A Phase 1 Dose-escalation Study of a PD-L1xCD27 Bispecific Antibody CDX-527 in Patients with Advanced Malignancies

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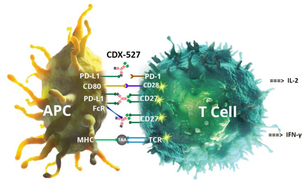
Introduction

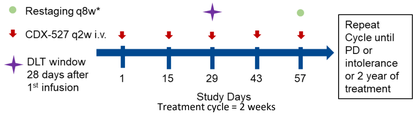
- CDX-527 is a bispecific antibody (BsAb) that is designed to block immune checkpoint PD-L1/PD-1 interactions while providing immune costimulation through CD27 signaling
- CD27 is a key immunostimulatory molecule that enhances T cell activation, effector function, and survival
- Combination of anti-PD-L1 and anti-CD27 mAbs is synergistic in preclinical studies, activating complementary cytotoxic and proliferative gene expression profiles, respectively[1]
- Agonist anti-CD27 mAbs (varlilumab and MK-5890) have been safely combined with checkpoint blockade with evidence of biological and clinical activity[2,3]
- Pre-clinical studies demonstrated enhanced T cell activation by CDX-527 and anti-tumor activity of a surrogate bispecific compared to individual mAb combinations[4]
- Preliminary safety, PK, and PD data are presented for the first 5 dose escalation cohorts in the CDX527-01 Phase 1 study



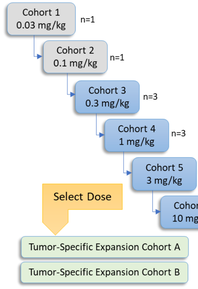
The PD-L1xCD27 bispecific antibody CDX-527 provides costimulatory signaling through CD27 when clustered through binding to FcR and/or PD-L1. Costimulation also occurs through CD28, mediated upon binding CD80 which becomes available by the blocking of cis-interactions between PD-L1 and CD80. CDX-527 binding to PD-L1 blocks PD-1 inhibition of T cell activation.

Methods

- First-in-human, open-label, non-randomized, multi-center, dose-escalation and tumor-specific expansion study to evaluate safety, PK, PD, and clinical activity of CDX-527 in patients with solid tumors refractory to SOC therapy



* After 1 year of treatment, tumor assessment will be every 12 weeks (± 1 week)



RESULTS

Baseline Patient Characteristics

	0.03 mg/kg (n=1)	0.1 mg/kg (n=1)	0.3 mg/kg (n=3)	1.0 mg/kg (n=3)	3.0 mg/kg (n=3)	Total (n=11)
Age, years median (range)	59	66	61 (56, 62)	59 (58, 63)	57 (56, 60)	59 (56, 66)
Sex, female	1 (100)	1 (100)	2 (67)	3 (100)	3 (100)	10 (91)
Race						
White	0	1 (100)	2 (67)	3 (100)	3 (100)	9 (82)
Black	1 (100)	0	1 (33)	0	0	2 (18)
Ethnicity, not Hispanic or Latino	1 (100)	1 (100)	3 (100)	3 (100)	2 (67)	10 (91)
Baseline ECOG						
1	1 (100)	1 (100)	3 (100)	3 (100)	3 (100)	11 (100)
Prior chemotherapy	1 (100)	1 (100)	3 (100)	3 (100)	2 (67)	10 (91)
Prior checkpoint inhibitor	0	0	1 (33)	1 (33)	1 (33)	3 (27)
No. prior regimens median (range)	4	6	3 (2, 11)	5 (3, 7)	4 (1, 8)	4 (1, 11)
Tumor type (n)*						
Breast	1		1			2
Ovarian		1		1	1	3
Endometrial			1	1		2
Cervical					1	1
Other			1	1	1	3

*Ovarian includes primary peritoneal carcinoma and fallopian tube carcinoma. Other tumor types: leiomyosarcoma (n=2) and thymic carcinoma.

- 11 patients have been treated as of the cut-off date; 3 remain on treatment; reason for treatment discontinuation: unconfirmed progression (n=5), confirmed progression (n=2), symptomatic deterioration (n=1); median treatment cycles = 4; median treatment follow-up = 55 days (30-134)

Treatment Related AEs*

CDX-527 Related AEs (Preferred Term)	0.03 mg/kg (n=1)	0.1 mg/kg (n=1)	0.3 mg/kg (n=3)	1.0 mg/kg (n=3)	3.0 mg/kg (n=3)	Total (n=11)
Arthralgia	1(100)	0	1(33.3)	0	1(33.3)	3(27.3)
Chills	0	0	0	1(33.3)	1(33.3)	2(18.2)
Fatigue	0	0	2(66.7)	0	0	2(18.2)
Influenza like illness	0	0	1(33.3)	1(33.3)	0	2(18.2)

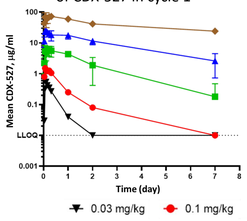
*CDX-527 related AEs occurring in 2 or more patients. CDX-527 related AEs occurring in 1 patient each were malaise, fever, pruritus, diarrhea, anemia, dyspepsia, herpes simplex reactivation, back pain, musculoskeletal chest pain, pain in extremity, headache, paraesthesia, atelectasis, and pleural effusion.

