Phase I Evaluation of an Agonist Anti-CD27 Human Antibody (Varlilumab [CDX-1127]) in Patients with Advanced Hematologic Malignancies

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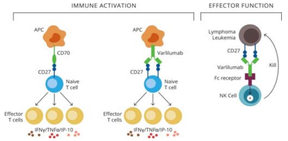
Varlilumab (CDX-1127): A Fully Human Monoclonal Antibody to CD27

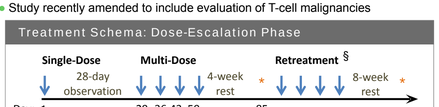
- CD27 is a potent co-stimulatory molecule that drives T cell activation and survival through interaction with CD70.
- Varlilumab is an agonist anti-CD27 IgG1 mAb that induces activation and proliferation of human T cells when combined with T-cell receptor stimulation.
  - Varlilumab has been shown effective in syngeneic murine tumor models alone, and in combination with chemotherapy or check-point inhibitors.
- CD27 can be expressed at high levels on lymphoma and leukemia cells, presenting a target for direct anti-tumor effects.
  - Varlilumab has potent anti-tumor effects in xenograft models of human lymphoma cell lines and promotes antibody-dependent cell-mediated cytotoxicity.
- In hematologic malignancies, varlilumab 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 (Abstract #3027/Poster Board: #19)
- Hematologic malignancy patient eligibility:
  - Histologic diagnosis of a B cell hematologic malignancy that may express CD27
  - 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 varlilumab
- Study recently amended to include evaluation of T-cell malignancies

Treatment Schema: Dose-Escalation Phase



↓ *Varlilumab: 90-minute IV infusion*
* *Diagnostic Imaging/Staging performed every 85 days*
§ *Up to 4 retreatment cycles (5 cycles total) permitted for patients with Stable Disease*

Patient Characteristics/Disease History

		Dose-Escalation (n=24)
Age, years [median (range)]		61 (23-92)
≥ 65 [n(%)]		8 (33%)
Male [n(%)]		16 (67%)
ECOG Performance Status [n (%)]	0	8 (33%)
	1	16 (67%)
Tumor Types [n (%)]	Diffuse large B-cell (DLBCL)	10 (42%)
	Follicular	5 (21%)
	Hodgkin	7 (29%)
	Non-Hodgkin B-cell, NOS	2 (8%)
Stage at Study Entry [n (%)]	II	1 (4%)
	III	5 (21%)
	IV	18 (75%)
Duration of Disease, years [median (range)]		4.7 (0.7-26.9)
Lines of treatment [median (range)]	Anticancer therapy	5.0 (1-12)
	Cytotoxic chemotherapy	3.0 (1-9)
Prior treatments received [n (%)]	Radiation	14 (58%)
	Autologous Transplant	11 (46%)
CD27 expression in tumor cells (IHC) [n (%)]	Follicular (n=2)	2 (100%)
	Hodgkin (n=3)	0 (0%)
	DLBCL (n=4)	0 (0%)

Dosing and Toxicity

- No dose-limiting toxicity (DLT) or identification of a Maximum Tolerated Dose (MTD)
- Infrequent treatment-related AEs; nearly all mild to moderate in severity
  - One patient discontinued treatment due to grade 1 vision changes
- No indication of immune-mediated adverse events (colitis, endocrinopathies, etc.) typically associated with check-point blockade

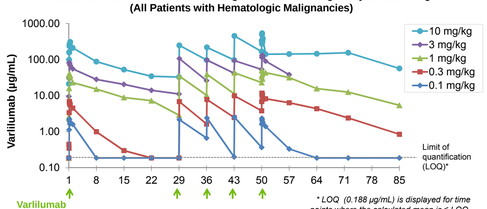
Treatment-Related Adverse Events

	CTCAE Grade 1	CTCAE Grade 2	All Grades
Any Treatment-Related Event	7 (29)	6 (25)	13 (54)
Fatigue	3 (13)	3 (13)	6 (25)
Decreased appetite	4 (17)		4 (17)
Anemia	2 (8)	1 (4)	3 (13)
Nausea	3 (13)		3 (13)
Diarrhea	2 (8)		2 (8)
Vomiting	2 (8)		2 (8)
ALT increased	1 (4)	1 (4)	2 (8)
AST increased	1 (4)	1 (4)	2 (8)
Headache	1 (4)	1 (4)	2 (8)
Blood alkaline phosphatase increased		1 (4)	1 (4)
Neutropenia		1 (4)	1 (4)
Hypotension		1 (4)	1 (4)

Table does not include grade 1 adverse events that occurred in one patient. Patients with multiple occurrences of an event are counted only once at the greatest severity experienced.
No grade 3, 4 or 5 treatment-related adverse events have been reported.

