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

Rachel E. Sanborn[1], Michael J. Pishvaian[2], Margaret K. Callahan[3], Amy Weise[4], Branimir I. Sikic[5], Osama Rahma[6], Daniel Cho[7], Naiyer Rizvi[8], Jose Lutzky[9], Rhonda L. Bitting[10], Alexander Starodub[11], Antonio Jimeno[12], Michael Yellin[13], Tracey Rawls[13], Laura Vitale[13], Abdel Halim[13], Hui Zhang[13] and Tibor Keler[13]

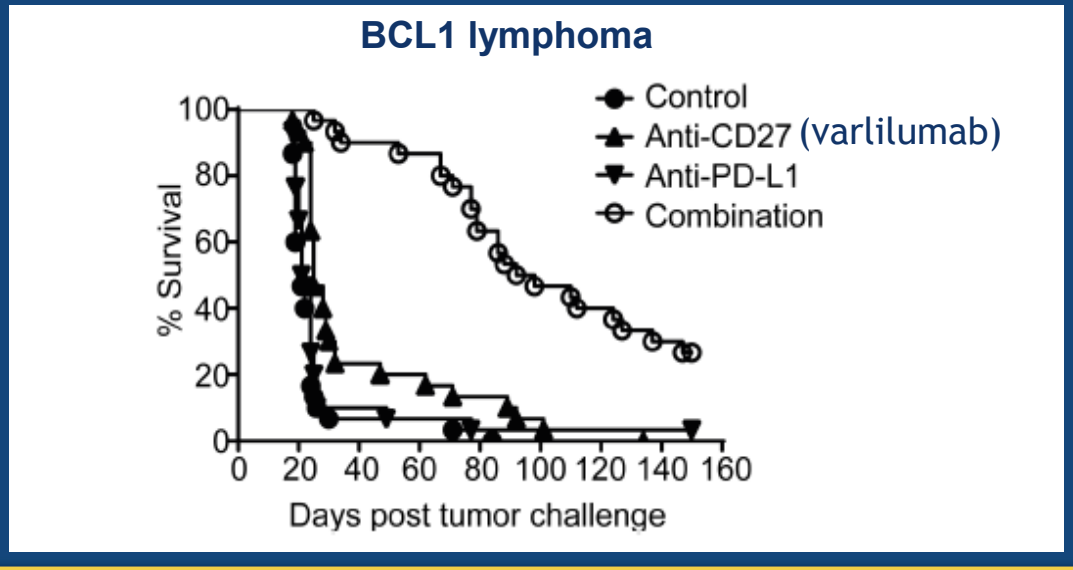
[1] Robert W. Franz Cancer Research Center, Earle A. Chiles Research Institute, Providence Cancer Center, Portland, OR, [2] Georgetown University, Washington, DC, [3] Memorial Sloan Kettering Cancer Center, New York, NY, [4] Karmanos Cancer Institute, Detroit, MI, [5]Stanford Medical Center, Stanford, 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

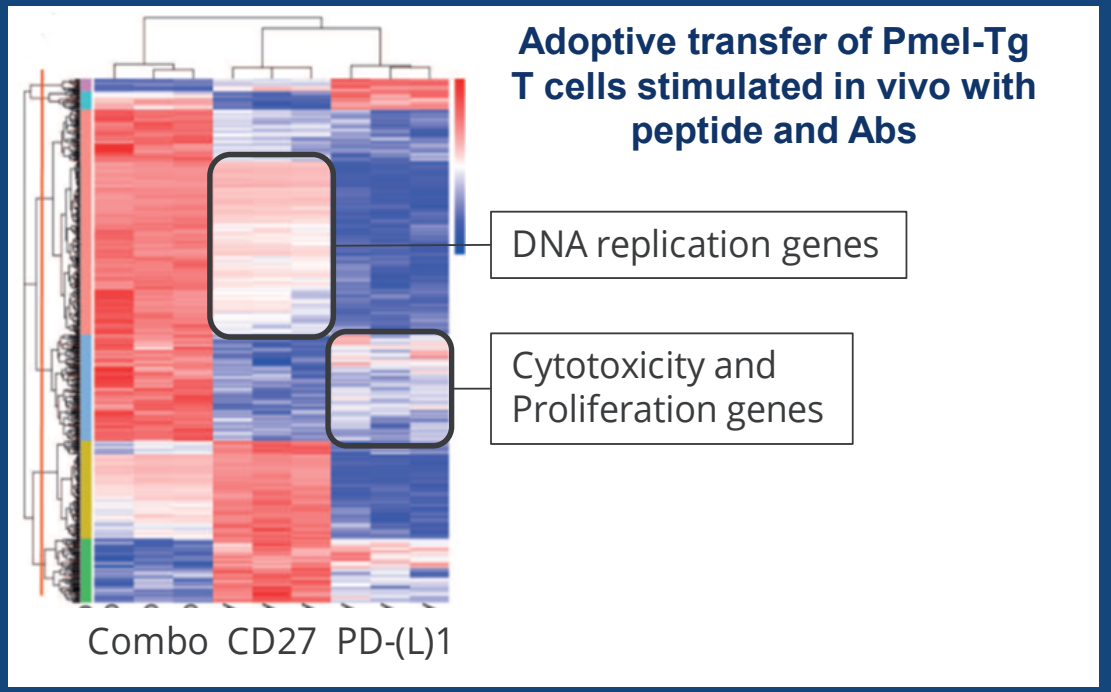
CD27: Member of the TNF-receptor superfamily