- All CDX-527 related AEs were grade 1 or grade 2
- No DLTs or CDX-527 related SAEs

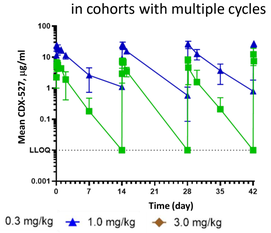
Data cut-off: April 16, 2021

Pharmacokinetics

Mean (± SD) serum concentration of CDX-527 in cycle 1

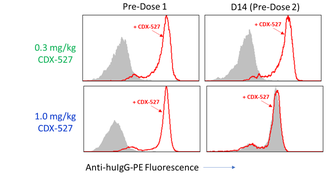


Mean (± SD) serum concentration of CDX-527 in cohorts with multiple cycles



- Exposure proportional to dose
- CDX-527 exposure maintained through dosing at 1 mg/kg
- No evidence of significant ADA impact

Receptor Occupancy

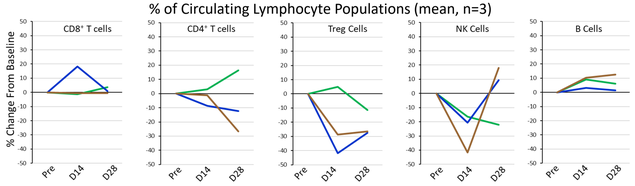


CDX-527 on T cells (CD4+) was detected with anti-hu-IgG-PE. Shaded histograms are direct staining, red histograms are with saturating amount of CDX-527 added. Representative histograms from 0.3 mg/kg and 1.0 mg/kg presented.

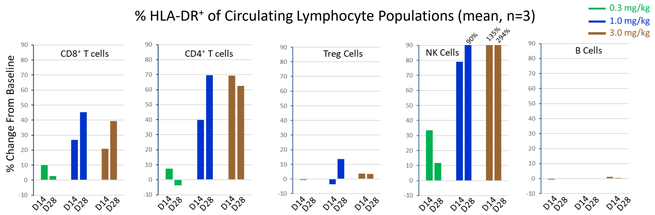
- Patients at 1 mg/kg maintain full receptor occupancy at day 14 prior to next dose

Flow Cytometry on PBMC

% of Circulating Lymphocyte Populations (mean, n=3)



% HLA-DR+ of Circulating Lymphocyte Populations (mean, n=3)

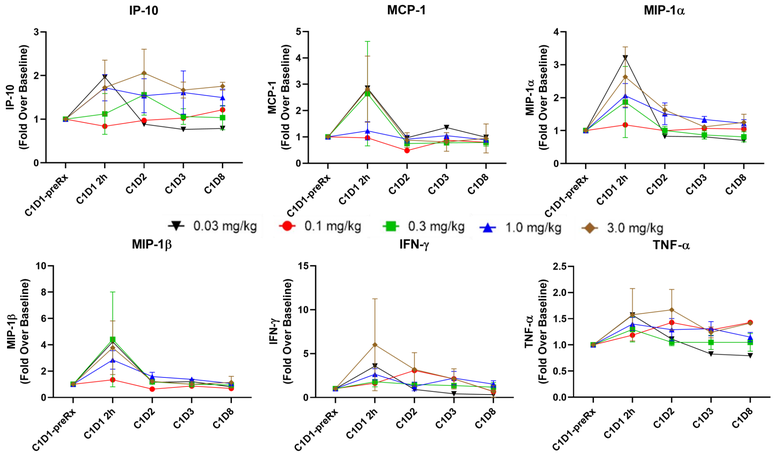


Flow cytometry analysis on PBMC collected from 0.3 and 1.0 mg/kg CDX-527 cohorts prior to dose 1-3.

- Maintained decrease in Treg and transient decrease in NK cells at higher dose levels
- Increase in T cell and NK cell activation at higher dose levels

Circulating Cytokines

Mean (± SEM) serum levels in cycle 1



Multiplex analysis of serum cytokines was carried out prior to dosing (C1D1-preRx) and through day 8 of the first cycle of treatment. Baseline-normalized means and SEMs are reported.

- Transient inflammatory cytokine increases consistent with CD27 stimulation were observed

SUMMARY & FUTURE DIRECTIONS

- These are the first-in-human data of CDX-527, a PD-L1xCD27 bispecific antibody that combines potent CD27-dependent T cell costimulatory signaling with blockade of the PD-1/PD-L1 inhibitory pathway
- Dose escalation of CDX-527 in patients with solid tumors has a good safety profile through 3 mg/kg
  - No DLT or treatment-related SAE
  - Currently enrolling at highest dose - 10 mg/kg
- Pharmacokinetics and receptor occupancy demonstrate good exposure starting at CDX-527 doses of 1 mg/kg
- Pharmacodynamic analysis demonstrate CDX-527 has biological activity consistent with immune activation
  - Transient increase in pro-inflammatory cytokines/chemokines
  - Upregulation of activation marker on T cells and particularly NK cells
  - Decrease in regulatory T cells
- These data support expansion into tumor specific cohorts for evaluation of clinical activity
  - Good safety, PK, PD and lack of immunogenicity are important hurdles for bispecific antibodies
  - Cohorts will be selected based on best opportunity to observe single agent activity

Abbreviations

Abbreviations: ADA, anti-drug antibody; AE, adverse event; C1D1, cycle 1 day 1; DLT, dose limiting toxicity; mAb, monoclonal antibody; PBMC, peripheral blood mononuclear cells; PD, pharmacodynamics; PK, pharmacokinetics; Rx, treatment; SAE, serious adverse event; SD, standard deviation; SEM, standard error of the mean; SOC, standard of care

References:

1. Buchan, S.L. et al. Clin. Can. Res. 2018
2. Sanborn, R.E. et al. ASCO 2018
3. Shapira-Frommer, R. et al. SITC 2019
4. Vitale, L.A. et al. Can. Immunol. Immunother. 2020

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