CDX1140-01, a Phase 1 dose-escalation/expansion study of CDX-1140 alone (Part 1) and in combination with CDX-301 (Part 2) or pembrolizumab (Part 3)

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BACKGROUND

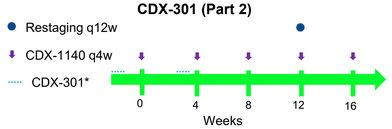
- CD40 signaling in the tumor microenvironment (TME) plays key roles in mediating anti-tumor innate and adaptive immune responses
  - Anti-CD40 mAb therapy augments anti-tumor immune responses, including rescuing PD-1^{hi} exhausted T cells[1] and synergizing with agents that induce immunogenic cell death, (e.g., chemotherapy and radiotherapy), in tumor models[2, 3]
- Toxicity concerns have limited agonist anti-CD40 therapy from achieving systemic dose levels likely sufficient for optimal TME CD40 engagement
- CDX-1140: fully human IgG2 agonist anti-CD40 mAb
  - Has linear dose-dependent agonist activity to potentiate higher systemic exposure levels and better TME penetration
  - CDX-1140 activity may be enhanced by combining with CDX-301 (recombinant Flt3L), a dendritic cell growth factor, pembrolizumab, an anti-PD-1 mAb, or chemotherapy[4]

Here we present updated data of CDX-1140 monotherapy and in combination with CDX-301 focusing on the MTD level, 1.5 mg/kg, that builds on the biologic and clinical data seen in dose-escalation and previously presented (SITC 2019). Preliminary safety data of CDX-1140 in combination with pembrolizumab is also presented

Study Design & Study Status

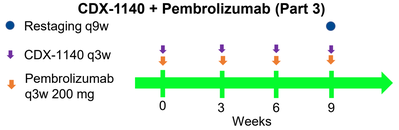
- Phase 1 dose-escalation and tumor-specific expansion study evaluating the safety, pharmacodynamic, pharmacokinetic, immunogenicity, and clinical activity of CDX-1140 as monotherapy or in combination in patients with advanced tumors who have progressed on standard of care treatment
- Primary clinical efficacy endpoint: ORR as determined by iRECIST (solid tumors) and LYRIC (lymphoma; monotherapy only)

CDX-1140 Monotherapy (Part 1) and CDX-1140 + CDX-301 (Part 2)



*Patients in Part 2 receive CDX-301 (75 μg/kg sc) x 5 days prior to 1st two CDX-1140 doses

CDX-1140 + Pembrolizumab (Part 3)



Monotherapy (Part 1)

CDX-1140 Dose (mg/kg q4w)	Patients (n)
Dose Escalation	
<1.5	25
1.5	13
3.0	7
Dose Expansion	
SCCHN 1.5	7
RCC 1.5	5
Total	57

CDX-1140 + CDX-301 (Part 2)

CDX-1140 Dose (mg/kg q4w)	Patients (n)
Dose Escalation	
<1.5	21
1.5	9
Dose Expansion	
SCCHN 1.5	7
Total	37

CDX-1140 + Pembro. (Part 3)

CDX-1140 Dose (mg/kg q3w)	Patients (n)
Safety run-in	
0.72	4
1.5	5
Dose Expansion pending	
Total	9

Data highlighted in poster

- At the MTD of 1.5 mg/kg, CDX-1140 has been administered to 46 patients (25 in Part 1, 16 in Part 2, and 5 in Part 3)
- CDX-1140 dose escalation in combination with CDX-301 has completed the highest dose studied, 1.5 mg/kg

References:
1. Ngiow, et al. Cancer Res., 2016
2. Beatty, et al. Science, 2011
3. Kawashita, et al. Radiat Res., 2014
4. Vitale, et al. Cancer Immunol Immunother. 2019

