 1 or grade 2 drug related adverse events
  - Mostly low grade, transient changes in serum liver transaminases
- 2 of 6 patients with pneumonitis at CDX-1140 3.0 mg/kg exceeding MTD
- No DLTs to date in the combination cohorts

Treatment Related AEs ≥10% of patients or ≥G3 in at least 2 patients

	Monotherapy (n=42)		Combination therapy (n=20)	
	Total	≥ Grade 3	Total	≥ Grade 3
Any event	**33 (79%)**	**12 (29%)**	**13 (65%)**	**3 (15%)**
Arthralgia	15 (36%)	1 (2%)	2 (10%)	0 (0%)
Chills	10 (24%)	0 (0%)	3 (15%)	0 (0%)
Pyrexia	10 (24%)	0 (0%)	3 (15%)	0 (0%)
Nausea	10 (24%)	2 (5%)	1 (5%)	0 (0%)
Fatigue	8 (19%)	3 (7%)	4 (20%)	0 (0%)
Myalgia	7 (17%)	1 (2%)	4 (20%)	0 (0%)
Diarrhea	7 (17%)	0 (0%)	1 (5%)	0 (0%)
Vomiting	6 (14%)	1 (2%)	0 (0%)	0 (0%)
Pneumonitis	3 (7%)	3 (7%)	0 (0%)	0 (0%)
AST increased	4 (10%)	2 (5%)	3 (15%)	1 (5%)
ALT increased	4 (10%)	1 (2%)	2 (10%)	1 (5%)
Hypoxia	2 (5%)	2 (5%)	1 (5%)	0 (0%)
Cytokine Release Syndrome	2 (5%)	1 (2%)	3 (15%)	0 (0%)
Anemia	2 (5%)	1 (2%)	2 (10%)	2 (10%)
Abdominal Pain	1 (2%)	0 (0%)	2 (10%)	0 (0%)
Hot flush	0 (0%)	0 (0%)	2 (10%)	0 (0%)

Other significant events occurring in single patients: Grade 3 iridocyclitis; Grade 4 encephalopathy

References
1. Vonderheide, et al. CCR 2013
2. Vitale, et al. CII 2018
3. Anandasabapathy, et al. BMT 2015
4. Borges, et al JI 1999
5. Thomas, et al. AACR, 2018

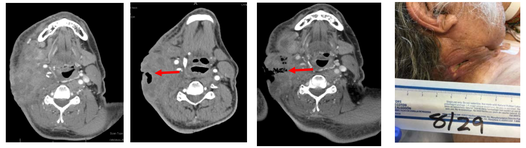
ClinicalTrials.gov: NCT03229950

Abbreviations: NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma head and neck; NHL, non Hodgkin's lymphoma; PK, pharmacokinetic; PD, pharmacodynamic; CRS, cytokine release syndrome; RP2D, recommended Phase 2 dose; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; DLT, dose limiting toxicity; Cmax, maximum serum concentration; iPR, immune partial response; iPD, immune progressive disease; iSD, immune stable disease; RT, radiation therapy; DC, dendritic cell; IV, intravenous; SC, subcutaneous; AE, adverse event; CPI, checkpoint inhibitor; SD, standard deviation; LOQ, limit of quantitation

Clinical Activity

- 1 unconfirmed iPR of 4 months duration in combination cohort (CDX-1140 0.36 mg/kg) – see below
- 6 patients with iSD; 4 in CDX-1140 monotherapy and 2 in CDX-1140 + CDX-301 with a duration of 1.8 months to 5.4 months; 1 iUPD in CDX-1140 + CDX301 with a duration of 10+ months
- Of 62 patients, 38 patients with activity assessments (scans) available and 7 have response data pending

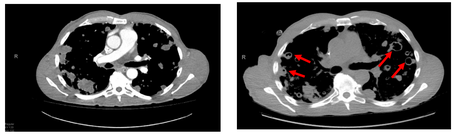
Patient 1005017, SCCHN (HPV+): CDX-1140 1.5 mg/kg (2 doses)



6/5/2019 (baseline) 8/20/2019 10/7/2019 8/29/2019

- Large baseline protruding neck mass decreased on physical exam, evidence of necrosis/cavitation on CT scan (arrow), and decreased tumor pain
- Prior regimens/response: Nivolumab/SD; BMS 986156 + nivolumab/SD; nivolumab/PR; cisplatin, docetaxel, cetuximab/unknown
- Grade 4 encephalopathy (DLT)
  - Recovered following treatment with steroids

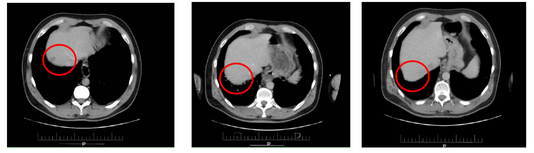
Patient 1005018, SCCHN (HPV+): CDX-1140 3.0 mg/kg (1 dose)