- Single ligand is CD70 (tightly regulated)
- Constitutively expressed on most T cells/subset of B and NK cells[1]
- 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

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



Cooperative roles of anti-CD27 and PD-(L)1 drives proliferation and cytotoxicity of T cells[1]



Varlilumab: 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) [2, 3, 4]

[1] Buchan. et al. Clin Can Res 2018
[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 identified*[1]
- *No clear varlilumab dose response*[1]

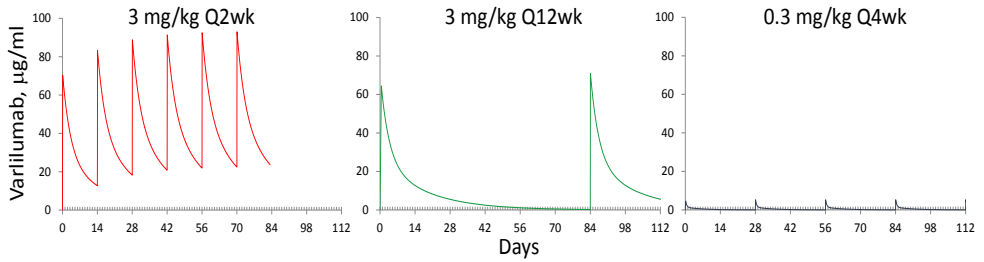
Phase 2 Cohorts*

Nivolumab flat dose (240 mg) q 2 weeks

CRC (n=18)** → Varlilumab 3 mg/kg q 2 weeks

Ovarian (n=54)** → Varlilumab
3 mg/kg q 2 weeks (n=18)
3 mg/kg q 12 weeks (n=18)
0.3 mg/kg q 4 weeks (n=18)

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%*[2]*, MSI-high 31%*[3]
- *Ovarian: 6-15%*[4,5]

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

Colorectal and Ovarian Cancer Experience

	Actual Enrollment			Status (cut-off 13Apr18)
	Phase 1	Phase 2	Overall	
Ovarian Cancer	8	58	66	7 continue treatment
CRC	21	21	42	2 continue treatment

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

* Varlilumab 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

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

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

Varlilumab & Nivolumab Combination Therapy is Well Tolerated

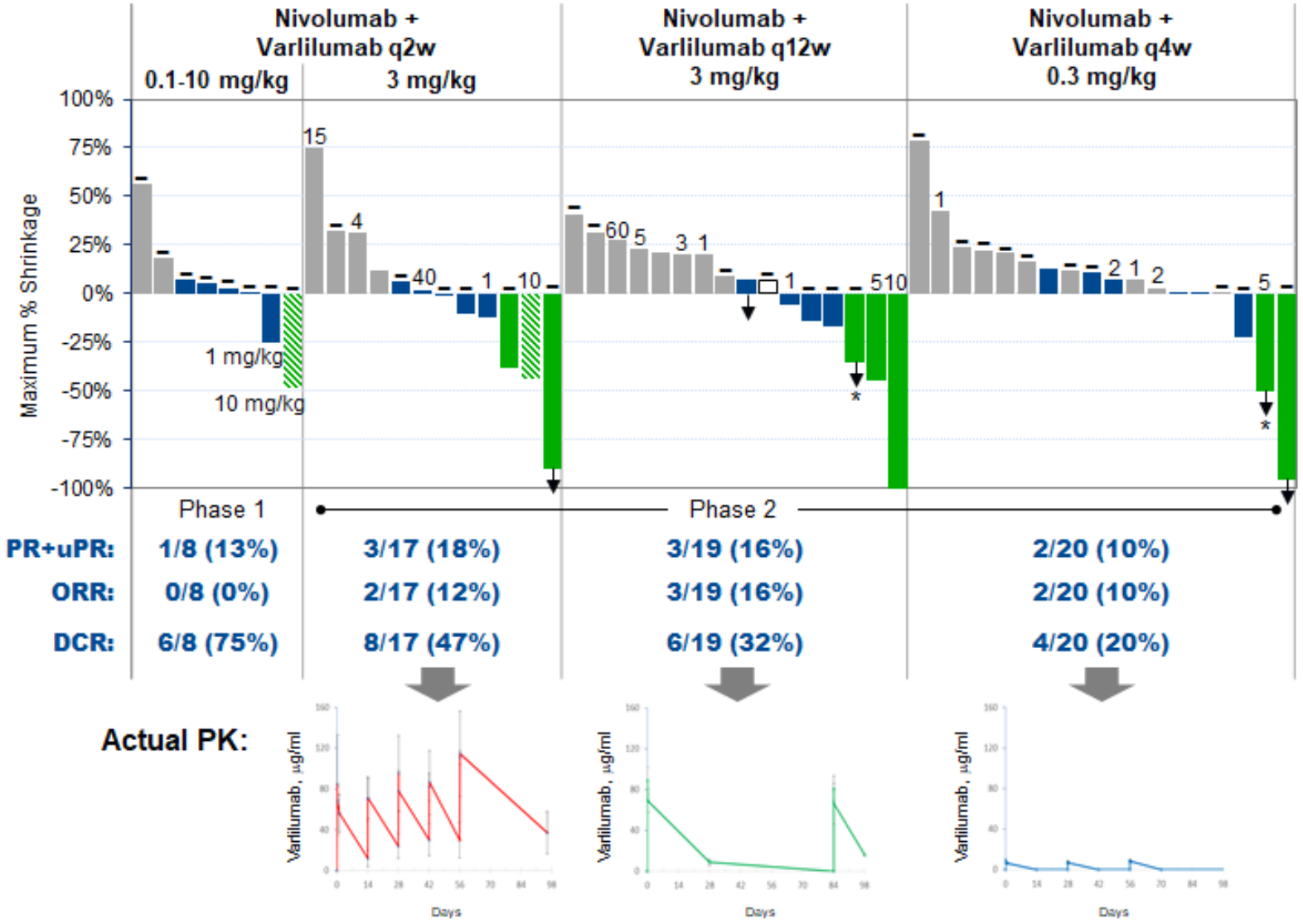
- No evidence of additive toxicity for the combination
- Toxicity profile similar across varlilumab dosing regimens
- 10% of patients with CRC and ovarian cancer discontinued study treatment due to toxicity
- 10 patients with treatment-related SAEs
- One treatment-related death (pneumonitis in a patient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

