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

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**Abstract #2015PosterBoard: P118**

**Varililumab (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.
- Varililumab is an agonist anti-CD27 IgG1 mAb that induces activation and proliferation of human T cells when combined with T-cell receptor stimulation.
- Varililumab has been shown effective in syngeneic murine tumor models alone, and in combination with chemotherapmy 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 hyporexia 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, asthama, and infusion reaction.
- No significant immune-mediated adverse events (collitis, 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.

**Patient Data**

- 28 year old female with Stage IV Hodgkin lymphoma with para-aortic involvement
  - Inadequate response to radiation, 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 varililumab (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

**Serum Biomarker Profile**

- Heat map of serum cytokines and chemokines from solid tumor patients treated with 1 µg/kg varililumab.
- Increased number of cytolytic NK cells
- No depletion of B, CD8+ T cells, some decrease in Treg
- Prominent than in the 3 mg/kg dose-escalation cohort

**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.
- Pt: D4-90D2 d29

**Flow Cytometry Analysis of Immune Cell Subsets**

- Varililumab'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.

**Varililumab Binding to Circulating T cells**

- Varililumab binding to T cells after single dose varililumab infusion.
- No anti-varililumab antibody responses detected in patients to date.
- Complete Response (CR) after three cycles of varililumab (0.3 mg/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).

**Phases 1 and 2 Conclusions:**

- Varililumab is associated with a favorable safety profile and clear evidence of clinical activity in selected patients.
- PIK shows good exposure even at lower dose levels, and results in continuous binding of varililumab to T cells in circulation.
- No anti-varililumab antibody responses detected.
- Biomarker analysis demonstrates significant immunological effects that are consistent with CD27 costimulation.
  - Increased HLA-DR expression on T cells
  - De novo response to NY-ESO(157); gp100(209)
  - 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 varililumab is combined with checkpoint inhibitors or with chemotherapy, the following studies are being planned and initiated:
  - Varililumab plus nivolumab (BMS) in advanced non-small cell lung cancer, melanoma, colorectal cancer, ovarian cancer and head and neck squamous cell carcinoma.
  - Varililumab combined with ONT-10 (MUC-1 vaccine, Oncorthyroin) in breast and ovarian cancers.
  - Varililumab and ipilimumab in patients with metastatic melanoma plus CDX-1401(DC-targeted NY-ESO-1 vaccine) in NY-ESO-1+ patients.
  - Varililumab and SBRt in prostate cancer (UVA investigator study).