CDX527-01, a phase 1 dose-escalation and expansion study of the PD-L1xCD27 bispecific antibody CDX-527 in patients with advanced malignancies

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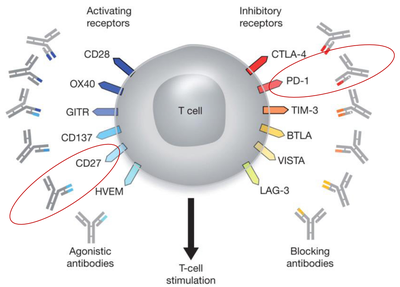
Background

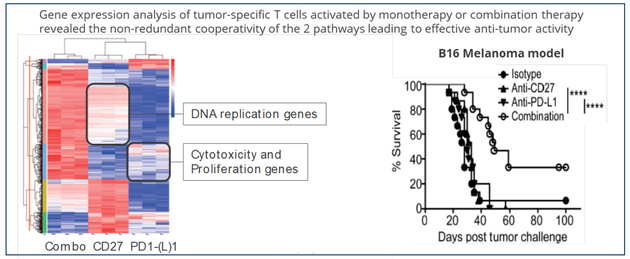
- Multiple pathways and receptor/ligand interactions have been shown to be important in controlling the immune response to cancer
- The use of bispecific antibodies (BsAbs) provides opportunities to engage two pathways with a single molecule and may provide advantages over combination therapy with separately administered antibodies
- In addition to simplifying development activities, combining two antibodies into one molecule can enhance the efficacy and improve the safety profile compared to separately administered antibodies
- CD27 agonism and PD-1 blockade elicit complementary signals mediating T cell activation and effector function
- Clinical studies combining an agonist anti-CD27 mAb, varlilumab[1,2], with nivolumab[3] (NCT02335918), or atezolizumab (NCT02543645), demonstrated that the combination regimen did not show additive toxicity and was associated with biological and clinical activity in a subset of patients
- CDX-527 is a novel human bispecific antibody containing a neutralizing, high affinity IgG1k PD-L1 mAb and the single chain Fv fragment (scFv) of an agonist anti-CD27 mAb genetically attached to the C-terminus of each heavy chain, thereby making CDX-527 bivalent for each target[4]

CD27 agonism and PD-1 inhibition are complementary pathways promoting T cell activation



Adapted from Mellman, I et al. Nature, 2011

Cooperative roles of anti-CD27 and PD-(L)1 drives proliferation and cytotoxicity of T cells



Clin. Cancer Res.; 24 (10), 2018

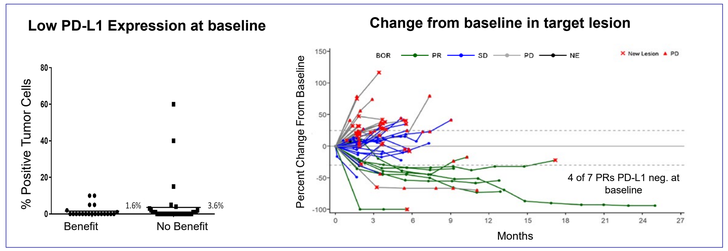
References:
1. Burris, et al. JCO, 2017
2. Ansell, et al. Blood Advances, 2019
3. Sanborn, et al. ASCO Annual Meeting, 2018
4. Vitale, et al. Cancer Immunol Immunother., 2020

ClinicalTrials.gov: NCT04440943

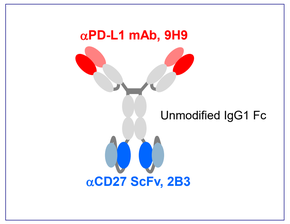
Clinical Experience with Varlilumab and PD-1 Blockade

- Combining varlilumab with either nivolumab or atezolizumab was well tolerated
  - Multiple regimens and varlilumab doses up to 10 mg/kg (nivolumab) with no MTD defined
- Durable responses observed in patients with "cold" tumors with low expectation of response to CPI monotherapy
  - Most experience in ovarian cancer cohort (response evaluable n=54 ORR 13%)
  - Very few patients had PD-L1 positive tumor cells at baseline, and these did not correlate with clinical benefit
  - Regimens with higher doses of varlilumab (3 mg/kg Q2W) trended towards better clinical activity than lower/less frequent dosing. Supports combining CD27 agonist and PD-1 blockade at fixed dose and schedule

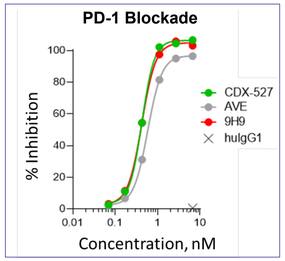
Ovarian Cancer patients treated with varlilumab and nivolumab[3]



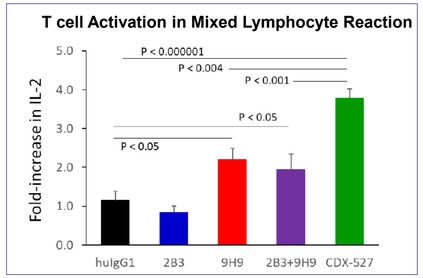
CDX-527



- Novel PD-L1 (9H9) and CD27 (2B3) mAbs were developed using human Ig transgenic mice
- Bispecific antibody generated with IgG-scFv format
  - Bivalent, high affinity binding for PD-L1 and CD27
  - Human IgG1 backbone to provide mAb-like pharmacokinetic (PK) profile
- CD27 cross-linking mediated by PD-L1 binding or binding to Fc receptors by the unmodified IgG1 Fc domain

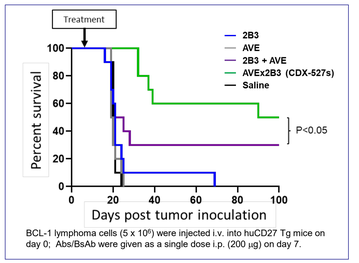


- CDX-527 is a potent PD-1 inhibitor
- PD-1 signal blockade was measured using a cell-based assay (Promega Cat # J1250). Anti-PD-L1 mAb, avelumab (AVE), used as reference



- CDX-527 is more effective than parental antibodies in MLR activity
- Allogeneic CD4 T cells and dendritic cells were prepared from independent PBMCs (n = 6) and incubated with mAbs or CDX-527 for 3 days.