Treatment-Related Adverse Events

	Ovarian Cancer (n=66)			CRC (n=42)		
	All	Grade 3-4	Grade 5	All	Grade 3-4	Grade 5
Infusion Reaction	11 (17)	0	0	13 (31)	0	0
Pruritus	12 (18)	0	0	6 (14)	0	0
Rash	12 (18)	0	0	6 (14)	0	0
Fatigue	5 (8)	0	0	5 (12)	0	0
Rash maculo-papular	8 (12)	0	0	4 (10)	1 (2)	0
Lymphopenia	4 (6)	2 (3)	0	7 (17)	5 (12)	0
Nausea	4 (6)	0	0	7(17)	0	0
ALT increased*	4 (6)	1 (2)	0	2 (5)	1 (2)	0
Lipase increased *	4 (6)	4 (6)	0	1 (2)	1 (2)	0
Abdominal pain *	3 (5)	1 (2)	0	0	0	0
Acute kidney injury *	3 (5)	2 (3)	0	0	0	0
Pneumonitis *	0	0	0	2 (5)	0	1 (2)
Tumor lysis syndrome *	1 (2)	1 (2)	0	0	0	0
Hepatitis *	1 (2)	1 (2)	0	0	0	0
Colitis *	1 (2)	1 (2)	0	0	0	0
Small intestinal obstruction *	1 (2)	1 (2)	0	0	0	0
Diarrhea *	4 (6)	0	0	5 (12)	0	0
Peripheral sensory neuropathy *	1 (2)	0	0	0	0	0

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

Tumor Response: Ovarian Cancer



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

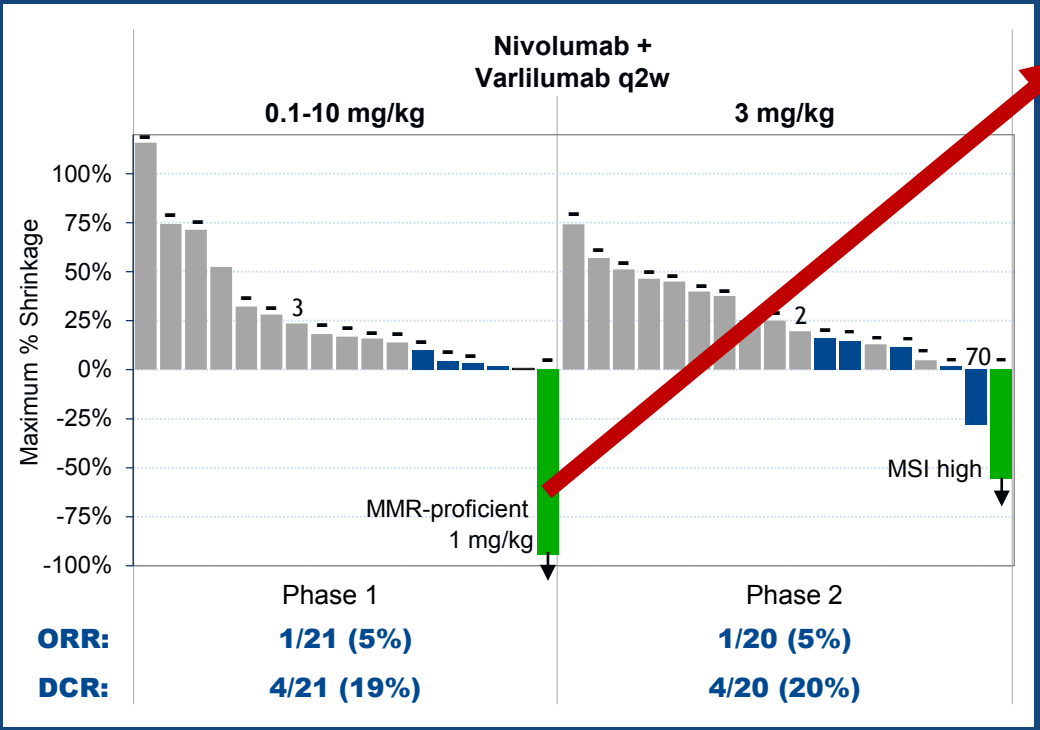
* Includes data provided after the analysis cut-off date

