Anti-CD27 Agonist Antibody Varlilumab with Nivolumab for Colorectal and Ovarian Cancer: Phase 1/2 Clinical Trial Results

Rachel E. Sanborn¹, Michael J. Pishvaian², Margaret K. Callahan³, Amy Weise⁴, Branimir I. Sikic⁵, Osama Rahma⁶, Daniel Cho⁷, Naiyer Rizvi⁸, Jose Lutzky⁹, Rhonda L. Bitting¹⁰, Alexander Starodub¹¹, Antonio Jimeno¹², Michael Yellin¹³, Tracey Rawls¹³, Laura Vitale¹³, Abdel Halim¹³, Hui Zhang¹³ and Tibor Keler¹³

¹ Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, ² Georgetown University, Washington, DC, ³ Memorial Sloan Kettering Cancer Center, New York, NY, ⁴ Karmanos Cancer Institute, Detroit, MI, ⁵ Stanford Medical Center, Stanford, CA, ⁶ Dana Farber Cancer Institute, Boston, MA, ⁷ Laura & Isaac Perlmutter Cancer Center, NY, NY, ⁸ Columbia University Medical Center, NY, NY, ⁹ Mount Sinai Comprehensive Cancer Center, Miami Beach, FL, ¹⁰ Wake Forest Baptist Heath, Winston-Salem, NC, ¹¹ Parkview Research Center, Fort Wayne, IN, ¹² University of Colorado Cancer Center, Aurora CO, ¹³ Celldex Therapeutics, Hampton, NJ
Combination of CD27 Costimulation with PD-(L)1 Blockade

CD27: Member of the TNF-receptor superfamily
- Single ligand is CD70 (tightly regulated)
- Constitutively expressed on most T cells/subset of B and NK cells
- CD27 activation:
  - Signaling through Traf2, Traf5
  - 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

Combining CD27 agonist Abs with PD-(L)1 blockade improves antitumor responses in several preclinical models

Varilumab: Fully human IgG1 CD27 agonist mAb
- Well tolerated as single agent, no MTD identified
- Single-agent antitumor activity demonstrated in advanced, refractory solid tumors or hematologic malignancies (n=90)

Adoptive transfer of Pmel-Tg T cells stimulated in vivo with peptide and Abs

DNA replication genes
Cytotoxicity and Proliferation genes

BCL1 lymphoma

Control
Anti-CD27 (varilumab)
Anti-PD-L1
Combination

% Survival

Days post tumor challenge

0 20 40 60 80 100 120 140 160

2 Bullock, et al. SITC 2014
3 Infante, et al. ASCO 2014
4 Burris, et al. JCO 2017
Phase 1/2 Study of Varlilumab in Combination with Nivolumab

**Key Eligibility Criteria**
- Progressive, recurrent or refractory ovarian cancer, CRC, SCCHN, melanoma, or NSCLC
- No prior anti-PD-(L)1
- ≥ 3 month washout for T cell directed mAbs (inc. anti-CTLA-4)
- ≤ 5 prior regimens for advanced disease
- No active CNS metastases
- No autoimmune disease
- CRC: Progression or intolerant to fluoropyrimidine, oxaliplatin, and irinotecan plus bevacizumab, cetuximab or panitumumab (if KRAS wild type), and regorafenib.
- Ovarian cancer: platinum-taxane frontline therapy

**Phase 1 Dose Escalation/Expansion**

Nivolumab 3 mg/kg q 2 weeks
Varlilumab escalating doses q 2 weeks:

- 0.1 mg/kg (n=6)
- 1 mg/kg (n=15)
- 10 mg/kg (n=15)

Well tolerated, MTD not identified1
No clear varlilumab dose response1

**Phase 2 Cohorts**

Nivolumab flat dose (240 mg) q 2 weeks

- CRC (n=18)**
- Ovarian (n=54)**

Varililumab 3 mg/kg q 2 weeks

- CRC 3 mg/kg q 2 weeks (n=18)
- Ovarian 3 mg/kg q 2 weeks (n=18)
- Ovarian 3 mg/kg q 12 weeks (n=18)
- Ovarian 0.3 mg/kg q 4 weeks (n=18)

