Results from a phase 1 study of CDX-1140, a fully human anti-CD40 agonist monoclonal antibody (mAb), in combination with pembrolizumab

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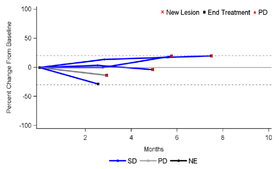
BACKGROUND

- CD40 signaling plays key roles in mediating anti-tumor innate and adaptive immune responses
  - In tumor models, anti-CD40 mAb therapy reinvigorates PD-1^{hi} exhausted T cells,[1] enabling anti-PD-1/L1 refractory tumors to respond to anti-PD-1/L1 therapy
  - In addition to enhancing anti-PD-1/L1 therapy, anti-CD40 mAb treatment has been shown to augment the activity of 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 engagement of CD40 within the tumor microenvironment (TME)
- CDX-1140: fully human IgG2 agonist anti-CD40 mAb[4]
  - 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 an anti-PD-1/L1 mAb (e.g., pembrolizumab), CDX-301 (recombinant Flt3L; a dendritic cell growth factor), or chemotherapy
- CDX1140-01 is a Phase 1 study of CDX-1140 alone or in combination with pembrolizumab, CDX-301, or chemotherapy in patients with advanced tumors (ClinicalTrials.gov: NCT03329950)
- Data from CDX-1140 monotherapy (n=58) and CDX-1140 in combination with CDX-301 (n=37) have been presented[5,6]. In summary:
  - MTD and RP2D was determined to be 1.5 mg/kg CDX-1140
  - Durable complete metabolic response was documented in a patient with Stage IV follicular lymphoma treated with CDX-1140
  - Unconfirmed iPR in 1 patient (gastric cancer) treated with CDX-1140 plus CDX-301
  - Tumor cavitation/necrosis and stable disease (see spider plot) was observed in some SCCHN patients, suggesting induction of productive anti-tumor immune responses and potential clinical benefit in patients who had previously progressed on anti-PD-1/L1 regimens
  - Expected pharmacodynamic activity observed in peripheral blood
  - CDX-1140 monotherapy resulted in marked changes in the TME consistent with a more inflammatory and less immunosuppressive state

Spider Plot of SCCHN Patients Treated with CDX-1140 Monotherapy at 1.5 mg/kg

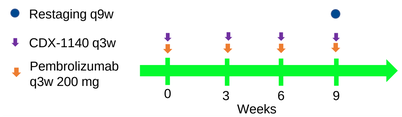


- Here we present data from the combination with pembrolizumab (data cut-off September 05, 2022)
  - Given the results observed with CDX-1140 monotherapy, SCCHN was chosen as an expansion cohort
  - NSCLC was also chosen as an expansion cohort
  - Both indications represent a large unmet medical need in patients with primary or secondary immune checkpoint refractory disease
  - The combination with pembrolizumab was done in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

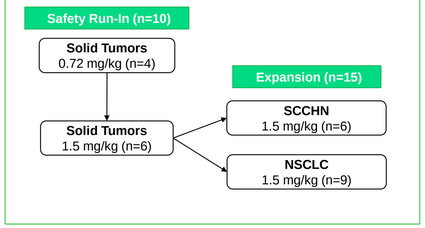
STUDY DESIGN AND METHODS

- Enrolled adults with locally advanced/metastatic solid tumors with documented progression on anti-PD-1/L1 regimen and no more than one prior anti-PD-1/L1 regimen
- Patients were treated with 0.72 mg/kg (safety run-in) or 1.5 mg/kg (safety run-in and expansion) CDX-1140 in combination with 200 mg pembrolizumab q3w; one cycle = 3 weeks
  - Protocol amendment permitted CDX-1140 dose reduction for patients treated with 1.5 mg/kg CDX-1140 (RP2D) in combination with 200 mg pembrolizumab who experience non-DLT grade 2 or grade 3 clinically significant treatment related adverse events, such as arthralgias, myalgias, and fatigue, that interfered with activities of daily living
- Primary clinical efficacy endpoint: ORR as determined by iRECIST

CDX-1140 + Pembrolizumab



CDX-1140 q3w + Pembrolizumab 200 mg q3w (n=25)