ClinicalTrials.gov: NCT03329950 Data cut-off September 05, 2020

RESULTS

Baseline Patient Characteristics

	Part 1 & Part 2 (CDX-1140 1.5 mg/kg)		Part 3	
	Monotherapy (Part 1) (N=25)	CDX-1140 + CDX-301 (Part 2) (N=16)	CDX-1140 (0.72 mg/kg) + Pembro (n=4)	CDX-1140 (1.5 mg/kg) + Pembro (n=5)
Age, years (median [range])	62 (41, 86)	60 (42, 73)	65 (51, 75)	71 (66, 74)
Sex, male	15 (60)	11 (69)	1 (25)	4 (80)
Race				
White	23 (92)	12 (75.0)	4 (100)	5 (100)
Black	1 (4)	2 (13.0)	0 (0.0)	0 (0.0)
Asian	0 (0)	2 (13.0)	0 (0.0)	0 (0.0)
Other	1 (4)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, not Hispanic or Latino	24 (96)	16 (100)	4 (100)	5 (100)
Baseline ECOG performance status				
0	9 (36)	6 (38)	2 (50)	1 (20)
1	15 (60)	10 (63)	2 (50)	4 (80)
2	1 (4)	0 (0)	0 (0)	0 (0)
Prior-chemotherapy	14 (56)	15 (94)	3 (75)	3 (60)
Prior-checkpoint inhibitor	18 (72)	14 (88)	4 (100)	4 (80)
Number of regimen (mean [range])	4.1 (1, 9)	4.0 (2, 12)	3.5 (2, 5)	4.0 (1, 10)
Tumor type (n)				
SCCHN	9	8	0	2
RCC	5	1	1	1
Ovarian	4	1	0	0
Melanoma	4	0	0	0
NHL	3	0	0	0
Bladder	0	2	0	0
Other*	0	4	3	2

Part 1 and Part 2 includes combined data of dose escalation and expansion cohorts with patients treated at 1.5 mg/kg
*Other tumor types: esophageal (2), NSCLC (2), thymoma, leiomyosarcoma, cholangiocarcinoma, CRC, endometrial
Data shown as n (%) unless otherwise specified

- Median duration of treatment for patients in Part 1 is 12 weeks with a range of 4 to 34 weeks
- Median duration of treatment for patients in Part 2 is 8 weeks with a range of 4 to 50 weeks

Safety

- CDX-1140 monotherapy and in combination with CDX-301 or pembrolizumab has been generally well tolerated with mostly grade 1 or grade 2 drug related adverse events
- Part 1 treatment related SAEs:
  - Encephalopathy (n=1; grade 4)
  - Pneumonitis (n=1; grade 3)
  - Elevated lipase (n=1; grade 3)
- Part 2 treatment related SAEs:
  - Cytokine release syndrome (n=1; grade 3, n=2; grade 2)
  - Pneumonitis (n=1; grade 3, reported after data cut-off)
  - Hypotension (n=1; grade 5)*
  - AST increased (n=1; grade 2)
  - ALT increased (n=1; grade 1)
- No treatment related SAEs in Part 3 safety run-in (n=9)

Treatment Related AEs of CDX-1140 at 1.5 mg/kg

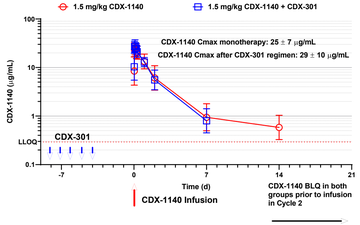
	All Grades (≥ 10%)				Grade 3 or higher (≥5%)
	Monotherapy (Part 1)	CDX-1140 + CDX-301 (Part 2)	CDX-1140 + Pembro. (Part 3)	Overall (N=46)	Overall (N=46)
Preferred Term	Total (N=25)	Total (N=16)	Total (N=5)		
Number of Patients with Any Treatment Related AE					
Arthralgia	13 (52)	5 (31)	3 (60)	21 (46)	5 (11)
Pyrexia	12 (48)	6 (38)	1 (20)	19 (41)	1 (2)
Chills	10 (40)	5 (31)	2 (40)	17 (37)	0 (0)
Vomiting	7 (28)	5 (31)	1 (20)	13 (28)	0 (0)
Fatigue	6 (24)	6 (38)	0 (0)	12 (26)	0 (0)
Nausea	5 (20)	5 (31)	1 (20)	11 (24)	0 (0)
Aspartate aminotransferase increased	5 (20)	3 (19)	2 (40)	10 (22)	4 (9)
Myalgia	6 (24)	3 (19)	1 (20)	10 (22)	1 (2)
Alanine aminotransferase increased	5 (20)	2 (13)	2 (40)	9 (20)	2 (4)
Diarrhoea	4 (16)	3 (19)	1 (20)	8 (17)	1 (2)
Blood alkaline phosphatase increased	4 (16)	2 (13)	2 (40)	8 (17)	1 (2)
Lipase increased	6 (24)	1 (6)	0 (0)	7 (15)	3 (7)
Amylase increased	4 (16)	1 (6)	1 (20)	6 (13)	0 (0)
Influenza like illness	3 (12)	2 (13)	0 (0)	5 (11)	0 (0)
Hypotension	0 (0)	3 (19)	2 (40)	5 (11)	1 (2)*