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)

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



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

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

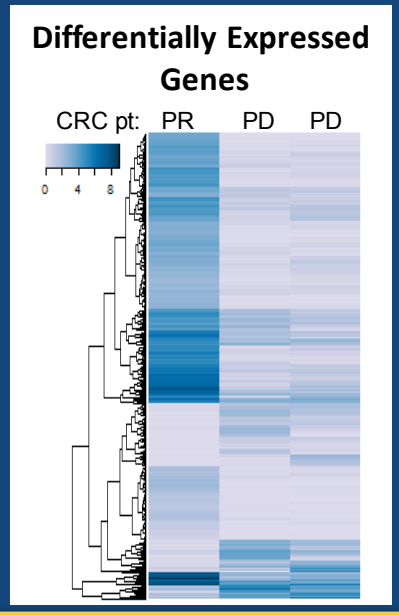
ORR, Objective response rate; DCR, Disease control rate (best response of SD or better for ≥ 3 months). Analyses based on response-evaluable population (includes patients with symptomatic deterioration or death in absence of post-treatment tumor assessment)

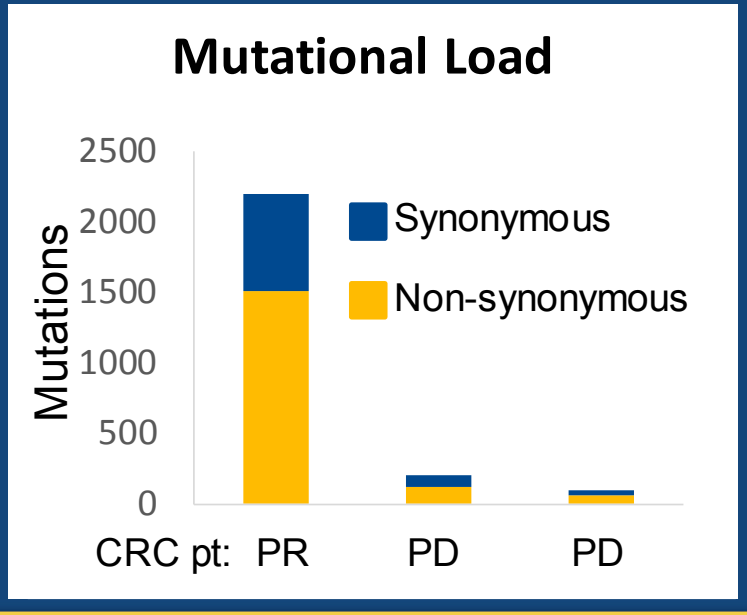
Patient with CRC initially considered MMR-proficient

- 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





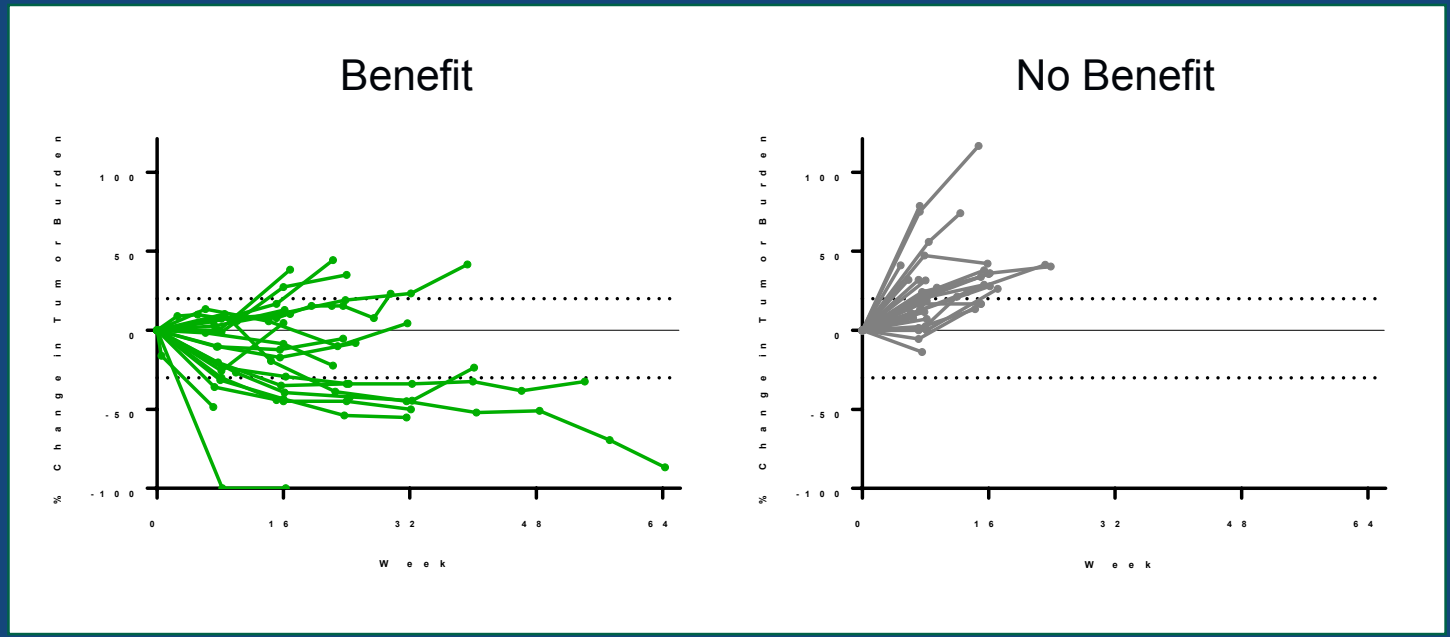
Analysis of Immune Monitoring and Correlations with Outcome