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RESULTS

CDX-1140 + Pembrolizumab Baseline Patient Characteristics

	Safety Run-in CDX-1140 + pembrolizumab		Expansion CDX-1140 + pembrolizumab	
	(N=4)	(N=6)	SCCHN (N=6)	NSCLC (N=9)
CDX-1140 dose	**0.72 mg/kg**	**1.5 mg/kg**	**1.5 mg/kg**	**1.5 mg/kg**
Age, years, median (min, max)	65.0 (51.0, 75.0)	68.5 (62.0, 74.0)	61.5 (53.0, 72.0)	70.0 (60.0, 78.0)
Sex, Male	1 (25.0)	5 (83.3)	6 (100)	4 (44.4)
Race				
White	4 (100)	5 (83.3)	5 (83.3)	9 (100)
White/Black	0	1 (16.7)	0	0
Asian	0	0	1 (16.7)	0
Ethnicity, not Hispanic or Latino, n (%)	4 (100)	6 (100)	6 (100)	9 (100)
Baseline ECOG performance status				
0	2 (50.0)	2 (33.3)	4 (66.7)	4 (44.4)
1	2 (50.0)	4 (66.7)	2 (33.3)	5 (55.6)
Median number of prior regimens (min, max)	3.5 (2.0, 6.0)	3.5 (2.0, 10.0)	3.0 (2.0, 5.0)	2.0 (1.0, 5.0)
Prior-chemotherapy	3 (75.0)	4 (66.7)	6 (100)	9 (100)
Prior-checkpoint inhibitor	4 (100)	6 (100)	6 (100)	9 (100)
Tumor type				
SCCHN	---	2 (33.3)	6 (100)	---
Oropharyngeal	---	1 (50.0)	3 (50.0)	---
HPV+	---	1 (100)	3 (100)	---
Prior cetuximab	---	1 (50.0)	3 (50.0)	---
PD-L1 status (historical data)	SCCHN: 1 patient PD-L1+; 7 patients PD-L1 status unknown			
NSCLC	1 (25.0)	---	---	9 (100)
Squamous	0	---	---	2 (22.2)
Non-squamous	1 (100)	---	---	7 (77.8)
PD-L1 status (historical data)	NSCLC: 2 patients PD-L1+; 4 patients PD-L1-; 4 patients PD-L1 status unknown			
Other (n=1 each subtype)	Colorectal Endometrial Renal Cell	Cholangiocarcinoma Esophageal Melanoma Renal Cell		

Data shown as n (%) unless indicated otherwise

Median duration of treatment for patients receiving CDX-1140 1.5 mg/kg + pembrolizumab 200 mg q3w was 2 cycles (range 1-16 cycles)

CDX-1140 + Pembrolizumab Safety

- CDX-1140 in combination with pembrolizumab has been generally well tolerated with most drug related adverse events being grade 1 or grade 2. There were no cases of pneumonitis and no drug related deaths
- 4 patients discontinued treatment due to CDX-1140 related toxicity (all at 1.5 mg/kg):
  - Arthralgia (n=2, grade 2)
  - Cytokine release syndrome (n=1, grade 2)
  - Diarrhea (n=1, grade 2)
  - Stomatitis (n=1, grade 3)
- CDX-1140 treatment related SAEs:
  - Cytokine release syndrome (n=1, grade 1; n=2, grade 2*)
  - Nausea (n=1, grade 3)
  - Esophagitis (n=1, grade 3*)
  - Vomiting (n=1, grade 3)
  - Diarrhea (n=1, grade 2)

*Esophagitis and cytokine release syndrome (n=1 grade 2) related to both CDX-1140 and pembrolizumab

CDX-1140 Treatment Related Adverse Events
CDX-1140 1.5 mg/kg + Pembrolizumab 200 mg q3w (n=21)

	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	≥ Grade 3
Preferred Term						
Number of Patients with Any Treatment Related AE	2 (9.5)	8 (38.1)	5 (23.8)	2 (9.5)	17 (81.0)	7 (33.3)
Arthralgia	3 (14.3)	4 (19.0)	3 (14.3)	0	10 (47.6)	3 (14.3)
Fatigue	2 (9.5)	6 (28.6)	2 (9.5)	0	10 (47.6)	2 (9.5)
Myalgia	4 (19.0)	3 (14.3)	1 (4.8)	0	8 (38.1)	1 (4.8)
Vomiting	3 (14.3)	3 (14.3)	1 (4.8)	0	7 (33.3)	1 (4.8)
Diarrhea	2 (9.5)	5 (23.8)	0	0	7 (33.3)	0
Pyrexia	4 (19.0)	2 (9.5)	0	0	6 (28.6)	0
Chills	6 (28.6)	0	0	0	6 (28.6)	0
Aspartate aminotransferase increased	3 (14.3)	1 (4.8)	2 (9.5)	0	6 (28.6)	2 (9.5)
Blood alkaline phosphatase increased	3 (14.3)	3 (14.3)	0	0	6 (28.6)	0
Hypotension	1 (4.8)	5 (23.8)	0	0	6 (28.6)	0
Nausea	3 (14.3)	1 (4.8)	1 (4.8)	0	5 (23.8)	1 (4.8)
Alanine aminotransferase increased	5 (23.8)	0	0	0	5 (23.8)	0
Cytokine release syndrome	2 (9.5)	2 (9.5)	0	0	4 (19.0)	0
Lymphocyte count decreased	0	1 (4.8)	1 (4.8)	2 (9.5)	4 (19.0)	3 (14.3)
Amylase increased	1 (4.8)	3 (14.3)	0	0	4 (19.0)	0
Lipase increased	0	0	3 (14.3)	1 (4.8)	4 (19.0)	4 (19.0)
Blood bilirubin increased	0	3 (14.3)	1 (4.8)	0	4 (19.0)	1 (4.8)
Platelet count decreased	1 (4.8)	1 (4.8)	0	0	2 (9.5)	0

