Evaluation of an Agonist Anti-CD27 Human Antibody (Varlilumab) and its Potential for Combination With Checkpoint Inhibitors

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Chief Scientific Officer
Enhancing immunity with immune modulating antibodies

Varilumab
Agonist human anti-CD27 mAb
(Hu IgG1k)

Adapted from Mellman, I et al. Nature, 2011
CD27; a critical regulator of T cells

**Member of the TNF-receptor superfamily (CD40, 4-1BB,OX-40)**
- Single ligand is CD70 (tightly regulated)
- Constitutively expressed on most T cells and a subset of B and NK cells

**Co-stimulatory molecule**
- Role in generation and long-term maintenance of T cell immunity
- Role in NK cell differentiation/activation

**CD27 activation:**
- Signaling through Traf2, Traf 5
- Activation of the NF-κB pathway
- Cell survival, activation, proliferation

*J. Denoeud and M. Moser J. Leuk. Biol. 2010*
CD27 as a target for immunotherapy

Enhancement of T cell responses

- Soluble CD70 augments antigen-specific CD8+ T cell response (Rowley FT, Al-Shamkhani, A JI 2004)
- CD70 expression on DC breaks tolerance to self antigens and promotes immunity (Keller AM et al, Immunity 2008)
- CD27 co-stimulation promotes a broad T cell repertoire (van Gisbergen KPJM et al, Immunity 2011)
- CD4+ T-cell help signal is transmitted from APC to CD8+ T-cells via CD27–CD70 (Feau et al, Nat. Com. 2012)
Anti-mouse CD27 mAb activity in tumor models

From Martin Glennie, Southampton University
Varilumab, A fully human mAb specific for CD27

- Human IgG1k
- Subnanomolar affinity: $1.9 \times 10^{-10}$ kD(M)
- Blocks CD70 binding to CD27
- Potent in vitro agonist activity (T cell activation/proliferation)
  - Requires simultaneous TCR stimulation
  - Requires varilumab to be cross-linked
- Potent in vivo activity (Increased CD8 response/anti-tumor activity)
  - Developed human CD27 tg mouse model
  - Potent activity in “immunogenic” tumor models
  - In vivo cross-linking occurs via Fc receptors
- Direct anti-tumor activity against human CD27+ tumors
  - Delayed tumor growth in xenograft models
  - May involve ADCC
No significant depletion of circulating lymphocytes in NHP

Cynomolgus macaques

1F5 (CDX-1127) dose: 1mg/kg □ 3 mg/kg ◇ 10 mg/kg △
Varlilumab Phase 1- 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

### Dose-Escalation Phase

<table>
<thead>
<tr>
<th>Single-Dose</th>
<th>Multi-Dose</th>
<th>Retreatment §</th>
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</thead>
<tbody>
<tr>
<td>28-day observation</td>
<td>4-week rest</td>
<td>8-week rest</td>
</tr>
<tr>
<td>Day: 1</td>
<td>29 36 43 50</td>
<td>85</td>
</tr>
</tbody>
</table>

### Expansion Cohorts

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<tr>
<td>8-week rest</td>
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</tr>
<tr>
<td>Day: 1 8 15 22</td>
<td>85</td>
</tr>
</tbody>
</table>

- 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
Varilimumab Phase 1- Safety and PK

Dosing and Toxicity:
- Completed dose escalation in various solid and hematologic tumor types
- No Maximum Tolerated Dose (MTD)
- A single 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

Pharmacokinetics and Pharmacodynamics:
- PK consistent with human IgG
  - Half life ~ 10-12 days
  - No immunogenicity detected
- PD changes consistent with expected MoA
  - Induction of cytokines/chemokines
  - Activation of T cells
  - Reduction in Treg
  - Increase in NK cells
• No evidence of significant depletion of lymphocytes
• Similar values across all dose levels
Serum Biomarker Profile