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:

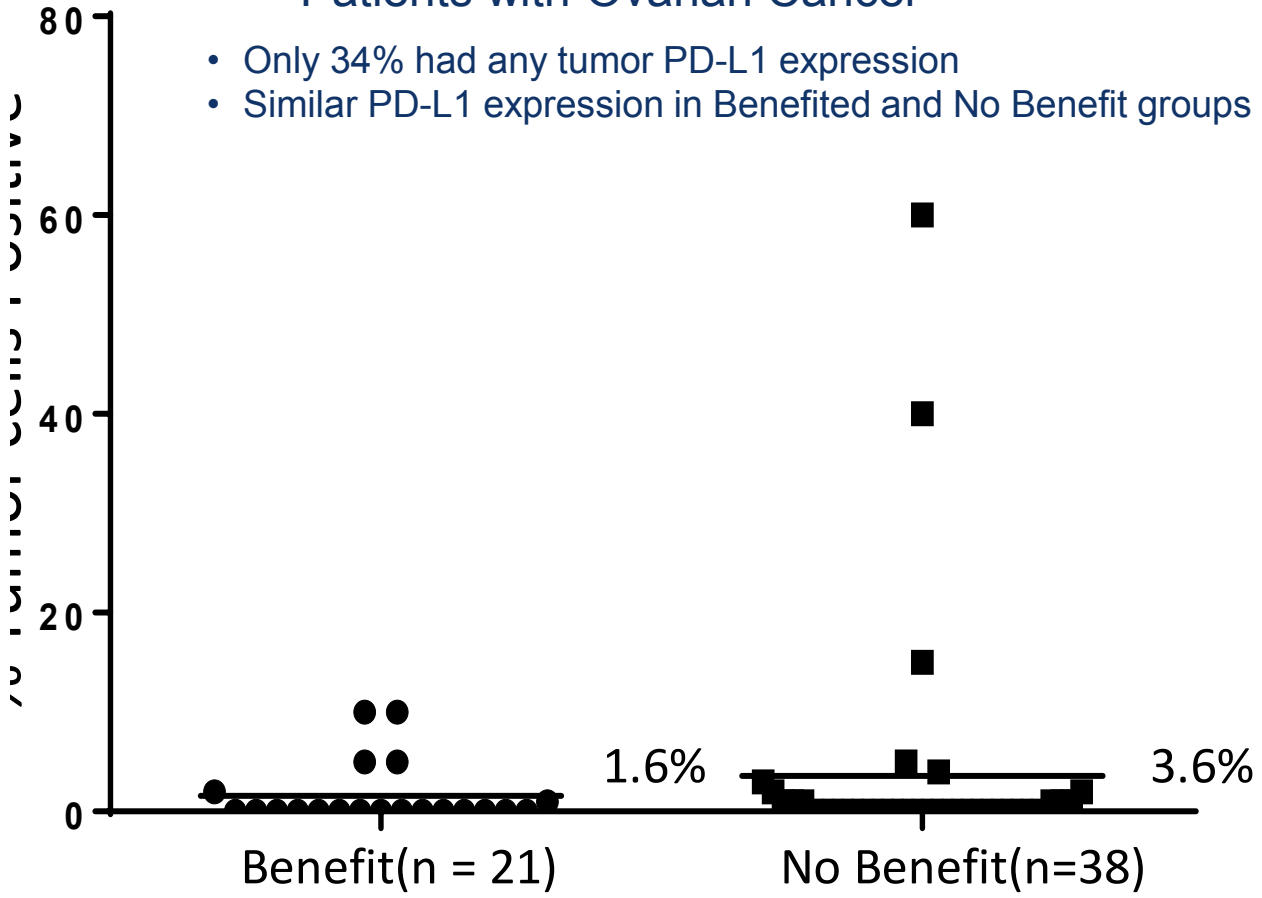
- Patients with ovarian cancer sorted by:
  - **"Benefit"** = SD ≥ 16wks, uPR, PR or CR
  - **"No Benefit"** = PD and SD < 16 wks
  - Correlative analysis included all ovarian patients
- Patients with CRC; Too few "Benefit" for analysis