Data shown as n (%)

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CR, complete response; DLT, dose limiting toxicity; IHC, immunohistochemistry; iPR, immune partial response; mAb, monoclonal antibody; mIF, multiplex immunofluorescence; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PD, progressive disease; PK, pharmacokinetics; PR, partial response; q3w, every 3 weeks; RP2D, recommended phase 2 dose; SAE, serious adverse event; SCCHN, squamous cell carcinoma head and neck; SD, stable disease TME, tumor microenvironment

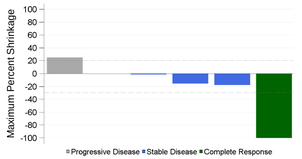
CDX-1140 + Pembrolizumab Clinical Activity

Clinical activity was seen in patients with SCCHN treated with CDX-1140 at 1.5 mg/kg in combination with pembrolizumab 200 mg q3w

Best Overall Response – Response Evaluable Population

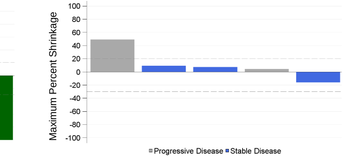
SCCHN

6 of 8 patients (includes safety run-in) were evaluable for response

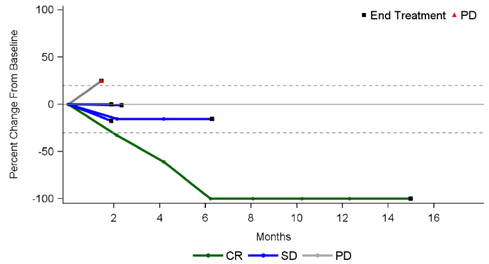


NSCLC

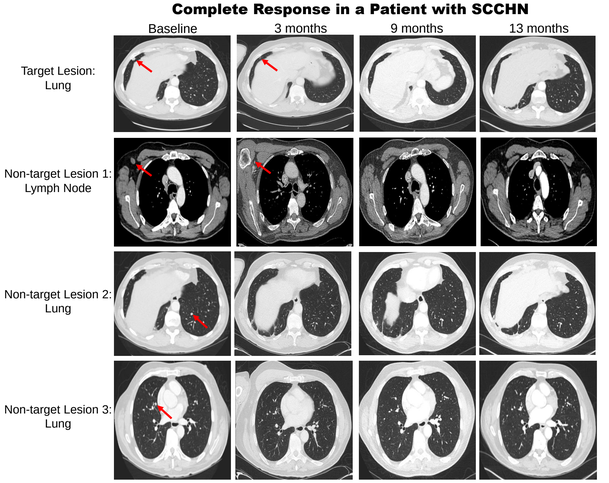
5 of 9 patients were evaluable for response



Spider Plot of SCCHN Patients Treated with 1.5 mg/kg CDX-1140 + pembrolizumab 200 mg q3w

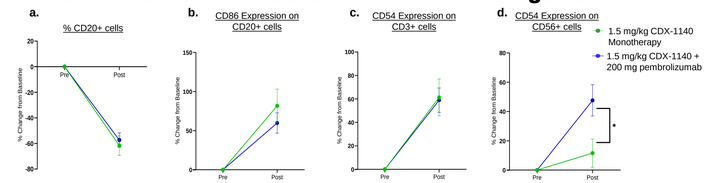


Complete Response in a Patient with SCCHN

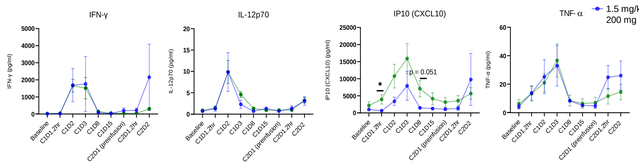


- 63-year-old male with HPV+ oropharyngeal SCCHN (PD-L1 status unknown)
- Prior treatments: cisplatin-RT; pembrolizumab; cetuximab; and docetaxel
  - Treated with pembrolizumab for 2 months, discontinued due to PD
- Discontinued CDX-1140 and pembrolizumab after 2 cycles due to arthralgias (grade 3) and CRS (grade 2)
- No subsequent anti-tumor therapy
- First restaging scan (3 months) demonstrated partial response; complete response noted at the 4th restaging scan (9 months)
- Durable CR maintained through most recent restaging scan, 16 months