9 Patients treated at 1 mg/kg varilulmab

Heat map of serum cytokines and chemokines from solid tumor patients treated with 1 mg/kg varilulmab

Serum cytokines and chemokines were analyzed by Luminex

- Robust and transient immune signature is associated with varilulmab 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
Decrease in the number of regulatory T cells

Individual Patients

% Treg (CD3+CD4+CD25+CD127-FoxP3+)

- 0.1 mg/kg
- 0.3 mg/kg
- 1 mg/kg
- 3 mg/kg
- 10 mg/kg

All patients, mean values

% Treg (CD3+CD4+CD25+CD127-FoxP3+)

Day 1, Day 8, Day 29, Day 85

p=0.039, p=0.012

CDX-1127
Evidence of T cell activation

All patients in 3 mg/kg cohort
- Before treatment: [Graph showing % HLA-DR+ memory T cells]
- Maximum level achieved on study: [Graph showing % HLA-DR+ memory T cells]

Patient in 3 mg/kg MD cohort
- Day 1: 6.9%
- Day 29: 13.2%
- Day 85: 21.3%
Increased Response to Melanoma Antigens in Some Melanoma Patients

**De novo response to MAGE-A1**
(Patient 04-9002)

**Expanding response to MART-1**
(Patient 06-9001)

**Day 1**

**Day 29**

**MAGE-A1-pentamer**

- CD8
- 0.013%
- 11.0%
- 0.469%

**MART-1 tetramer**

- CD8
- 0.118%
- 9.97%
- 0.227%
Varlilumab Phase 1- Clinical Activity

- Thirteen patients with stable disease (up to 30.7+ months)

- Significant and durable responses in 2 patients
  - 28 year old female stage IV Hodgkin lymphoma patient (0.3 mg/kg varli)
    - Progressed through 5 lines of chemo and stem cell therapy in 1.6 yrs. since diagnosis
    - Experienced complete resolution of B symptoms (drenching sweats, pruritus and weight loss) on 1st cycle of varlilumab
    - Experienced PR on 2nd cycle and CR on 3rd cycle of varlilumab
    - CR ongoing at 18.9+ months

- 67 year old male RCC patient (3.0 mg/kg)
  - Progressed through 3 prior lines of therapy
  - Achieved PR with 31% decrease in tumor after 1st cycle
  - Continued PR with 52% decrease in tumor after 2nd cycle
  - Remains in follow up- at 11 months- 67% decrease in tumor with 2 of 5 target lesions resolved
Rationale for Combination of Varlilumab with Checkpoint Inhibitors

• Combining costimulatory signals with blockade of inhibitory signals can enhance the magnitude and quality of the anti-tumor T cell response
  • May increase immune related adverse events

• Potential for increasing responses to CI
  • CI response is associated with pre-existing T cell infiltrate
  • Varlilumab may lead to increase in T cells in tumor
  • Varlilumab may enhance broader immune response
    • Activation of additional T cell specificities and innate immunity (NK cells)

• Varlilumab safety profile
  • Strong biological activity without evidence of significant toxicity
    • No liver inflammation or CRS
    • No overlapping toxicities with CI
Efficacy correlates with tumor burden
(human CD27tg: CT26 model)

Varli (600 μg x 5)
saline

p<0.0001

p = 0.016
Combination of varlilumab with anti-PD-L1
(human CD27tg: CT26 model)

Saline group: 200 µl days 9, 11, 13, 15, & 17 (n= 8)
1F5 dosed at 600 µg on days 9, 11, 13, 15, & 17 (n=8)
α-PD-L1 (10F.9G2) dosed at 100 µg on days 15, 17& 19 (n=8)
Combination of varililumab with anti-PD-L1