PD-L1 Expression of Baseline Biopsy Samples

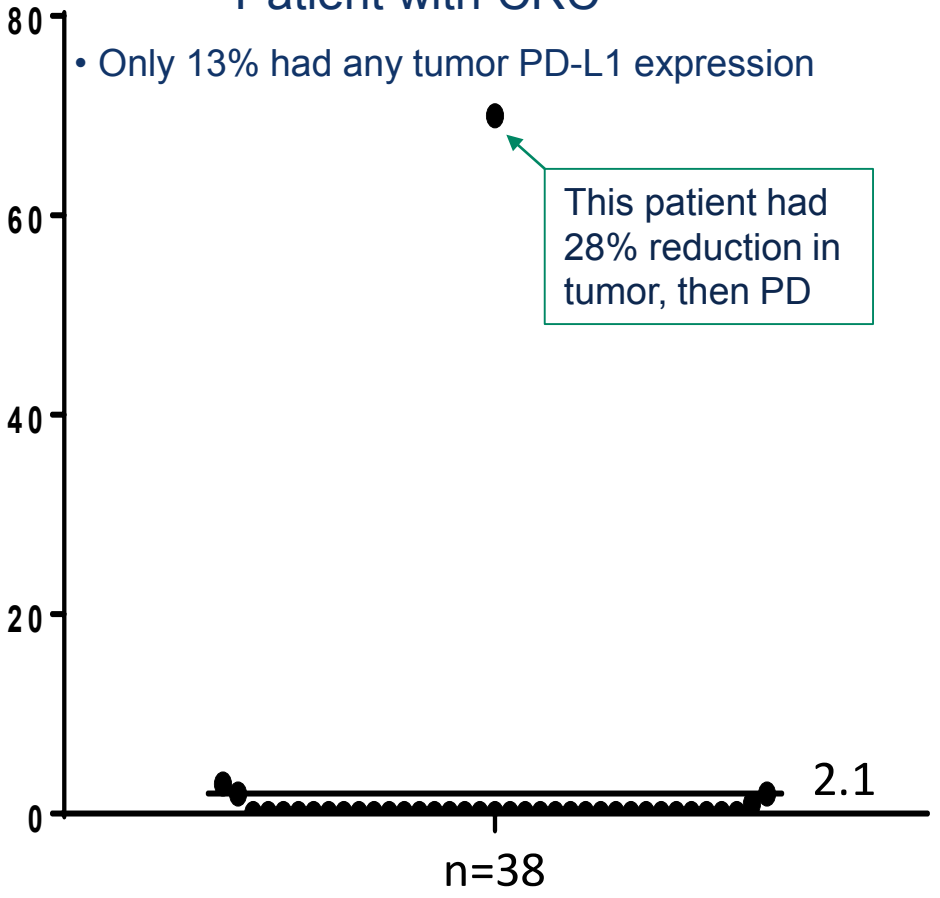
Patients with Ovarian Cancer

- 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

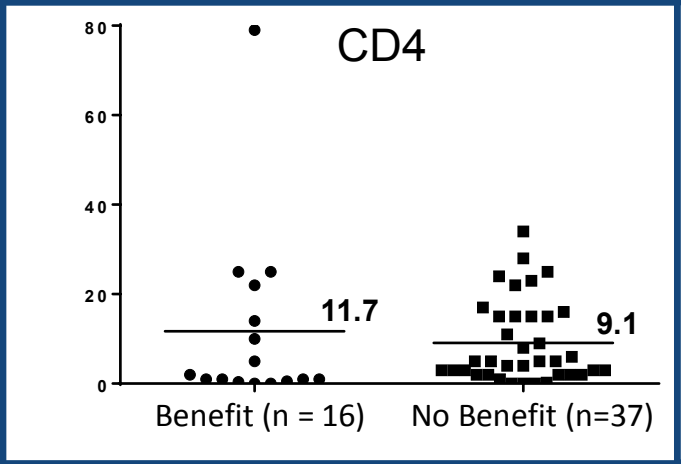


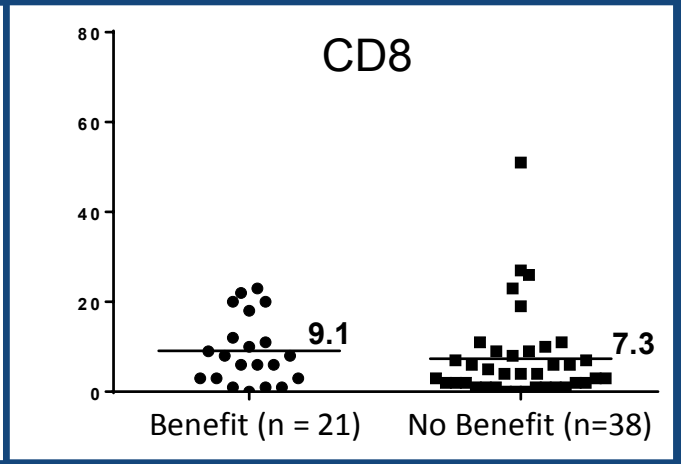
Includes all patients with ovarian cancer and CRC