**Colorectal and Ovarian Cancer Experience**

<table>
<thead>
<tr>
<th></th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Overall</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Cancer</td>
<td>8</td>
<td>58</td>
<td>66</td>
<td>7 continue treatment</td>
</tr>
<tr>
<td>CRC</td>
<td>21</td>
<td>21</td>
<td>42</td>
<td>2 continue treatment</td>
</tr>
</tbody>
</table>

Actual Enrollment (cut-off 13Apr18)

CNS, central nervous system; CRC, colorectal cancer; MTD, maximum tolerated dose; MSI, microsatellite instability; OS, overall survival; PD, pharmacodynamics; PFS, progression free survival; PK, pharmacokinetics

Predicted PK: Alternate dosing regimens/Intermittent CD27 signaling

Primary objective: Estimation of objective response rate (ORR)

ORR observed with nivolumab monotherapy:
- CRC: MSI-low 0-5%, MSI-high 31%
- Ovarian: 6-15%

Additional objectives: PFS, OS, Immunogenicity, PK, PD

* Varililumab administered for up to ~32 weeks (q2w and q4w schedules) or ~48 weeks (q12w schedule); nivolumab continues until progression
** Planned enrollment

1. Sanborn, ASCO 2017
2. Overman, ASCO 2016
3. Overman, Lancet 2017
4. Brahmer, NEJM 2012
5. Hamanishi, JCO 2015
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Ovarian Cancer (n=66)</th>
<th>CRC (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median [range])</td>
<td>64 (40-89)</td>
<td>55 (29-76)</td>
</tr>
<tr>
<td>Female (n [%])</td>
<td>66 (100%)</td>
<td>16 (38%)</td>
</tr>
<tr>
<td>ECOG performance status (n [%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>22 (33%)</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>1</td>
<td>44 (67%)</td>
<td>24 (57%)</td>
</tr>
<tr>
<td>Stage IV at study entry (n [%])</td>
<td>60 (91%)</td>
<td>42 (100%)</td>
</tr>
<tr>
<td>No. of prior treatment regimens (median [range])</td>
<td>3 (1-8)</td>
<td>4 (1-9)</td>
</tr>
<tr>
<td>Immunotherapy/cytokine</td>
<td>2 (3%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>PD-L1+ tumor (n/n [%])¹</td>
<td>20/59 (34%)</td>
<td>5/38 (13%)</td>
</tr>
<tr>
<td>MSI Status (n [%])</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSI-High</td>
<td>N/A</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>MSI-Low or MMR proficient</td>
<td>N/A</td>
<td>21 (50%)</td>
</tr>
<tr>
<td>MSI unknown</td>
<td>N/A</td>
<td>20 (48%)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; MSI, microsatellite instability; N/A, not applicable

¹ Denominator represents patients with tumor assessed for PD-L1 status. PD-L1+ criteria: ≥ 1% tumor cells staining positive, using the BMS developed PD-L1 IHC method at a central lab.

Data cut-off as of April 13, 2018
Varililumab & Nivolumab Combination Therapy is Well Tolerated

- No evidence of additive toxicity for the combination
- Toxicity profile similar across varililumab dosing regimens
- 10% of patients with CRC and ovarian cancer discontinued study treatment due to toxicity
- 10 patients with treatment-related SAEs
- One treatment-related death (pneumonitis in a patient with pulmonary metastases and prior history of chemotherapy-induced pneumonitis)

### Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Ovarian Cancer (n=66)</th>
<th>CRC (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>11 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>12 (18)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>8 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (6)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (6)</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased*</td>
<td>4 (6)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Lipase increased *</td>
<td>4 (6)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Abdominal pain *</td>
<td>3 (5)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Acute kidney injury *</td>
<td>3 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Pneumonitis *</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tumor lysis syndrome *</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hepatitis *</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Colitis *</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Small intestinal obstruction *</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Diarrhea *</td>
<td>4 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy *</td>
<td>1 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data shown as N (%). Table includes adverse events assessed as related to either varililumab or nivolumab for > 10% of patients overall and treatment-related SAEs (*)

Presented by: Rachel E. Sanborn
Tumor Response: Ovarian Cancer

Nivolumab dosing: 3 mg/kg q2w in Phase 1 and 240 mg q2w in Phase 2

ORR, Objective response rate; DCR, Disease control rate (best response of SD or better for ≥ 3 months). Analyses based on response-evaluable population (includes patients with symptomatic deterioration or death in absence of post-treatment tumor assessment).

