Immune Correlates of Varlilumab (CDX-1127) Treated Cancer Patients are Consistent with CD27 Costimulatory Activity

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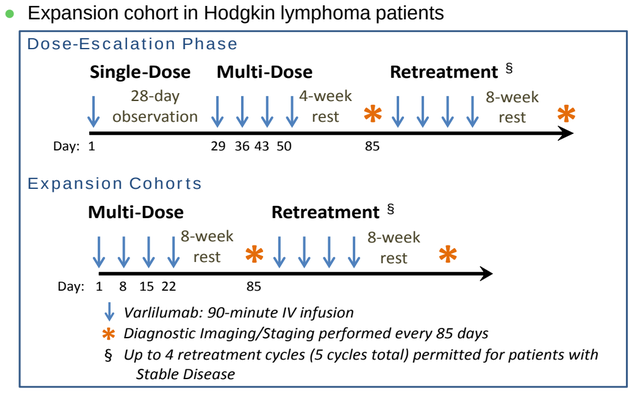
Abstract #52514/Poster Board: P115

Varlilumab (CDX-1127): A 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

Phase 1 Clinical Study Design

- Standard 3+3 dose-escalation (0.1, 0.3, 1, 3 or 10 mg/kg)
- Expansion cohorts of RCC (n =16) and Melanoma (n=15)
- Expansion cohort in Hodgkin lymphoma patients



Summary of Clinical Data

Dosing and Toxicity:

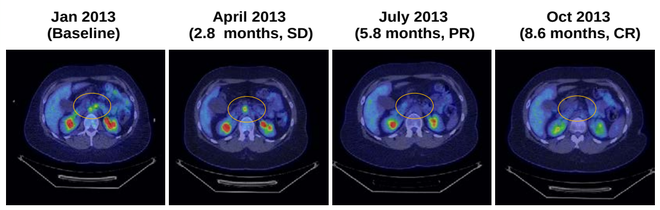
- To date a total of 86 patients have been dosed; 55 patients have been dosed in dose escalation cohorts (various solid and hematologic tumors), 31 patients have been dosed in the expansion cohorts (melanoma and RCC) at 3 mg/kg, the expansion cohort in Hodgkin lymphoma is ongoing
- In both the solid tumor and hematologic dose-escalations, the pre-specified maximum dose level (10 mg/kg) was reached without identification of a Maximum Tolerated Dose (MTD)
- One Dose-Limiting Toxicity (DLT) of transient, asymptomatic Grade 3 hyponatremia was reported
- The majority of AE's related to treatment have been mild to moderate in severity, with only 3 SAEs related to treatment reported: bronchospasm, asthma, and infusion reaction
- No significant immune-mediated adverse events (colitis, hepatitis, etc.) typically associated with check-point blockade

Clinical activity:

- Significant responses in 2 patients
  - Hodgkin patient has experienced a Complete Response (ongoing at 18.9+ months; see below)
  - RCC patient has experienced a Partial Response (ongoing at 5.5+ months; see below)
- Thirteen patients with stable disease (3-25.5+ months)
  - Includes patients with uveal melanoma (M1c) with SD for 11.5 months, RCC with SD for 25.5+ months, and follicular lymphoma with SD for 14 months

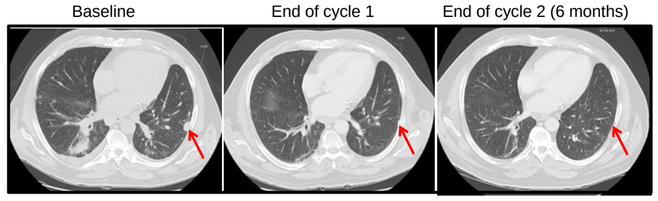
- 28 year old female with Stage IV Hodgkin lymphoma with para-aortic involvement
  - Inadequate response to induction, and progression through or shortly thereafter four subsequent salvage attempts
  - Most recently, had progressed 4 months after multiple sequential myeloablative chemotherapy with hematopoietic 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 18.9+ months
- Reed-Sternberg cells lacked detectable CD27 expression

Jan 2013 (Baseline)	April 2013 (2.8 months, SD)	July 2013 (5.8 months, PR)	Oct 2013 (8.6 months, CR)



