Clinical Results with Combination of Anti-CD27 Agonist Antibody, Varilimumab, with Anti-PD1 Antibody, Nivolumab, in Advanced Cancer Patients

Rachel E. Sanborn¹, Michael J. Pishvaian², Harriett Kluger³, Margaret K. Callahan⁴, Amy Weise⁵, Jose Lutzky⁶, Michael Yellin⁷, Tracey Rawls⁷, Laura Vitale⁷, Abdel Halim⁷, Tibor Keler⁷, Tom Davis⁷ and Naiyer Rizvi⁸

¹ Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, ² Georgetown University, Washington, DC, ³ Smilow Cancer Hospital at Yale-New Haven, New Haven, CT, ⁴ Memorial Sloan Kettering Cancer Center, New York, NY, ⁵ Karmanos Cancer Institute, Detroit, MI, ⁶ Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, ⁷ Celldex Therapeutics, Hampton, NJ, ⁸ Columbia University Medical Center New York-Presbyterian Hospital, Herbert Irving Pavilion, New York, NY
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Enhancing the Efficacy of Immune Checkpoint Blockade

Nivolumab, a fully human IgG4 mAb that binds to PD-1 and inhibits PD-1/PD-L1 interactions, is approved for multiple indications but many opportunities to improve efficacy remain. Combination strategies that target T cell costimulation molecules such as CD27 may enhance clinical responses to checkpoint blockade.

**CD27: Member of the TNF-receptor superfamily**
- Single ligand is CD70 (tightly regulated)
- Constitutively expressed on most T cells and a subset of B and NK cells
- CD27 activation:
  - Signaling through Traf2, Traf 5
  - Activation of the NF-κB pathway
  - Cell survival, activation, proliferation
  - Role in generation and long-term maintenance of T cell immunity
  - Role in NK cell differentiation/activation

**Varililumab: Fully human IgG1 CD27 agonist mAb**
- Strong preclinical data demonstrating single agent and combination activity in tumor models
Varilumab Clinical Experience: Phase 1 Monotherapy Trial

- Safety profile appears favorable in its class of agonist mAbs; minimal toxicities; no significant immune-mediated AEs 1, 2, 3

- Potent immunologic activity consistent with MOA1, 2, 3
  - Rapid induction of pro-inflammatory IFN-γ driven chemokines, increased expression of T cell activation markers, and marked decrease in T regs without evidence of broad T cell depletion

- Single-agent antitumor activity demonstrated in advanced, refractory patients with solid tumors or hematologic malignancies (n=90) 1, 2, 3
  - Three patients experienced objective responses
    - Patient with HL achieved a CR after 3 cycles of varilumab (0.3 mg/kg). Remains in remission at 33.1+ months without further anticancer therapy
    - Patient with RCC achieved a PR with varilumab (3 mg/kg). PR persists at 2.5 years without further anticancer therapy (see graph below)
    - Patient with RCC completed 5 cycles of varilumab (3 mg/kg) and maintained stable disease until achievement of a single-time point PR at 4.2 years without additional anticancer therapy
  - Twelve patients experienced SD up to 14 months

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1 Bullock, et al. SITC 2014
2 Infante, et al. ASCO 2014
3 Burris, et al, JCO 2017

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**Decrease in Tregs with Varilumab**

- Day 1: p=0.0041
- Day 29: p=.0039
- Day 85: p=ns

**Durable Partial Response for a Patient with RCC**

- Length of Target Lesion (mm)
- Study Month
- Varilumab dosing

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**Graph Details:**
- **Patient with HL:** Achieved a CR after 3 cycles of varilumab (0.3 mg/kg). Remains in remission at 33.1+ months without further anticancer therapy.
- **Patient with RCC:** Achieved a PR with varilumab (3 mg/kg). PR persists at 2.5 years without further anticancer therapy (see graph below).
- **Patient with RCC:** Completed 5 cycles of varilumab (3 mg/kg) and maintained stable disease until achievement of a single-time point PR at 4.2 years without additional anticancer therapy.
Phase 1: Dose escalation/expansion of varlilumab (0.1, 1, and 10 mg/kg) with nivolumab 3 mg/kg

- 6 initial patients per cohort, with option for expansion to 15 patients
- Objectives:
  - Primary: safety and tolerability, identify varlilumab doses for Phase 2 cohorts
  - Secondary: DOR, TTR, PFS, OS, Immunogenicity and PK
  - Exploratory: Pharmacodynamic effects on peripheral blood and tumor markers

- Key eligibility criteria:
  - Recurrent or refractory SCCHN, ovarian cancer, melanoma, NSCLC, or CRC
  - Documented progressive disease
  - ≤ 5 prior anticancer regimens for advanced disease
  - ≥ 3 month washout for anti-CTLA-4 or other T cell directed mAbs
  - No prior anti-PD-(L)1 therapy
  - No active, untreated CNS metastases
  - No autoimmune disease