Varlilumab Pharmacokinetics

Varlilumab Serum Levels After a Single Dose and through 1 Cycle of Dosing (All Patients with Hematologic Malignancies)



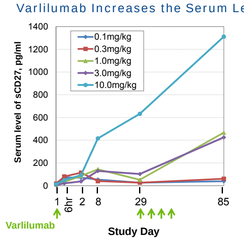
** LOQ (0.188 µg/mL) is displayed for time points where the calculated mean is ≤ LOQ.*

Pharmacokinetics similar for patients with solid tumors and hematologic malignancies.
For all pooled patients:
- $T_{1/2}$ ranged from 6 days at 1.0 mg/kg to 10.6 days at 10 mg/kg in day 1 dosing
- Vd range 21-51 mL/kg (1680-4080 mL) ≡ serum volume of 3000 mL
- Exposure was linear across dose groups from 0.3-10 mg/kg

Immunogenicity

- No anti-varlilumab antibody responses detected in patients with hematologic malignancies

Varlilumab Increases the Serum Level of Soluble CD27

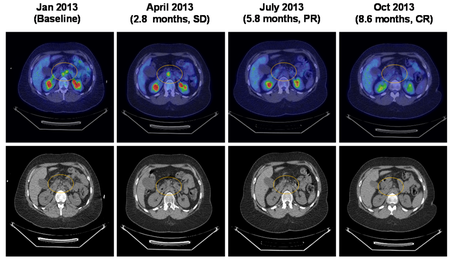


- sCD27 was measured with an ELISA using antibodies that bind to CD27 at non-competing sites with varlilumab.
- Increases in sCD27 are dose dependent and increase with time.
- Nonclinical models indicate that the increase in sCD27 is largely mediated through stabilization of sCD27 by complexing with the antibody. The anti-VEGF antibody (bevacizumab) similarly stabilizes serum VEGF levels (ref. 1,2).
- Increased sCD27 is consistent with an inflammatory effect and has been recently associated with improved response to immunotherapy (ref. 3).

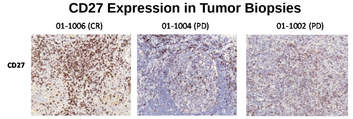
Clinical Activity

- Dose-escalation is complete with 24 patients enrolled.
  - 2 patients (10 mg/kg) continue on treatment with first response assessment pending
- One patient has experienced a Complete Response (ongoing at 12.9 months; see adjacent panel)
- Three patients have had Stable Disease (durations of 4.5, 5.6 and 14 months).
  - 67 year old male with Stage III non-Hodgkin lymphoma who received varlilumab (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
    - Nine 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 varlilumab (0.3 mg/kg for single dose, then 0.1 mg/kg for 5 treatment cycles)
  - 58 year old male with Stage IV follicular lymphoma had a PFS of 4.5 months while receiving varlilumab (0.1 mg/kg)
    - Six prior courses of therapy including combination chemotherapy, rituximab, ibritumomab tiuxetan, and experimental therapy.

Stage IV Hodgkin Lymphoma Patient with Complete Response



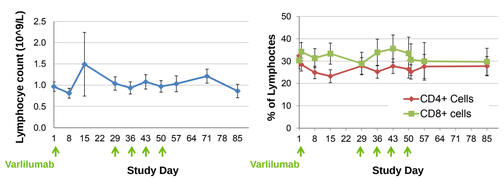
CD27 Expression in Tumor Biopsies



- 28 year old female with Stage IV Hodgkin lymphoma with para-aortic involvement
  - Inadequate response to induction, and progression through or shortly thereafter four subsequent salvage attempts
  - Most recently, had progressed 4 months after multiple sequential myeloablative chemotherapy with hematopoietic stem cell rescue followed by brentuximab vedotin consolidation
- Complete Response (CR) after three cycles of varlilumab (0.3 mg/kg)
  - Area of measurable lesions first increased by 9%, then regressed to achievement of CR.
  - B symptoms (drenching sweats, pruritus and weight loss) completely resolved
  - Remains in remission at 12.9+ months
- Reed-Sternberg cells lacked detectable CD27 expression
- CD27 expressing lymphocytes present in inflammatory infiltrate
  - CD27+ T cell infiltrates more pronounced relative to 2 other Hodgkin patients