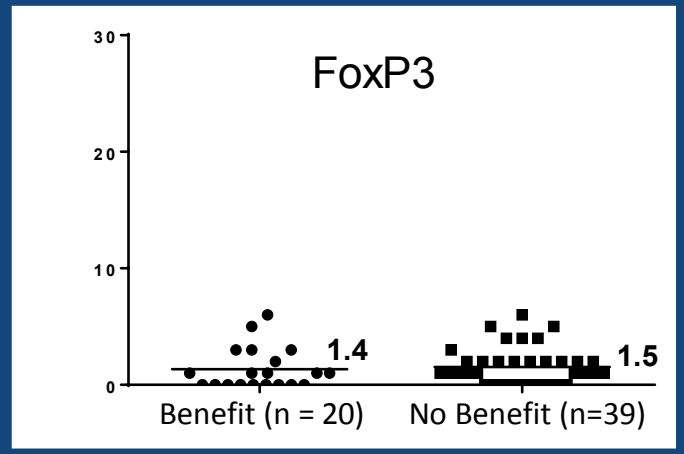
PD-L1 testing was performed using the BMS developed PD-L1 IHC method (Dako PD-L1 IHC 28-8 pharmDx assay); PD-L1+ defined as ≥ 1% of tumor cells

Generally Low TIL Levels in Baseline Biopsy Samples

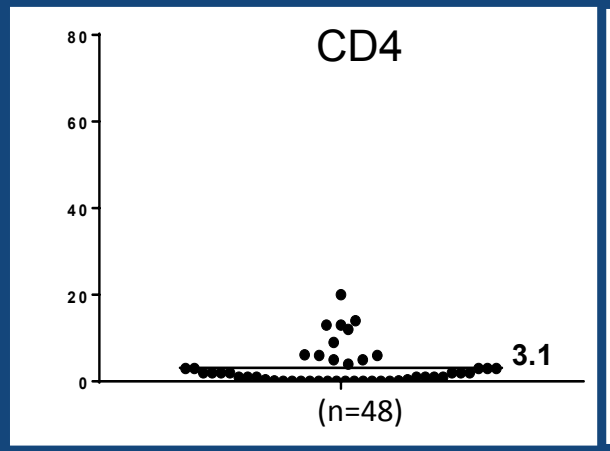
Ovarian Cohort (all pts) - Baseline

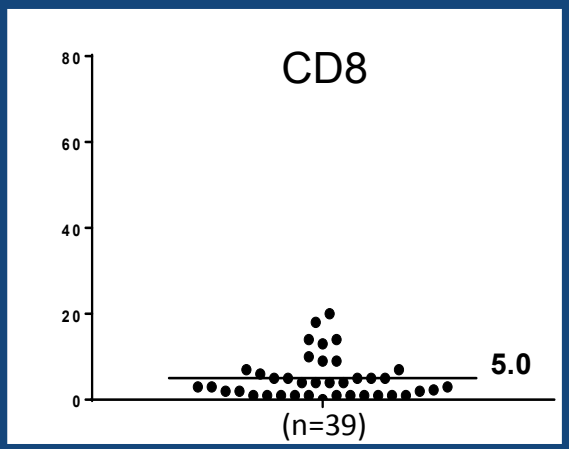


