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

Early Data from Ongoing Dose-Escalation in Hematologic Malignancies

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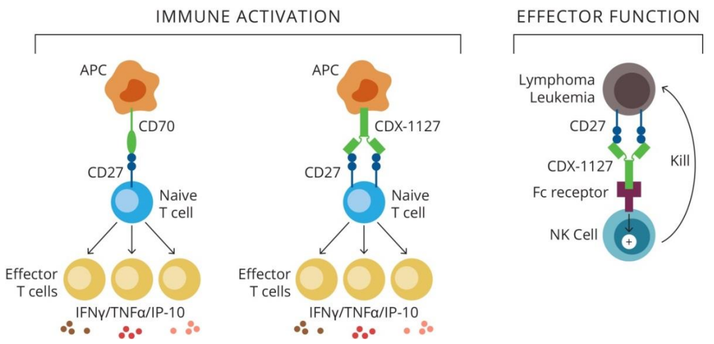
CDX-1127: A fully human mAb to CD27

- 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).
- CD27 can be expressed at high levels on lymphoma and leukemia cells, presenting a target for direct anti-tumor effects.
  - CDX-1127 promotes antibody-dependent cell-mediated cytotoxicity of lymphoma cells and has potent anti-tumor effects in xenograft models of human lymphoma cell lines.
- In hematologic malignancies, CDX-1127 may induce anti-tumor activity by both immune activation and direct effector function:

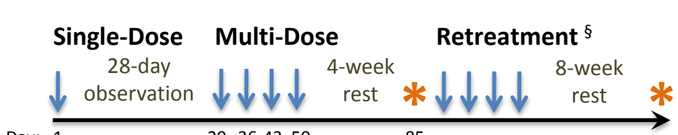


Phase 1 Clinical Study Design

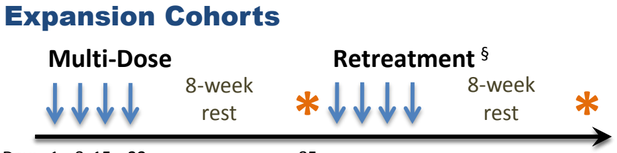
- Two study arms: Hematologic Malignancies and Solid Tumors (poster 146)
- Hematologic malignancy eligibility:
  - Histologic diagnosis of a B cell hematologic malignancy that may express CD27, including but not limited to:
    - chronic lymphocytic leukemia
    - Burkitt's lymphoma
    - mantle cell lymphoma
    - primary lymphoma of the central nervous system
    - marginal zone B cell lymphoma
  - 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
- Potential for 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*

Dose-Escalation Phase Results To Date

- Seventeen patients have been treated with CDX-1127 from 0.1 to 3 mg/kg.
- The final dose level (10 mg/kg) is open to accrual.

Baseline Patient Characteristics (n=17)

Age, years [median (range)]		63 (23-92)
Male [n(%)]		12 (71%)
ECOG Performance Status [n (%)]	0	5 (29%)
	1	12 (71%)
Tumor Types [n (%)]	Diffuse large B-cell	8 (47%)
	Follicular	4 (24%)
	Hodgkin	3 (18%)
	Marginal zone	1 (6%)
	Non-hodgkin B-cell, NOS	1 (6%)
Stage at Study Entry [n (%)]	I	2 (12%)
	II	1 (6%)
	III	3 (18%)
	IV	11 (65%)
Duration of Disease, years [median (range)]		5.3 (0.7-26.9)
Lines of treatment [median (range)]	Anticancer therapy	4.0 (1-12)
	Cytotoxic chemotherapy	3.0 (1-9)
Prior treatments received [n (%)]	Radiation	8 (47%)
	Autologous Transplant	7 (41%)

Safety

- No DLT, treatment-related SAEs, or toxicity resulting in discontinuation of CDX-1127 reported to date

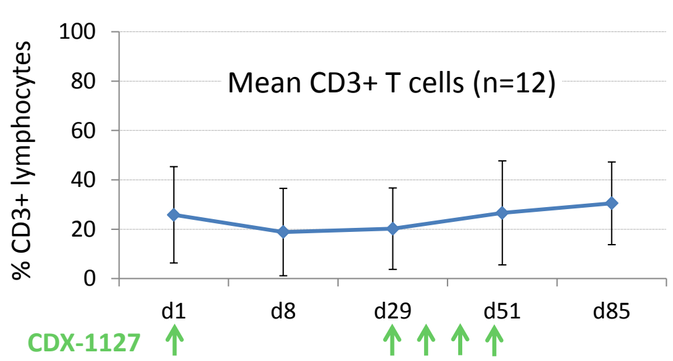
Treatment-Related Adverse Events (n=12)

	CTCAE Grade 1	CTCAE Grade 2	Overall
Fatigue	3 (25%)	3 (25%)	6 (50%)
Anemia	3 (25%)		3 (25%)
Decreased appetite	3 (25%)		3 (25%)
Nausea	3 (25%)		3 (25%)
Abdominal pain	2 (17%)		2 (17%)
Blood alkaline phosphatase increased		2 (17%)	2 (17%)
Hyperglycemia	2 (17%)		2 (17%)
Vomiting	2 (17%)		2 (17%)
Neutropenia		1 (8%)	1 (8%)

Adverse Event data has been reported for twelve patients treated with CDX-1127 from 0.1 to 1 mg/kg. Table does not include grade 1 adverse events that occurred in one patient.