7/31/2019 (baseline) 8/27/2019

- Cavitation of >50% lung metastases on CT scan (arrows)
- Prior regimens/response: Nivolumab + RT; nivolumab/PD; cetuximab, fluorouracil, carboplatin/PD
- Grade 3 pneumonitis (DLT)
  - Recovered following treatment with steroids, mycophenolate mofetil, infliximab, tocilizumab

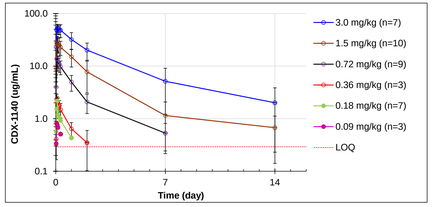
Patient 1012009, Gastroesophageal adenocarcinoma: CDX-1140 0.36 mg/kg (6 doses) + CDX-301



3/12/2019 (baseline) 7/1/2019 8/29/2019

- Unconfirmed iPR (duration of 4 months) because patient subsequently received RT to non-target esophageal lesion that included LN target lesion in RT field
- Prior regimens/response: Cisplatin, taxol, carboplatin/PR; TSR-042, niraparib/PR
- 41% shrinkage of liver and lymph node target lesions

CDX-1140 Monotherapy Pharmacokinetic Analysis



Mean (± SD) serum concentration of CDX-1140 in cycle 1 (LOQ 292 ng/mL)

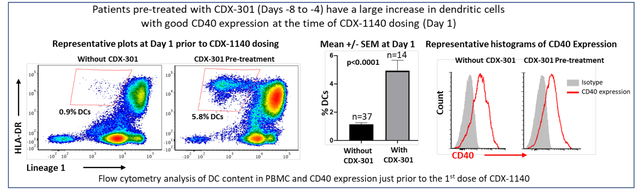
Mean (SD) noncompartmental parameters from CDX-1140 monotherapy in Cycle 1

Cohort	CDX-1140 Dose (mg/kg)	Cmax (µg/mL)	AUCall (day*µg/mL)	Half-life (day)
3	0.09	0.8 (0.2)	0.2 (0.0)	0.46 (0.24)
4	0.18	2.2 (1.6)	0.8 (0.3)	0.55 (0.17)
5	0.36	2.4 (0.5)	1.5 (0.7)	0.59 (0.13)
6	0.72	16.5 (6.0)	19.4 (8.3)	1.62 (0.64)
7	1.5	29.3 (8.3)	48.6 (31.7)	1.75 (0.74)
8	3.0	54.9 (9.9)	139.5 (67.7)	2.64 (1.29)

Similar values observed in CDX-301 combination cohort

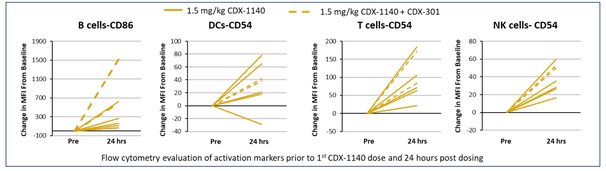
Expansion of Dendritic Cells with CDX-301

Patients pre-treated with CDX-301 (Days -8 to -4) have a large increase in dendritic cells with good CD40 expression at the time of CDX-1140 dosing (Day 1)



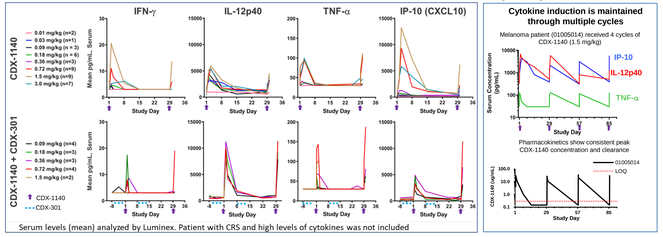
Flow cytometry analysis of DC content in PBMC and CD40 expression just prior to the 1st dose of CDX-1140

Activation of Peripheral Blood Immune Cells



Flow cytometry evaluation of activation markers prior to 1st CDX-1140 dose and 24 hours post dosing

Transient Induction of Pro-Inflammatory Cytokines



Serum levels (mean) analyzed by Luminex. Patient with CRS and high levels of cytokines was not included

SUMMARY AND NEXT STEPS

Interim data from this Phase 1 dose escalation study demonstrates CDX-1140 has promising biological and clinical activity:

- MTD and recommended dose defined as 1.5 mg/kg, which is sufficient to provide good systemic exposure and tumor penetration
- CDX-1140 has been generally well tolerated as monotherapy and in combination with CDX-301, with minimal transaminase elevations and AEs related to immune activation
- Potent pharmacological effects associated with immune activation at each dosing cycle
- Clinical activity observed including unconfirmed iPR in a patient with gastroesophageal adenocarcinoma and early evidence of tumor necrosis in 2 patients with SCCHN

Next steps:

- Complete CDX-1140 + CDX-301 dose escalation and further define the potential for this combination
- Explore CDX-1140 monotherapy activity in SCCHN in an expansion cohort of up to 15 patients
- An amendment adding pembrolizumab is planned and additional combinations with chemotherapy and/or radiation therapy are being considered

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