Phase 2: Tumor-specific cohorts (CRC, GBM, Ovarian, SCCHN, and RCC) to evaluate clinical activity of selected varlilumab dose(s) and schedules with nivolumab flat dose (240 mg)

- Restaging Scans
- Nivolumab
- Varlilumab

- Cycle 1
- Cycle 2
- Cycle 3
- Cycle 4

- Week 0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36 38 40

- Tumor biopsies at baseline and on-study (4-6 weeks)
- Four 8-week cycles of combination therapy, followed by nivolumab monotherapy
- Treatment until dose-limiting toxicity or disease progression

NCT02335918
**Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>0.1 mg/kg (n=6)</th>
<th>1 mg/kg (n=15)</th>
<th>10 mg/kg (n=15)</th>
<th>All Phase 1 (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years (median [range])</strong></td>
<td>66 (57-76)</td>
<td>54 (40-66)</td>
<td>50 (29-84)</td>
<td>57 (29-84)</td>
</tr>
<tr>
<td><strong>Male (n [%])</strong></td>
<td>3 (50)</td>
<td>8 (53)</td>
<td>7 (47)</td>
<td>18 (50)</td>
</tr>
<tr>
<td><strong>Primary Diagnosis (n [%])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC</td>
<td>5 (83)</td>
<td>8 (53)</td>
<td>8 (53)</td>
<td>21 (58)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>1 (17)</td>
<td>4 (27)</td>
<td>3 (20)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>0</td>
<td>1 (7)</td>
<td>3 (20)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>SCCHN</td>
<td>0</td>
<td>2 (13)</td>
<td>1 (7)</td>
<td>3 (8)</td>
</tr>
<tr>
<td><strong>ECOG performance status (n [%])</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2 (33)</td>
<td>3 (20)</td>
<td>9 (60)</td>
<td>14 (39)</td>
</tr>
<tr>
<td>1</td>
<td>4 (67)</td>
<td>12 (80)</td>
<td>6 (40)</td>
<td>22 (61)</td>
</tr>
<tr>
<td><strong>Stage IV at Study Entry (n [%])</strong></td>
<td>5 (83)</td>
<td>15 (100)</td>
<td>14 (93)</td>
<td>34 (94)</td>
</tr>
<tr>
<td><strong>No. of prior treatment regimens (median [range])</strong></td>
<td>3 (2-4)</td>
<td>4 (0-9)</td>
<td>3 (0-8)</td>
<td>3 (0-9)</td>
</tr>
<tr>
<td><strong>Prior immunotherapy (n [%])</strong></td>
<td>1 (17)</td>
<td>1 (7)</td>
<td>1 (7)</td>
<td>3 (8)</td>
</tr>
<tr>
<td><strong>PD-L1+ tumor (n/n [%])</strong></td>
<td>0/6 (0)</td>
<td>1/11 (9)</td>
<td>2/11 (18)</td>
<td>3/28 (11)</td>
</tr>
</tbody>
</table>

1 Two stage III patients were ovarian cancer (0.1 mg/kg group) and SCCHN (10 mg/kg group).

2 Denominator represents patients with tumor assessed for PD-L1 status. PD-L1+ criteria: \( \geq 1\% \) tumor cells staining positive, using the BMS developed PD-L1 IHC method at a central lab.
Varilumab & Nivolumab Combination Therapy is Well Tolerated

- All dose levels well tolerated, without identification of a maximally tolerated dose
- No evidence of additive toxicity for the combination of varilumab with nivolumab
- 3 patients discontinued the study due to treatment related AEs
- 3 patients with treatment-related* SAEs (all 10 mg/kg varilumab):
  - Peripheral sensorimotor neuropathy (grade 2)
  - ALT increased (grade 3)
  - Acute kidney injury (grade 3) and hepatitis (grade 4 and a dose-limiting toxicity)

*The above SAEs were related to varilumab and nivolumab

### Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>All Phase 1 (n=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Severity</td>
</tr>
<tr>
<td>Any treatment-related adverse event</td>
<td>31 (86%)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (22%)</td>
</tr>
<tr>
<td>Rash</td>
<td>11 (19%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (19%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>AST increased</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Table includes adverse events assessed as related to either varilumab or nivolumab for ≥ 10% of patients overall, or at grade ≥ 3 severity any patient.

