A Phase I Study of an Agonist Anti-CD27 Human Antibody (CDX-1127) in Patients with Advanced Hematologic Malignancies or Solid Tumors

Initial Report of Dose-Escalation in Solid Tumors

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CDX-1127: A fully human mAb to CD27

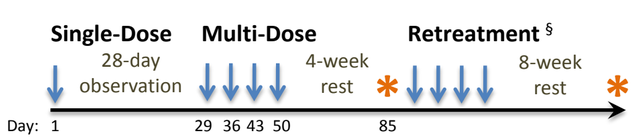
- CD27 is a potent co-stimulatory molecule that drives T cell activation and survival through interaction with CD70.
- CDX-1127 is an agonist anti-CD27 IgG1 mAb that induces activation and proliferation of human T cells when combined with T-cell receptor stimulation.
  - CDX-1127 has been shown effective in murine tumor models alone, and now in combination with chemotherapy or check-point inhibitors (poster 85).

Phase 1 Clinical Study Design

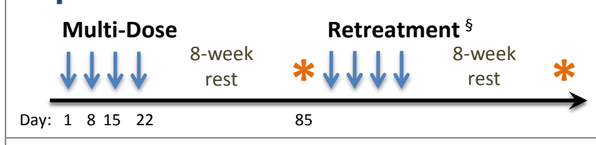
- Two study arms: Hematologic Malignancies (poster 144) and Solid Tumors
- Solid tumor patient eligibility:
  - Histologic diagnosis of:
    - metastatic melanoma
    - renal cell carcinoma
    - hormone-refractory prostate adenocarcinoma
    - ovarian cancer
    - colorectal adenocarcinoma
    - non-small cell lung cancer
  - Progressive disease subsequent to previous therapies; no remaining approved therapy options
  - Washout from prior therapies including:
    - ≥4 weeks for chemotherapy (or 5 half-lives, if longer), monoclonal based therapies and systemic radiation
    - ≥2 weeks for all other immunotherapy
- Standard 3+3 dose-escalation (0.1, 0.3, 1, 3 or 10 mg/kg)
  - Weekly dosing to establish safety with maximum exposure
- Subsequent malignancy-specific expansion cohorts to further characterize activity of CDX-1127

Treatment Schema

Dose-Escalation Phase



Expansion Cohorts



CDX-1127: 90-minute IV infusion

Diagnostic Imaging/Staging performed every 85 days

§ *Up to 4 retreatment cycles (5 cycles total) permitted*

Solid Tumor Dose-Escalation Results

- Dose-Escalation is complete

Pre-Treatment Patient Characteristics (n=25)

Age, years [median (range)]		66 (42-83)
Male [n(%)]		16 (64%)
ECOG Performance Status [n (%)]	0	11 (44%)
	1	14 (56%)
Tumor Types [n (%)]	CRC	10 (40%)
	Melanoma	7 (28%)
	Ovarian	3 (12%)
	Prostate	2 (8%)
	RCC	2 (8%)
	NSCLC	1 (4%)
Stage at Study Entry [n (%)]	III	2 (8%)
	IV	23 (92%)
Duration of Disease, years [mean (range)]		6.7 (1-24)
Lines of treatment [median (range)]	Anticancer therapy	5 (0-8)
	Cytotoxic chemotherapy	3 (0-8)
Prior treatments received [n (%)]	Radiation	14 (56%)
	Immunotherapy	6 (24%)

Solid Tumor Dose-Escalation Results (continued)

Safety

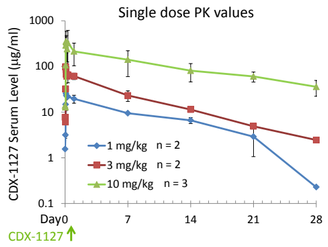
- CDX-1127 administration associated with minimal toxicity
- 10 mg/kg dose level reached without identification of a Maximum Tolerated Dose (MTD)
- One DLT: Grade 3 transient asymptomatic hyponatremiia 14 days after the single dose (1.0 mg/kg)
- No additional DLT or treatment-related toxicity resulting in treatment discontinuation

Treatment-Related Adverse Events (n=25)