Peripheral Immune Activation Is Observed in Monotherapy and Combination Arms Consistent with CD40 Agonism



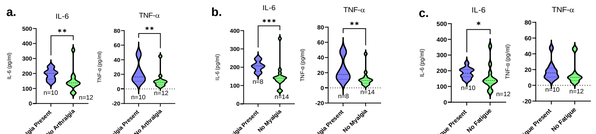
- Anticipated CD40 agonist pharmacodynamic effects were observed on total B cells **(a)** CD86+ B cells **(b)** CD54+ T cells **(c)** and CD54+ NK cells **(d)** in the monotherapy and combination treatment arms. Unpaired t-test were done to determine significance between the monotherapy (n = 13) and combination (n = 18) treatment arms. * = p ≤ 0.05



IFN-γ **(a),** IL12p70 **(b)**, IP10 **(c)** and TNF-α **(d)** concentrations detected in patient serum at baseline and on-treatment timepoints. The graphs are depicting the mean across patients in each group and standard error is shown. Multiple comparison unpaired t-tests with Welch correction were done comparing treatment arms at each timepoint. * = p ≤ 0.05

- There was no observed correlation between circulating immune markers and clinical outcome in either treatment arm.

CDX-1140 + Pembrolizumab Related Arthralgias, Myalgias, and Fatigue Are Associated with Cytokine Increases



On-treatment (C1D2) concentrations of TNF-α and IL-6 were associated with commonly reported adverse events; arthralgia **(a)** and myalgia **(b)** and/or fatigue **(c)** in the combination arm. No associations were noted between IL-6 or TNF-α concentrations with myalgias or fatigue in the monotherapy treatment arm (not shown). Nonparametric Mann Whitney Test was done to detect significance. * = p ≤ 0.05; ** = P ≤ 0.01; *** = P ≤ 0.001

CDX-1140 + Pembrolizumab Pharmacokinetics and Immunogenicity

- The PK profile of CDX-1140 1.5 mg/kg in combination with pembrolizumab 200 mg (mean half-life 2.0 days) is similar to the CDX-1140 1.5 mg/kg monotherapy PK profile (mean half-life 1.9 days) (not shown)
- The frequency of ADA response in patients that received CDX-1140 + pembrolizumab (32%) was similar to the frequency of ADA response in patients that received CDX-1140 monotherapy (24%); no impact on PK was observed

SUMMARY AND NEXT STEPS

- CDX-1140 at the RP2D of 1.5 mg/kg in combination with pembrolizumab 200 mg was generally well tolerated
  - The most common treatment related ≥ grade 3 adverse events were lipase increase (19%), arthralgia (14.3%), lymphocyte count decreased (14.3%), fatigue (9.5%) and aspartate transaminase increase (9.5%)
- Patients enrolled in the study had progressive disease on prior anti-PD-1/L1 based therapy yet evidence of clinical benefit was observed, particularly in patients with SCCHN
  - Of 8 SCCHN patients treated there was 1 CR ongoing at 16 months and 1 SD of 6 months duration
  - Of 9 NSCLC patients treated there were 4 patients with SD, including 1 SD of 13 months duration with a nadir in target lesions of -15% (not shown)
- Expected pharmacodynamic effects were observed in circulating immune populations and soluble immune markers from patients treated with CDX-1140 monotherapy and combination, with a significant difference detected in on-treatment IP10 (CXCL-10) concentrations and CD54 expression on NK cells from patients in the combination arm compared to the monotherapy arm
- Ongoing analyses of immune profiling of the tumor microenvironment using transcriptomics, as well as IHC and mIF of patient tumor biopsies
- Significant associations were observed with on-treatment concentrations of TNF-α and IL-6 in patients treated with CDX-1140 + pembrolizumab who experienced arthralgia, myalgia, and fatigue
  - The finding that increased pro-inflammatory cytokines associated with particular CDX-1140 related adverse events may suggest future preventative or treatment strategies
- This study adds to a growing body of evidence that anti-CD40 based therapy may help to overcome immune checkpoint resistance mechanisms[7]
- Future studies should focus on strategies to improve the activity of CDX-1140 in combination with checkpoint blockade, which may include exploring additional combinations as well as sequencing of combination agents, particularly in patients with SCCHN

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