* 1 patient had all AEs (excluding 1 incident of ALT increased)
Tumor Response

**0.1 mg/kg varlilumab and 3 mg/kg nivolumab**

- **Best Response:**
  - PR
  - uPR
  - SD
  - PD
  - New Lesion

- **% Change from Baseline (RECIST 1.1 Target Lesions):**
  - 0%
  - 50%
  - 100%
  - 150%

- **Week:**
  - 0
  - 10
  - 20
  - 30
  - 40
  - 50
  - 60

- **Patient with PD-L1-negative CRC (pMMR) achieved PR (95% shrinkage) and continues to receive treatment at 22 months.**

**1 mg/kg varlilumab and 3 mg/kg nivolumab**

**Disease Control Rate***
- 0.1 mg/kg varli + nivo: 1/5 (20%)
- 1 mg/kg varli + nivo: 5/15 (33%)
- 10 mg/kg varli + nivo: 6/15 (40%)

* DCR; best response of SD or better ≥ 3 months

**10 mg/kg varlilumab and 3 mg/kg nivolumab**

- **Patient with low PD-L1 (5%) SCCHN achieved PR (59% shrinkage) and experienced PFS of 6.7 months.**

- **Patient with PD-L1-negative ovarian cancer experienced a single-time point PR (49% shrinkage; uPR) at 1.6 months, but discontinued treatment due to a DLT.**
Durable Response in MMR-proficient CRC Patient

4-23-2015 (Baseline)  6-29-2015 (Cycle 1)  3-06-2017 (Cycle 12)

- PD-L1-negative, pMMR colorectal adenocarcinoma with metastatic disease to liver, adrenal gland, abdomen and mesenteric nodule1
- 2 prior chemotherapy based regimens (1 with EGFR targeted therapy)
- On study, had a 95% decrease in target lesions, including resolution of 4/5 target lesions. One 6 mm mesenteric nodule remains
- Completed all 4 cycles of varilumab and nivolumab therapy and continues to receive nivolumab monotherapy at 22+ months
- Treatment-related toxicity limited to grade 1 pruritus, fatigue, chills and fever

1Expected response rate for nivolumab in MSI-low (pMMR) CRC is 0% (Overman, et al, ASCO 2016)
Extensive Immune Monitoring Incorporated into the Study

- Peripheral blood: serum factors, flow cytometry
- Tumor biopsies: baseline and on-treatment immunohistochemistry

Peripheral blood analysis
- Prominent decrease in CD4 and Treg cells observed across all cohorts
- Serum chemokine changes consistent with varilumab monotherapy
- Transient increase in inflammatory chemokines (CXCL10, MCP-1, MIP-1β and MIG) observed across all cohorts

The correlative analysis contains patients from Phase 1 and patients with data from Phase 2
Immunohistochemistry of Biopsy Samples

Baseline biopsies were generally low in T cell markers and PD-L1 expression on tumor

- T cell infiltrates and PD-L1 expression increased significantly during treatment in some patients
- This was particularly evident in a sub-group analysis focused on ovarian patients

Includes patients from Phase 1 (n=28) and Phase 2 (n=37)
Tumor Expression of PD-L1 is Increased in Ovarian Patients

- Baseline biopsies were generally negative or low PD-L1 positive
  - 10 of 26 (38%) had PD-L1 + tumors; range 1%-15% (mean = 5.1%)

- Patients with paired biopsies (n=13):
  - 2 of 13 patients were positive at baseline (10%, 15%)
  - 10 of 13 (77%) were PD-L1 + on-treatment (4-6 weeks); range 1-65% (mean = 20.8%)

Baseline On-treatment

PD-L1 testing was performed using the BMS developed PD-L1 IHC method (Dako clone 28-8); PD-L1+ defined as ≥1% of tumor cells
Enhanced PD-L1 Expression and CD8 TIL in Ovarian Patients

Ovarian patients with paired baseline and on-treatment biopsies to date

Phase 1 patients n=6
Phase 2 patients n=7

P value: 2-tailed Paired T-Test
Optimization of Dosing Regimen

- Chronic CD27 stimulation may not be optimal
  - Evidence of T cell infiltration, but also PD-1 expression
  - Potential for immune exhaustion
- Alternate dosing regimens selected using receptor occupancy data and PK modeling

Continuous saturation or clearance following high or low dose of varilumab

Planned Phase 2 Cohorts:
- CRC (n=18), GBM (n=20) and RCC (n=25): varilumab 3 mg/kg q 2 weeks
- Ovarian and SCCHN:
  - Varilumab 3 mg/kg q 2 weeks (n=18)
  - Varilumab 3 mg/kg q 12 weeks (n=18)
  - Varilumab 0.3 mg/kg q 4 weeks (n=18)
- All receive nivolumab flat dose (240 mg) q 2 weeks
Conclusions and Next Steps

• The combination of varlilumab and nivolumab was well tolerated at all varlilumab dose levels tested
• The majority of tumors were PD-L1 negative at baseline and 80% of patients enrolled in Phase 1 had CRC or ovarian cancer
  – Representing patient populations expected to have minimal response to checkpoint blockade
• Clinical responses were observed in the Phase 1 portion of the study, including a durable partial response in a patient with pMMR CRC
• Increase in CD8 TILs and tumor PD-L1 expression in some patients
  – In ovarian patients, trend for better disease control
• Alternative varlilumab dosing regimens added to the study to explore intermittent CD27 signaling
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