Best Response:
- Partial Response (PR)
- Single time-point PR (uPR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Not Evaluable (NE)

Response rate by PD-L1 status:
- PDL-1 positive: 20% (n=4 of 20; 3 PR, 1 uPR)
- PDL-1 negative: 14% (n=5 of 37; 4 PR, 1 uPR)

Best Response:
- Partial Response (PR)
- Single time-point PR (uPR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Not Evaluable (NE)

PD-L1 Status:
- Negative

Numerical values represent % cells positive

Patient continues treatment

* Includes data provided after the analysis cut-off date

Actual PK:

Nivolumab dosing: 3 mg/kg q2w in Phase 1 and 240 mg q2w in Phase 2

ORR, Objective response rate; DCR, Disease control rate (best response of SD or better for ≥ 3 months). Analyses based on response-evaluable population (includes patients with symptomatic deterioration or death in absence of post-treatment tumor assessment).
Tumor Response: CRC

Patient with CRC initially considered MMR-proficient
- Experienced near-CR (95% tumor shrinkage), continues at 35 months
- Path IHC report: PMS2, hMLH-1, hMSH-2, hMSH-6 all present

Molecular analysis on baseline tumor
- Tissue from 2 patients with progressive disease used for comparison
- Strong pattern of differentially expressed genes
  - Similar expression of DNA repair enzymes
- High mutational burden likely contributed to response
  - May be result of mutations in MLH-1 and MSH-6

Nivolumab dosing: 3 mg/kg q2w in Phase 1 and 240 mg q2w in Phase 2
ORR, Objective response rate; DCR, Disease control rate (best response of SD or better for ≥ 3 months). Analyses based on response-evaluable population (includes patients with symptomatic deterioration or death in absence of post-treatment tumor assessment)

Best Response:
- Partial Response (PR)
- Single time-point PR (uPR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Not Evaluable (NE)

PD-L1 Status:
- Negative
  - Numerical values represent % cells positive
- Patient continues treatment

Differentially Expressed Genes

Mutational Load

CRC pt: PR    PD    PD

gDNA Mutational Load

Mutations

CRC pt: 0  500  1000  1500  2000  2500

Synonymous Non-synonymous

Rachel E. Sanborn

Molecular analysis on baseline tumor:
- Path IHC report: PMS2, hMLH-1, hMSH-2, hMSH-6 all present
Analysis of Immune Monitoring and Correlations with Outcome

Immune Monitoring Parameters:
- Peripheral blood: serum factors by multiplex; flow cytometry on whole blood/PBMC
- Tumor biopsies: baseline and on-treatment (day 29) immunohistochemistry
- Molecular profiling (in progress)

Correlative analysis:
- Patients with ovarian cancer sorted by:
  - “Benefit” = SD ≥ 16 wks, uPR, PR or CR
  - “No Benefit” = PD and SD < 16 wks
  - Correlative analysis included all ovarian patients
- Patients with CRC; Too few “Benefit” for analysis
PD-L1 Expression of Baseline Biopsy Samples

Patients with Ovarian Cancer
- Only 34% had any tumor PD-L1 expression
- Similar PD-L1 expression in Benefited and No Benefit groups

Patient with CRC
- Only 13% had any tumor PD-L1 expression

This patient had 28% reduction in tumor, then PD

Includes all patients with ovarian cancer and CRC

PD-L1 testing was performed using the BMS developed PD-L1 IHC method (Dako PD-L1 IHC 28-8 pharmDx assay); PD-L1+ defined as ≥ 1% of tumor cells

Rachel E. Sanborn
Generally Low TIL Levels in Baseline Biopsy Samples

Ovarian Cohort (all pts) - Baseline

CRC Cohort (all pts) - Baseline

- **CD4**
  - Benefit (n = 16): 11.7
  - No Benefit (n = 37): 9.1

- **CD8**
  - Benefit (n = 21): 9.1
  - No Benefit (n = 38): 7.3

- **FoxP3**
  - Benefit (n = 20): 1.4
  - No Benefit (n = 39): 1.5

- **CD4**
  - (n = 48): 3.1

- **CD8**
  - (n = 39): 5.0

- **FoxP3**
  - (n = 39): 2.7
Combination Treatment Increases Tumor PD-L1 and CD8 in Patients with Ovarian Cancer