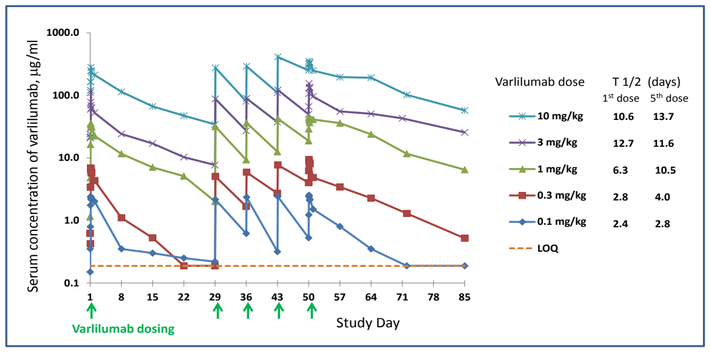
- 67 year old male with stage IV RCC
  - Progressed through 3 prior regimens
    - lenalidomide and sunitinib treated for 11 months before PD
    - everolimus treated for 25 months before PD
    - ASONEP treated for less than 1 month before PD
  - Partial Response (PR) after 1 cycle of varlilumab (3mg/kg)
  - Decrease in all target lesions (31.3% end of cycle 1, 52.1% end of cycle 2)
  - Lung nodule completely resolved (shown in scans)

Baseline | End of cycle 1 | End of cycle 2 (6 months)



Target Lesion 1; Left subpleural nodual

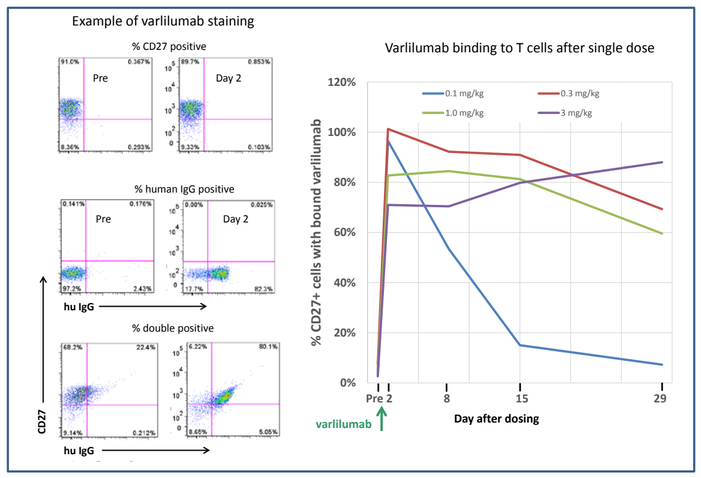
Varlilumab Pharmacokinetics and Immunogenicity



Pharmacokinetics similar for patients with solid and hematologic tumors

- $T_{1/2}$ ~10-13 days
- Exposure was linear across dose groups from 0.3-10 mg/kg
- No anti-varlilumab antibody responses detected in patients to date

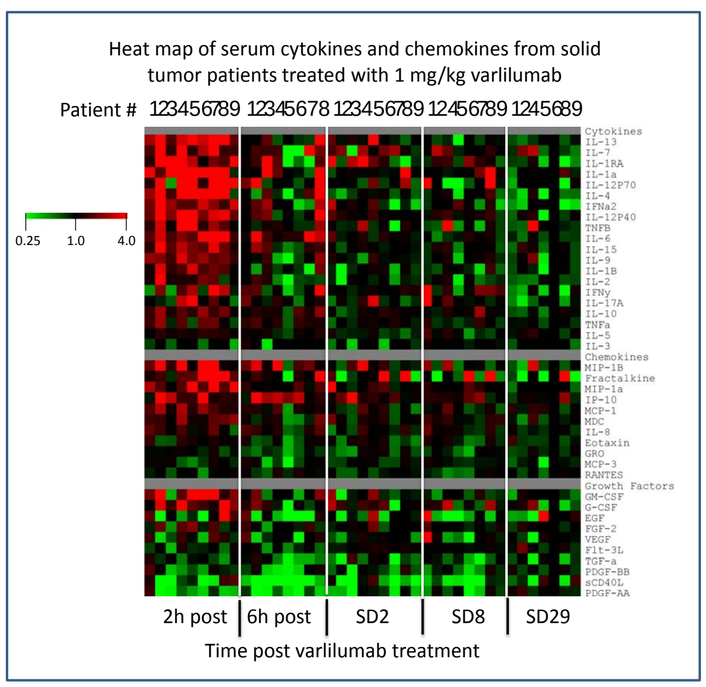
Varlilumab Binding to Circulating T cells