Six additional Hodgkin patients treated:
- One (10 mg/kg) has not yet been seen for the first tumor response assessment
- One (10 mg/kg) discontinued study due to treatment-related vision changes prior to first response assessment
- Three (0.1, 0.3 and 10 mg/kg) had progression of disease by the first response assessment
- One (10 mg/kg) died due to disease progression prior to first response assessment

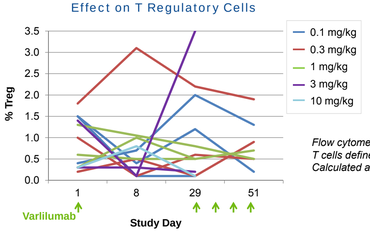
Varlilumab Does Not Significantly Deplete Lymphocyte, B or T Cell Count



Mean values shown for all patients across all dose levels

- Absolute lymphocyte counts are not markedly changed.
- Flow cytometry showed similar levels of CD4+ and CD8+ T cells throughout treatment.

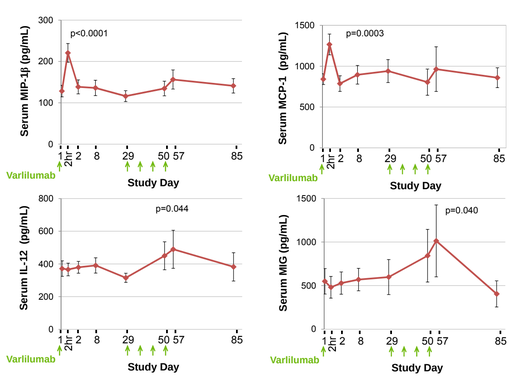
Effect on T Regulatory Cells



Flow cytometry analysis of regulatory T cells defined as CD4+FoxP3+ cells. Calculated as % of total lymphocytes.

- Significant reduction in T regulatory cells observed in 50% of varlilumab-treated patients analyzed to date

Varlilumab Induces Pro-inflammatory Cytokine Secretion



Mean values shown for all patients across all dose levels
Cytokines measured by Luminex

- Early induction of MIP-1β and MCP-1 (at 2 hours post dose) and later induction of IL-12 and MIG
  - Other cytokines with significant early induction include IL-6, IL-8 and MIP-1α (not shown)
- No increase in IP-10 noted (increased IP-10 was observed in dose-escalation in patients with solid tumors)

Conclusions:

- Varlilumab has minimal toxicity in patients with B cell lymphoma, even in the elderly
- PK profile is dose proportional, consistent with human antibodies and similar in patients with solid tumors and hematologic malignancies
  - Dose accumulation is observed during multi-dose phase
  - Good drug exposure even at lower dose levels
  - Clearance is seen at low doses given less frequently than weekly
- No anti-varlilumab antibody responses detected
- No significant depletion in absolute lymphocyte counts, T cells or B cells
- Evidence of increased immunologic activity, consistent with expected mechanism of action:
  - Increased soluble CD27
  - Reduction of circulating Tregs
  - Induction of pro-inflammatory cytokines
- Anti-lymphoma activity is supported by a Complete Response seen in a patient with heavily pretreated Hodgkin Disease

Future Directions

- The combined safety and activity data from the hematologic and solid tumor arms of this phase 1 study strongly support the further development of varlilumab, particularly in combination therapy.
- Optimal dosing regimen to be defined
  - Preliminary data suggest low dose, intermittent activation may be preferable
  - Future studies to explore continuous receptor saturation vs. 'on-off' signaling
- Next steps:
  - Await data in T-cell lymphomas
  - Analyze biologic characteristics of Hodgkin patients to explore potential for biomarkers of sensitivity to varlilumab and optimal dosing
  - Plan combination development (phase 1/2 studies) with rituximab, pomalidomide and ibrutinib

References:
1. Gordon, et al. *J Clin Oncol*. 2001; 19:843-50.
2. Yang, et al. *N Engl J Med*. 2003; 349:427-34.
3. Huang, et al. *J Immunol* 2013 Jun 15;190(12):6250-8.

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