Pharmacokinetics and Immune Monitoring

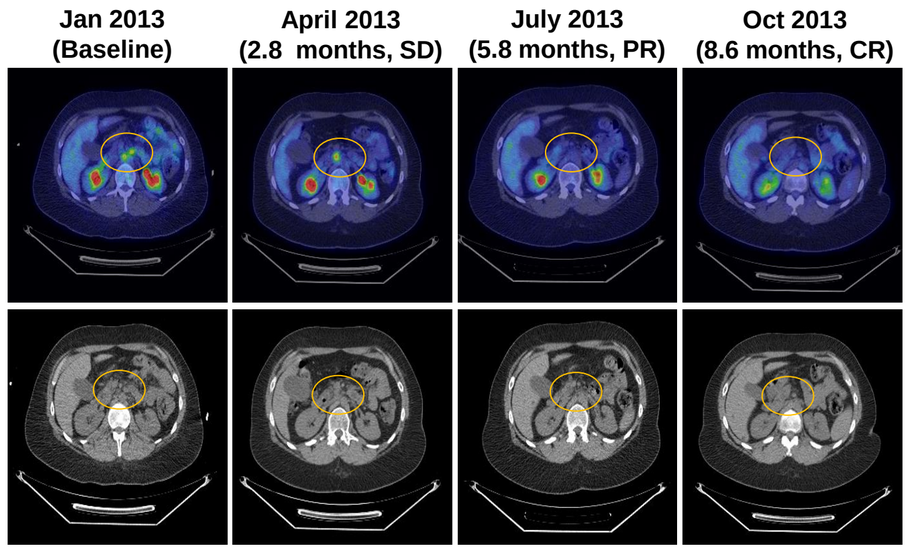
- Pending analyses:
  - Flow cytometry on PBMC
  - Serum cytokine and chemokine levels
  - Gene expression profiling on PBMC
- Preliminary analysis shows no significant depletion of T cells



Preliminary Activity

- Through the 1 mg/kg dose level, one patient has experienced a Complete Response (ongoing at 8.6 months) and three patients have had Stable Disease (durations of 4.5, 5.6 and 14 months).
- 28 year old female with Stage IV Hodgkin lymphoma with para-aortic involvement achieved a Complete Response after three cycles of CDX-1127 (0.3 mg/kg), and remains in remission at 8.6+ months (shown below).
  - Area of measurable lesions first increased by 9%, then regressed to achievement of a complete response. Pattern is consistent with an immune-mediated response.
  - Response was associated with complete resolution of B symptoms (drenching sweats, pruritus and weight loss).
  - Patient had previously received 5 lines of chemotherapy, including:
    - AVBD for two months, then switched to BEACOPP, with progression at 5 months
    - Carboplatin/gemcitabine, with progression at one year
    - Brentuximab vedotin with ICE, with progression at < 1 month
    - BEAM and autologous transplant, with progression at four months
- 67 year old male with Stage III marginal zone B-cell lymphoma who received CDX-1127 (0.3 mg/kg) experienced 36% shrinkage of measurable disease, including complete disappearance of disease in inguinal and iliac regions
  - PFS of 5.6 months
  - Repeatedly treated with 9 prior courses of therapy including combination chemotherapy, rituximab, ibritumomab tiuxetan and traditional radiation therapy
- 52 year old male with Stage IV follicular lymphoma had a PFS of 14 months while receiving CDX-1127 (0.3 mg/kg for single dose, then 0.1 mg/kg for 5 treatment cycles).
- Response assessments are pending for 1 patient treated with CDX-1127 at 1 mg/kg and all 3 patients treated at 3 mg/kg.

Stage IV Hodgkin lymphoma patient with Complete Response after three cycles of CDX-1127 (0.3 mg/kg)



Conclusions:

- CDX-1127 (through 3 mg/kg) has been well-tolerated with minimal toxicity in patients with B cell lymphoma
- Immune activation data are pending. Preliminary analysis shows no significant change in circulating T cell levels.
- Anti-lymphoma activity is supported by a Complete Response seen in a patient with heavily pretreated Hodgkin Disease
  - Activity data for the 3 and 10 mg/kg cohorts are pending
- 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