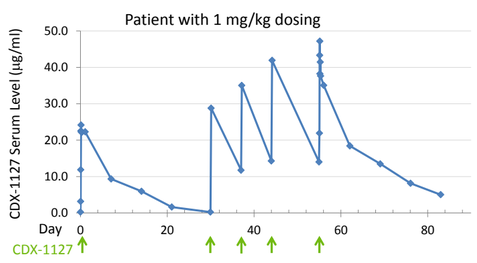
	Grade 1	Grade 2	Grade 3	Overall
Decreased appetite	2 (8%)	-	1 (4%)	3 (12%)
Fatigue	3 (12%)	-	-	3 (12%)
Chills	1 (4%)	1 (4%)	-	2 (8%)
Diarrhea	2 (8%)	-	-	2 (8%)
Hyperhidrosis	2 (8%)	-	-	2 (8%)
Peripheral edema	2 (8%)	-	-	2 (8%)
Rash maculo-papular	2 (8%)	-	-	2 (8%)
Herpes zoster	-	1 (4%)	-	1 (4%)
Hyponatremia	-	-	1 (4%)	1 (4%)
Lymphopenia	-	-	1 (4%)	1 (4%)

Table does not include grade 1 adverse events that occurred in one patient.

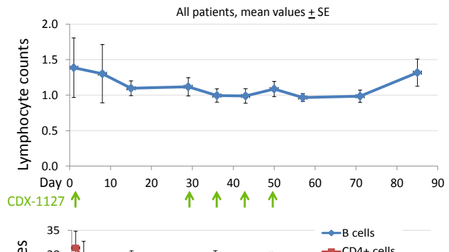
Preliminary pharmacokinetic analysis

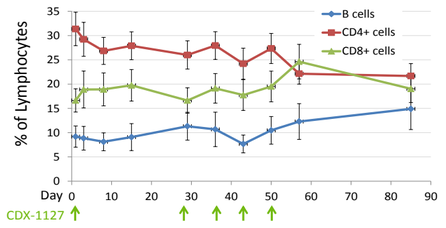


- Preliminary PK was performed on several patients
- Dose accumulation is observed during multi-dose phase
- Good drug exposure even at lower dose levels



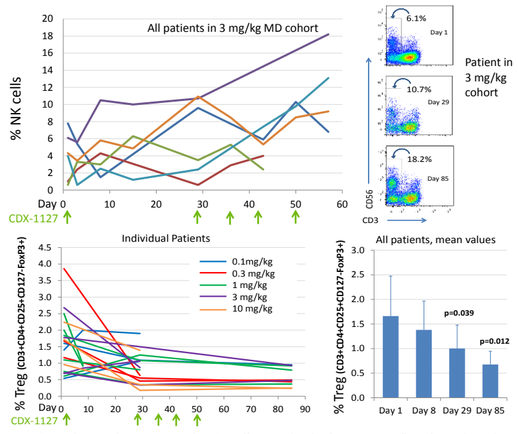
Circulating lymphocyte levels





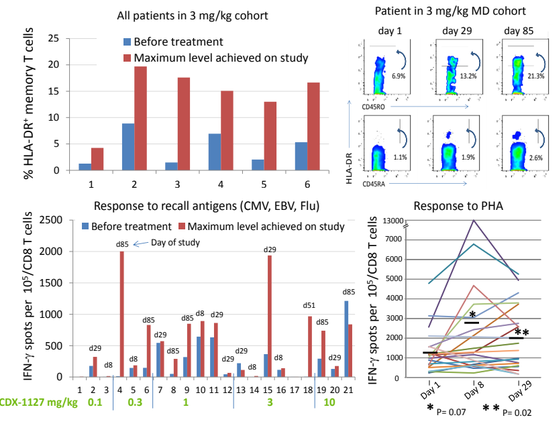
- No evidence of major depletion of lymphocytes
- Some trends observed without correlation to dose levels

Circulating levels of NK cells and Tregs



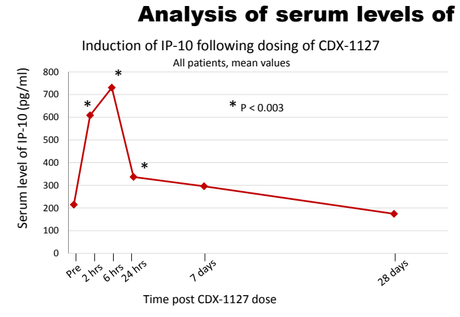
- Consistent increase of NK cells particularly at 3 mg/kg dose level
- NK cells are CD56 dim, consistent with higher cytolytic function
- Significant decrease in regulatory T cells across various dose levels
- Similar changes observed when analyzed as absolute numbers