Human CD27tg: BCL1 Disseminated Lymphoma Model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days Post Tumor Inoculation</th>
</tr>
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<tbody>
<tr>
<td>Saline, n=30</td>
<td>4, 6, 8, 10, 12</td>
</tr>
<tr>
<td>Varililumab, n=30</td>
<td>4, 6, 8, 10, 12</td>
</tr>
<tr>
<td>Anti-PD-L1, n=30</td>
<td>4, 6, 8, 10, 12</td>
</tr>
<tr>
<td>Varililumab + anti-PD-L1, n=30</td>
<td>4, 6, 8, 10, 12</td>
</tr>
</tbody>
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HuCD27-Tg mice –BALB/c background
10^7 BCL1 cells i.v. Day 0
Saline Day 4, 6, 8, 10, 12
Varililumab (200 µg) Day 4, 6, 8, 10, 12
Anti-PD-L1 (100 µg) Day 4, 6, 8,
Combination of varlilumab with anti-PD-L1

BCL1 model: Increased Teff:Treg ratio

Activated CD8 T cells

Activated CD4 T cells

Ratio of CD8/Tregs

* ns

- Saline
- Anti-PD-L1
- CDX-1127
- Combo

- Increased Teff:Treg ratio

- Combination of varlilumab with anti-PD-L1
Combination of varililumab with anti-CTLA-4

Human CD27tg: EG.7 Subcutaneous Thymoma Model

A

Treatment period (day 5-22)

- α-CTLA-4 (0.1 mg x 3)
- CDX-1127 (0.1 mg x 3)
- CDX-1127 + α-CTLA-4

Percent survival vs. Days post tumor inoculation

P=0.02

B

Treatment period (day 4-21)

- No treatment
- CDX-1127 (0.1 mg x 5)
- CDX-1127 (0.1 mg x 5) + α-CTLA-4 (0.1 mg x 3)

Percent survival vs. Days post tumor inoculation

2/8, P=0.01

Hu CD27-Tg mice, C57BL/6 background
Mice (n= 8-10) were inoculated with 10^6 E.G7 tumor cells
Abs were given i.p. either 3 or 5 times during the indicated treatment periods.
Varilumab and Checkpoint Combination Trials
Phase I/II: Varililumab + Nivolumab
Celldex/BMS

Primary Objectives:

Phase I: To access safety and tolerability of varililumab (0.1, 1.0, and 10 mg/kg i.v. Q2W) in combination with nivolumab (3 mg/kg i.v. Q2W) and identify the recommended Phase II dose

Phase II: To access the preliminary anti-tumor activity of the combination of varililumab and nivolumab as determined by ORR

Design: Phase I/II, open label dose-escalation study with 5 disease-specific phase II cohorts.

Population: Patients with specific advanced (unresectable or metastatic) solid tumors (non-small cell lung cancer, melanoma, colorectal cancer, ovarian cancer and head neck squamous cell carcinoma)

Patients/Centers: Up to about 190 patients / 15 centers in the US

Status: Currently enrolling
Phase I/II: Varlilumab + Ipilimumab +/- CDX-1401
Celldex

Primary Objectives:

**Phase I**
Safety and tolerability of varlilumab (0.3 and 3 mg/kg i.v. every 3 weeks) in combination with ipilimumab (3 mg/kg) and identify the recommended Phase II dose

**Phase II**
Assess anti-tumor activity of combination. NY-ESO-1+ pts also receive CDX-1401 (NY-ESO-1 vaccine)

Design: Phase I/II, Open-label, Dose-escalation Study

Population: Patients with unresectable Stage III or IV melanoma

Patients/Centers: Up to 100 patients / 20-30 centers in the US

Status: FPI – Q2 2015
Phase I/II: Varlilumab + MPDL3280A (anti-PD-L1)
Celldex/Roche

**Primary Objectives:**

**Phase I**  
Safety and tolerability of varlilumab in combination with MPDL3280A and identify the recommended Phase II dose

**Phase II**  
Assess anti-tumor activity of combination.

**Design:**  
Phase I/II, Open-label, Dose-escalation Study

**Population:**  
Patients with metastatic renal cell carcinoma

**Status:**  
FPI - 2015
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