Varlilumab binding to T cells was assessed by flow cytometry and calculated as % of CD27+ cells that are human IgG+

- 0.1 mg/kg dose resulted in transient binding to T cells, while ≥ 0.3 mg/kg maintained high level binding for at least 1 month
- Data are consistent with the pharmacokinetics

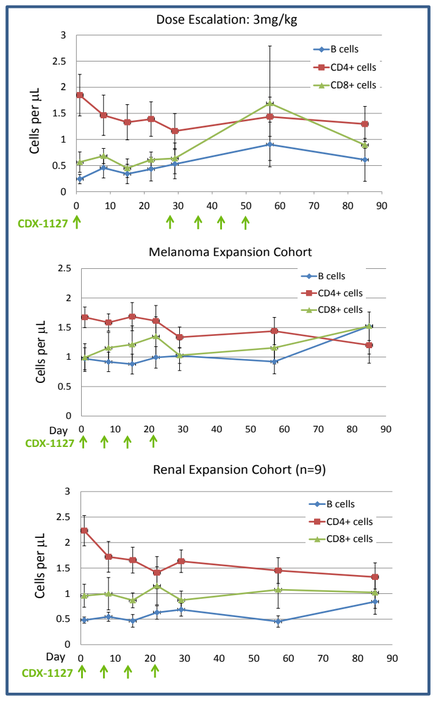
Serum Biomarker Profile



Serum cytokines and chemokines were analyzed by Luminex

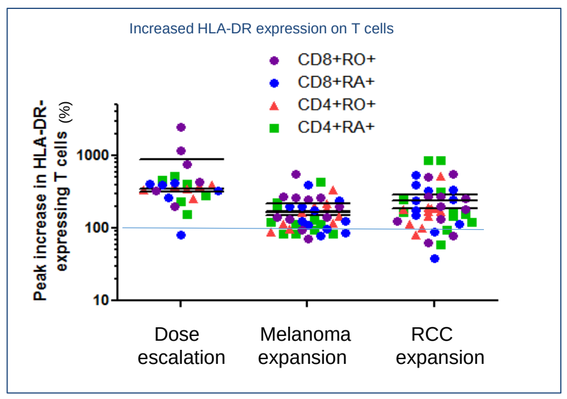
- Robust and transient immune signature is associated with varlilumab infusion
- The 1 mg/kg cohort was chosen for this analysis because this dose level had the most patients.
- Serum cytokine/chemokine increases were observed at all dose levels

Flow Cytometry Analysis of Immune Cell Subsets



Varlilumab's effect on the numbers of circulating B and T cells was assessed by flow cytometry

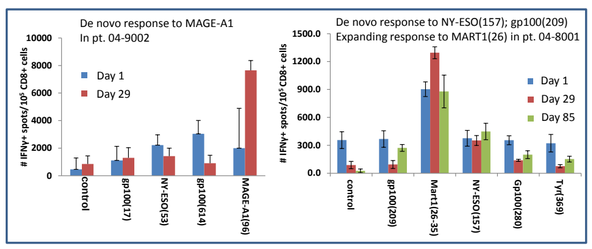
- As previously reported for the patients in the dose escalation, we did not observe depletion of B or $CD8^+$T cells, but $CD4^+$ T cells are decreased



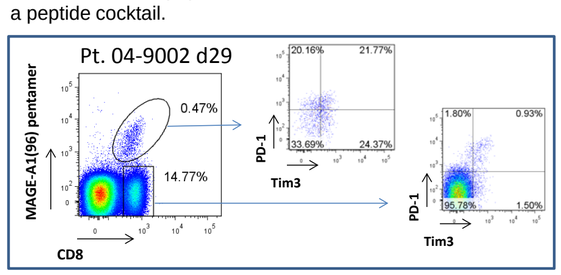
Varlilumab's effect on HLA-DR-expression on T cell subsets was assessed by flow cytometry

- A significant enhancement of HLA-DR expression was observed in all cohorts, but most extensively in the dose escalation patients
- The increased HLA-DR expression is not restricted to a single subset of T cells