- IHC analysis of all patients with ovarian cancer and CRC with paired biopsies (On-study - day 29)
- Patients with ovarian cancer had significant increase in tumor expression of PD-L1 and CD8+ TIL
  - 14 of 23 patients (61%) had increase in PD-L1 and 14 of 24 patients (58%) had increase in CD8
- These changes were rarely observed in CRC patient samples

(dashed line represents mean)
Enhanced PD-L1 Expression and CD8 TIL is Associated with Better Outcome in Ovarian Patients

All ovarian patients with paired biopsy samples (Day 29)

**Benefit/No Benefit**

<table>
<thead>
<tr>
<th></th>
<th>Benefit (n=14)</th>
<th>No Benefit (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 % Positive Tumor Cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired T-Test P=</td>
<td>0.016</td>
<td>0.52</td>
</tr>
</tbody>
</table>

**CD8 % Positive Tumor Cells**

<table>
<thead>
<tr>
<th></th>
<th>Benefit (n=14)</th>
<th>No Benefit (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired T-Test P=</td>
<td>0.025</td>
<td>0.22</td>
</tr>
</tbody>
</table>

**PFS**

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
<th>PR+uPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit</td>
<td>7.4</td>
<td>38%</td>
</tr>
<tr>
<td>No Benefit</td>
<td>3.5</td>
<td>13%</td>
</tr>
<tr>
<td>HR</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.066</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
<th>PR+uPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit</td>
<td>7.4</td>
<td>42%</td>
</tr>
<tr>
<td>No Benefit</td>
<td>2.6</td>
<td>0%</td>
</tr>
<tr>
<td>HR</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.015</td>
<td></td>
</tr>
</tbody>
</table>

(dashed line represents mean)
Expression of TIM-3, LAG-3 Does Not Distinguish Refractory Ovarian Patients

Analysis on ovarian patients with ↑CD8 TIL but varying clinical outcome

The inhibitory/exhaustion markers TIM-3 and LAG-3 increased in correlation with CD8 T cells independent of outcome.
Analysis of peripheral blood

- T cells and NK cells had marked up-regulation of HLA-DR
- Stark Treg decreases were seen in majority of patients
- Rapid increase in chemokines (CCL2, CCL4, CXCL9)
- Changes observed across all varilumab dose cohorts and similar between patients with CRC and Ovarian cancer
- No apparent correlation of peripheral blood parameters that we investigated with clinical outcome
Conclusions

- Varilumab and nivolumab combination therapy was generally well tolerated at all varilumab dose levels tested.
- Patients' baseline tumor biopsies were mostly “cold” (PD-L1 neg. or low and low TIL) with low expectation of responding to check-point inhibition monotherapy.
- Uniquely in ovarian cancer cohort, increased PD-L1 and CD8 TIL were observed in ~60% of patients with paired biopsy samples.
  - The increase in PD-L1 and CD8 TIL is associated with better clinical outcome.
- 3 mg/kg dosing of varilumab may have more clinical activity than other doses studied.
- Among CRC patients, durable clinical responses were observed in a patient with MSI-High tumor and one with a high mutational burden.
- Opportunities for further evaluation of varilumab/nivolumab:
  - Molecular analysis may identify biomarkers in baseline biopsies of ovarian patients whose tumors can be predicted to change from “cold” to “hot”.
  - Expanding the experience in CRC (or other tumors) with MSI-High or high mutational burden.
Acknowledgments

Thank you to the patients and their families who participated in this study

- Study CDX1127-02 investigators and their staff
  - Rachel Sanborn
  - Michael Pishvaian
  - Margaret Callahan
  - Amy Weise
  - Branimir I Sikic
  - Osama Rahma
  - Daniel Cho
  - Naiyer Rizvi
  - Jose Lutzky
  - Rhonda L. Bitting
  - Alexander Starodub
  - Antonio Jimeno

- Celldex Therapeutics
- Bristol-Myers Squibb