* One grade 5 treatment related AE of hypotension in Part 2: patient developed grade 3 cytokine release syndrome and grade 2 pneumonitis, treated with corticosteroids and tocilizumab, improved and was discharged from hospital; subsequently was readmitted to non-study hospital during COVID crisis and died reportedly due to hypotension

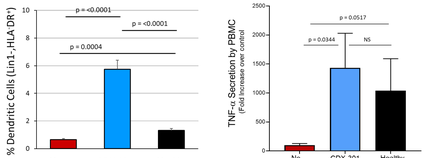
Abbreviations: NSCLC, non-small cell lung cancer; SCCHN, squamous cell carcinoma head and neck; NHL, non-Hodgkin's lymphoma; RCC, renal cell carcinoma; CRC, colorectal cancer; DLBCL, diffuse large B cell lymphoma; MTD, maximum tolerated dose; DLT, dose limiting toxicity; Cmax, maximum serum concentration; IPD, immune progressive disease; iSD, immune stable disease; AE, adverse event; SAE, serious adverse event; TME, tumor microenvironment; AST, aspartate aminotransferase; ALT, alanine aminotransferase

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics at 1.5 mg/kg CDX-1140



Impact of CDX-301 Pretreatment on PBMC



Flow cytometric analysis of PBMC at day 0 prior to first dose of CDX-1140

PBMC's from Day 0 were cultured for 6 days with 5 μg/mL of CDX-1140 or human IgG2 isotype control. Supernatants were harvested and TNF-α was measured by ELISA

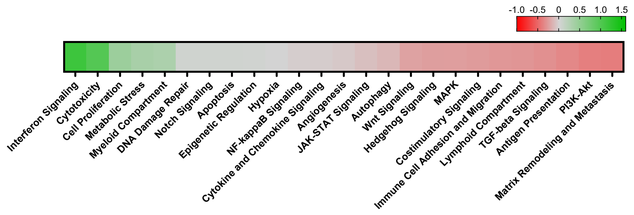
- CDX-1140 dosed at 1.5 mg/kg results in good systemic exposure that is not impacted by CDX-301 pretreatment
- CDX-301 pretreatment enhances circulating DCs and improves PBMC response to CDX-1140 in vitro

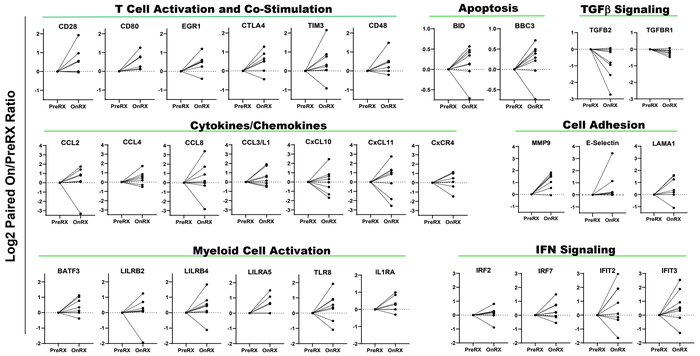
Immune Modulation in the Tumor Microenvironment

- Nanostring analysis from 8 paired biopsies from patients dosed at 0.72 mg/kg (n=1), 1.5 mg/kg (n=6) and 3 mg/kg (n=1)
- On treatment (On-Rx) biopsies were performed approximately 4 weeks after the 1st dose of CDX-1140
- Upregulation of gene signatures indicative of innate and adaptive immune activation were observed, consistent with CD40 agonism in the TME

Modulation of Immune Pathways

- Scores for each pathway determined using nSolver 4.0 Advanced Analysis
- Heat map generated by calculating mean differences of pathway scores from all paired biopsies
- Interferon signaling and cytotoxicity pathways were the most highly upregulated