Increased Response to Melanoma Antigens in Some Melanoma Patients

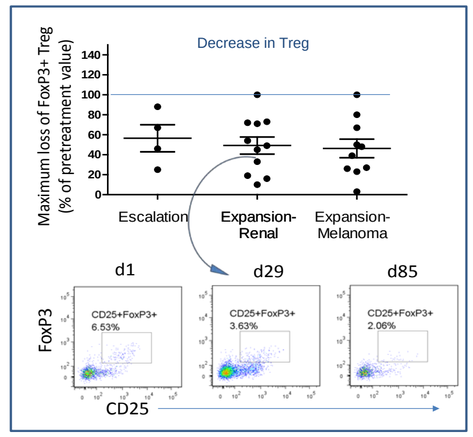


ELISPOT: PBMC from Day 1, 29, or 85 treatment time points were assayed for IFNγ production in response to APC pulsed with the indicated peptide after 2 weeks in vitro stimulation with a peptide cocktail.



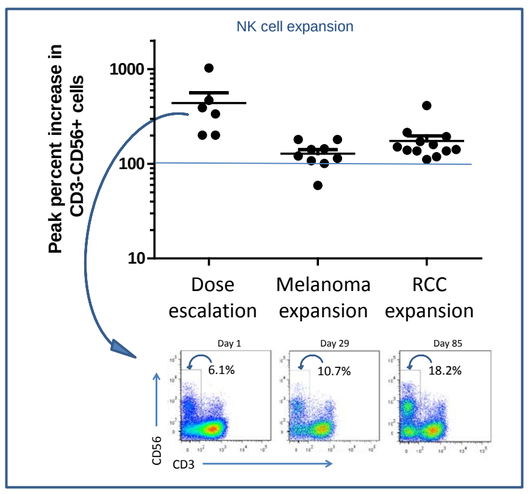
Flow Cytometry: To confirm ELISPOT data, PBMC were directly stained for MHC-multimer binding and assessed for expression of checkpoint inhibitor expression.

- Select patients demonstrated an expansion of existing response or de novo responses to melanoma antigens
- The frequency of enhance responses (either de novo or enhancement of existing response) was greater in the dose escalation regimen (4 of 5) relative to the melanoma expansion cohort (1 of 13)



Varlilumab's effect on the numbers of circulating Treg cells was assessed by flow cytometry

- Significant decreases were observed in all cohorts.



Varlilumab's effect on the numbers of circulating NK cells was assessed by flow cytometry

- Patients in the expansion cohorts also demonstrated increases in NK cell numbers, but this was less prominent than in the 3 mg/kg dose-escalation cohort
- The expanding NK cells are primarily within the CD56dim (cytolytic) population
- Expanding NK cells were associated with increased NKG2D expression (not shown)

Phase 1 Conclusions:

- Varlilumab is associated with a favorable safety profile and clear evidence of clinical activity in selected patients
- PK shows good exposure even at lower dose levels, and results in continuous binding of varlilumab to T cells in circulation
- No anti-varlilumab antibody responses detected
- Biomarker analysis demonstrates significant immunological effects that are consistent with CD27 costimulation:
  - Transient stimulation of multiple cytokine and chemokine pathways
  - No depletion of B, $CD8^+$ T cells, some decrease in $CD4^+$ T cells
  - Decreased number of Tregs
  - Increased number of cytolytic NK cells
  - Induction of activation marker on T cells
  - Evidence of enhanced melanoma specific T cell response
- Immune correlates suggest weekly dosing may be less immune activating compared to less frequent dosing

Combination Trials initiating:

Based on the Phase 1 experience and our preclinical studies that show synergistic activity when varlilumab is combined with checkpoint inhibitors or with chemotherapy, the following studies are being planned and initiated:

- Varlilumab plus nivolumab (BMS) in advanced non-small cell lung cancer, melanoma, colorectal cancer, ovarian cancer and head and neck squamous cell carcinoma
- Varlilumab combined with ONT-10 (MUC-1 vaccine, Oncothyreon) in breast and ovarian cancers
- Varlilumab and ipilimumab in patients with metastatic melanoma; plus CDX-1401(DC-targeted NY-ESO-1 vaccine) in NY-ESO-1+ patients
- Varlilumab and SBRT in prostate cancer (UVA investigator study)

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