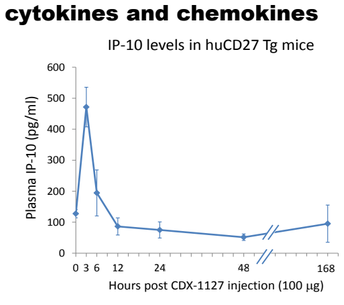
T cell Activation and Functional analysis

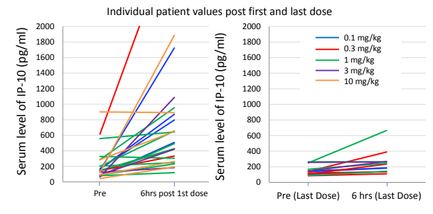


- Increased expression of the activation marker, HLA-DR
- No evidence of decreased T cell memory response, some patients show marked increases in response to recall antigens
- improved response to a non-specific stimulant

Analysis of serum levels of cytokines and chemokines







Cytokine/chemokine response consistent with MoA

- Significant increase in serum IP-10 levels implicates INF-γ release by T or NK cells activated via CD27
- Smaller increase in IL-6 and MCP-1 levels with similar kinetics, other cytokines showed variable patterns among patients
- The induction of IP-10 is consistent with the response to CDX-1127 administration to human CD27 transgenic mice

Activity to Date

- Four patients with stable disease (3.0, 3.8, 5.7, 14+ months)
- An 83 year old male with Stage IV renal cell carcinoma metastatic to liver and lung has completed 5 cycles of CDX-1127 (3.0 mg/kg) and remains progression-free without tumor growth at 14+ months after study entry
  - Patient previously progressed on prior therapies at 3 months (sorafenib/everolimus) and 9 months (capecitabine)
- A 69 year old man with Stage IV colorectal cancer metastatic to liver, lung and peritoneum was treated with CDX-1127 (1 mg/kg) and had 33% unidimensional shrinkage of measurable disease at 5.7 months
  - Shrinkage was associated with new lesions, representing a mixed response. By immune related (IR) response criteria (Wolchok 2009) the patient had irSD with 45% shrinkage.
  - Patient had previously received 3 lines of therapy, including bevacizumab/FOLFIRI/investigational therapy, and progressed after two weeks of capecitabine/radiation.
- A 66 year old male with Stage IV melanoma with visceral metastases was progression-free until 3.8 months.
  - Patient previously progressed through IL-2 at 2 months, ipilimumab within 4 months and two rounds of chemotherapy

Solid Tumor Expansion Cohort Status

- Expansion cohorts initiated to estimate single agent activity and better define safety in potential combination study populations
- 3 mg/kg dose selected based upon immunological activity in dose escalation and preclinical modeling
- CDX-1127 well-tolerated to date
- Several tumor biopsies have been collected to assess the effect of treatment on the tumor microenvironment

Melanoma:

- 14 patients enrolled; 8 continue treatment
- 7 patients not yet seen for 1st response assessment
- A uveal melanoma patient has maintained stable disease for 5.7 months and is entering third treatment cycle.
  - 12% shrinkage of measurable disease

Renal Cell:

- 8 patients enrolled
- 7 patients not yet seen for 1st response assessment
- 1 patient had progressive disease at day 85

Conclusions:

- CDX-1127 (up to 21 infusions over 14 months) have been well-tolerated with minimal toxicity
- CDX-1127 induces immunologic activity, consistent with mechanism of action
  - Increase in serum IP-10 levels
  - Decrease in Treg
  - Increased NK cells
  - T cell activation (MHC Class II & functional response)
  - No evidence of broad T cell depletion
- Preliminary evidence of anti-tumor activity in refractory tumors, which is being explored in expansion cohorts
- The combined safety and activity data from the hematologic and solid tumor arms of this phase 1 study strongly support the further development of CDX-1127, particularly in combination therapy.

Celldex therapeutics