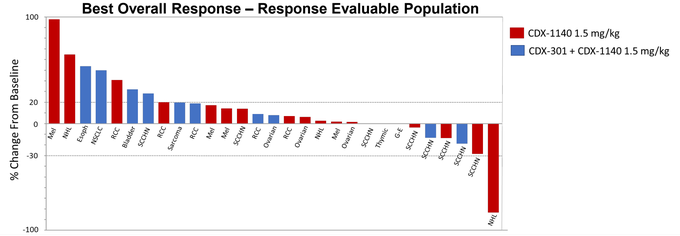




Clinical Activity for Patients in Part 1 and Part 2 at 1.5 mg/kg

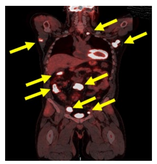
- Complete metabolic response in a patient with follicular lymphoma
- Tumor cavitation in patient with HPV+ SCCHN
- 10 patients with tumor types of SCCHN (4), RCC (2), ovarian (2) leiomyosarcoma (1) and thymoma (1), had iSD for a duration of 11 to 32 weeks
- Of 41 patients, 29 with activity assessments (scans) available and 5 have response data pending
- Part 3 (pembrolizumab combination) had insufficient data at the time of data cut-off

Best Overall Response – Response Evaluable Population

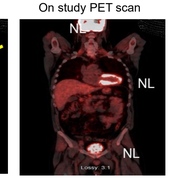


Complete metabolic response in a patient with follicular lymphoma

Baseline PET scan

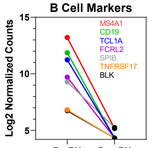


On study PET scan



NL represents normal physiological uptake

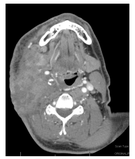
B Cell Markers



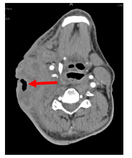
Nanostring analysis of paired lymph node biopsies demonstrates reduction of B cell signatures to or near assay detection limits

- 57 yr old white male; Stage IV follicular lymphoma diagnosed in 2016, [t(14;18)] rearrangement, 17p deletion
- Prior Rx (best response)
  - Rituximab (PR)
  - Ublituximab (anti-CD20) + umbralisib (PI3Ki) (PR)
- 1st CDX-1140 dose administered January 2020
- Treated with corticosteroids for increased LFTs
- First restaging in April 2020 (after 3 doses) demonstrated complete metabolic response (CMR)
- CMR ongoing at 6 months; patient currently on treatment cycle 9

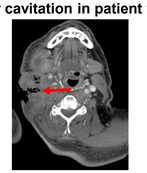
Tumor cavitation in patient with HPV+ SCCHN



Baseline Scan



On study scan



On study scan

- Prior regimens/response: Nivolumab/SD; BMS 986156 + nivolumab/SD; nivolumab/PR; cisplatin, docetaxel, cetuximab/unknown
- Administered 2 doses of CDX-1140
- Large baseline protruding neck mass decreased on physical exam, evidence of necrosis/cavitation on CT scan (arrow), and decreased tumor pain
- Grade 4 encephalopathy (DLT)
  - Recovered following treatment with steroids

SUMMARY AND NEXT STEPS

CDX-1140 at the recommended dose of 1.5 mg/kg provides good systemic exposure that enhances the distribution into tissues and tumor

- CDX-1140 has been generally well tolerated in monotherapy as well as in combination with CDX-301 and pembrolizumab
  - Most common grade 3 or higher treatment related AEs were arthralgia (11%), AST increased (9%), lipase increased (7%), and ALT increased (4%)
- CDX-1140 resulted in marked changes in the tumor microenvironment (TME) consistent with a more inflammatory and less immunosuppressive state
  - Interferon signaling and cytotoxicity pathways were most highly upregulated, while immunosuppression via TGFβ signaling and metastatic pathways were downregulated
  - First demonstration in patients of biological activity within the TME for systemically administered agonist anti-CD40 mAb
- Pretreatment of patients with CDX-301 greatly increases the number of circulating DCs prior to CDX-1140 administration
  - PBMC isolated from CDX-301 pretreated patients are more responsive to CDX-1140 than PBMC from non-pretreated patients
- Clinical activity was observed with CDX-1140 monotherapy and in combination with CDX-301
  - Ongoing complete response in a patient with follicular lymphoma along with stable disease and evidence of tumor necrosis in other patients treated with CDX1140 at 1.5 mg/kg
  - Clinical activity including uPR and tumor cavitation also observed during dose-escalation (SITC 2019)

Overall CDX-1140 with or without CDX-301 is well positioned for combination therapies which have initiated:

- Part 3: combination of CDX-1140 with pembrolizumab is concluding the safety run-in and will initiate expansion cohorts in SCCHN and NSCLC
- Part 4: combination of CDX-1140 + gemcitabine/nab-paclitaxel, which recently opened for patients with previously untreated metastatic pancreatic adenocarcinoma