Pre-clinical in vivo studies



BCL-1 lymphoma cells (5 x 10^6) were injected i.v. into huCD27 Tg mice on day 0; Abs/BsAb were given as a single dose i.p. (200 μg) on day 7.

- CDX-527 surrogate is more effective than parental antibodies in BCL-1 lymphoma model
- The CDX-527 mouse surrogate construct replaces the 9H9 PD-L1 CDRs with sequences from the PD-L1 mAb, avelumab (AVE). AVE binds to both human and mouse PD-L1. 2B3 does not cross-react with rodent CD27 but can be used in human CD27 transgenic mice

- PK study in cynomolgus macaques demonstrated T1/2 ~ 110 hours and development of anti-drug antibodies after 8 days
- Well tolerated in cynomolgus toxicology studies except for 2 animals at the highest dose tested who developed high titer anti-drug antibodies[4]

CDX-527-01 Study Design

- Phase 1 first-in-human, open-label, non-randomized, multi-center, dose-escalation and tumor-specific expansion study to evaluate safety, PK, pharmacodynamics (PD), and clinical activity of CDX-527
- The dose-escalation phase initiates with a single patient enrolled in cohort 1. In the absence of a dose limiting toxicity or any ≥ grade 2 treatment related AE, cohort 2 will enroll in a similar manner as cohort 1. Subsequent dose-escalation cohorts will be conducted in 3+3 manner
- In the tumor-specific expansion phase, up to 4 individual expansion cohort(s) of patients with specific solid tumors of interest may be enrolled to further characterize the safety, PK, PD, and efficacy of CDX-527

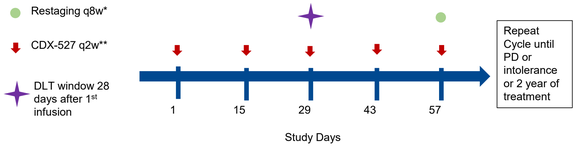
Study Portion	Cohort	CDX-527 Dose Level (mg/kg q2w)	Initial Patients (n)
Dose-Escalation	1	0.03	1-6
	2	0.1	1-6
	3	0.3	3-6
	4	1.0	3-6
	5	3.0	3-6
	6	10.0	3-6
Tumor-Specific Expansion Cohorts	7-10	Dose(s) chosen during escalation	Up to 15 per cohort

Abbreviations: BsAbs, bispecific antibodies; mAb, monoclonal antibody; scFv, single chain Fv fragment; ORR, overall response rate; IgG1, immunoglobin G; PK pharmacokinetics; PD, pharmacodynamics, AE, adverse events; AVE, avelumab; MLR, mixed lymphocyte reaction; PBMC, peripheral blood mononuclear cell; iRECIST, immune Response Criteria in Solid Tumors; DLT, dose limiting toxicity; i.v. intravenous injection; i.p., intraperitoneal injection; MTD, maximum tolerated dose

Eligibility Criteria

Key Inclusion	Key Exclusion
Male or female patient ≥ 18 years of age	Previous treatment with any anti-CD27 antibody
Recurrent, locally advanced or metastatic solid tumor cancer excluding the following: MSI-low colorectal cancer, glioblastoma multiforme, prostate cancer, pancreatic cancer, mucosal and ocular melanoma	Patients must have no more than one prior anti-PD-1/L1 for tumor types which have anti-PD-1/L1 approved for that indication and no prior anti-PD-1/L1 for tumor types that do not have anti-PD-1/L1 approved for that indication
Receipt of all standard therapies for the tumor type	Major surgery within 4 weeks prior to study treatment
Measurable (target) disease by iRECIST	History of (non-infectious) pneumonitis or has current pneumonitis
Life expectancy ≥ 12 weeks	Use of immunosuppressive medications within 4 weeks or systemic corticosteroids within 2 weeks prior to study treatment

Treatment Scheme



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

**A treatment cycle is 2 weeks long

Key Study Objectives

- Primary dose escalation objective is to determine the CDX-527 maximum tolerated dose and to select a dose level for study in the expansion phase
- Key secondary clinical objectives include characterization of the safety profile, and to determine the preliminary anti-tumor activity, the PK and PD profile, and the immunogenicity of CDX-527
- Exploratory objectives include determination of the PD effects of CDX-527 in blood and tumor tissue

Summary and Study Status

- CDX-527: highly potent inhibitor of PD-1 signaling and strong CD27 agonist combines key mechanisms for generating anti-tumor immune responses
- The CDX527-01 study is open for enrollment
- Participating study sites:
  - Providence Cancer Center, Portland, OR
  - Northside Hospital, Georgia Cancer Specialists, Atlanta, GA
  - Duke University Medical Center, Durham, NC
  - University of Chicago, Comprehensive Cancer Center, Chicago, IL