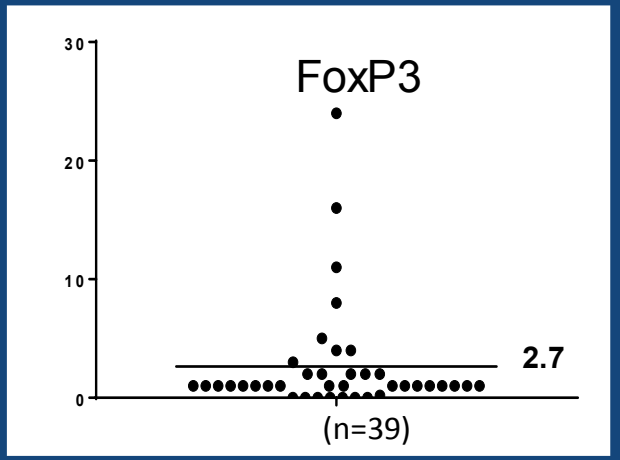




CRC Cohort (all pts)- Baseline

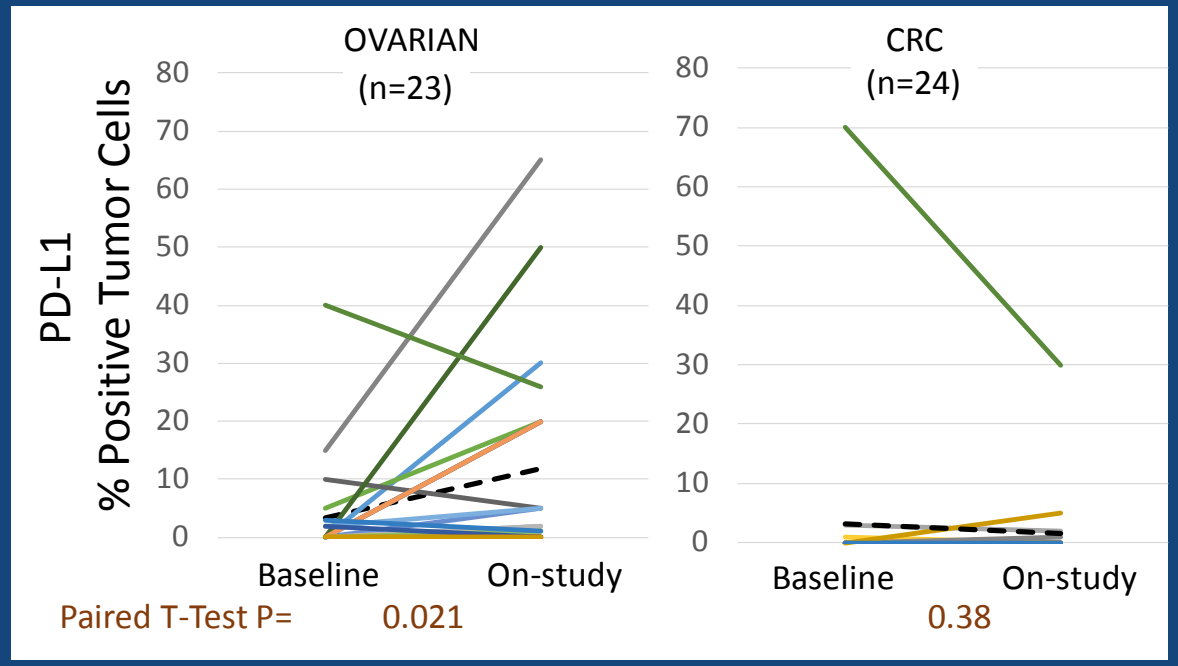


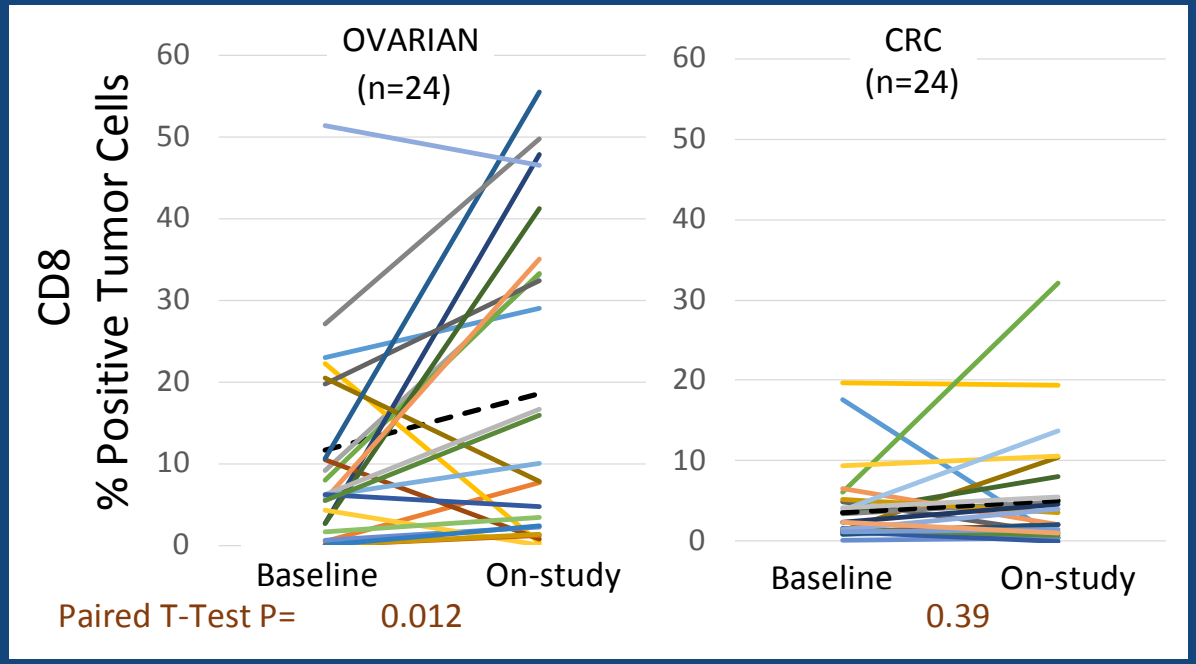




Combination Treatment Increases Tumor PD-L1 and CD8 in Patients with Ovarian Cancer

- 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



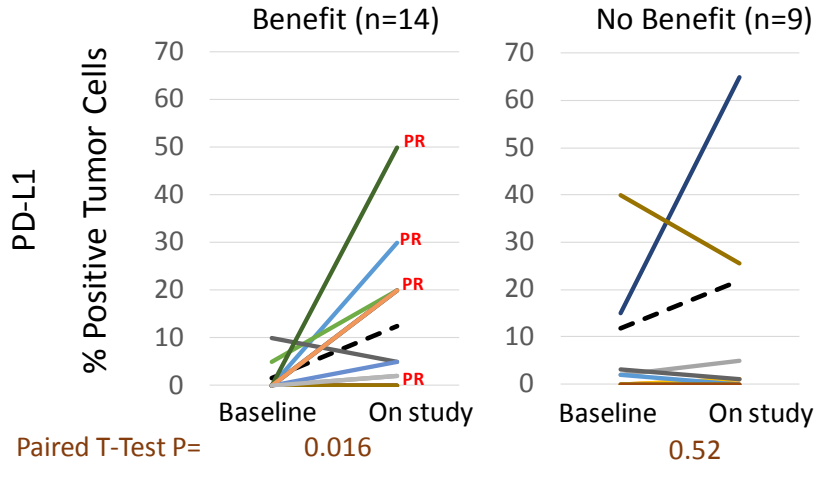


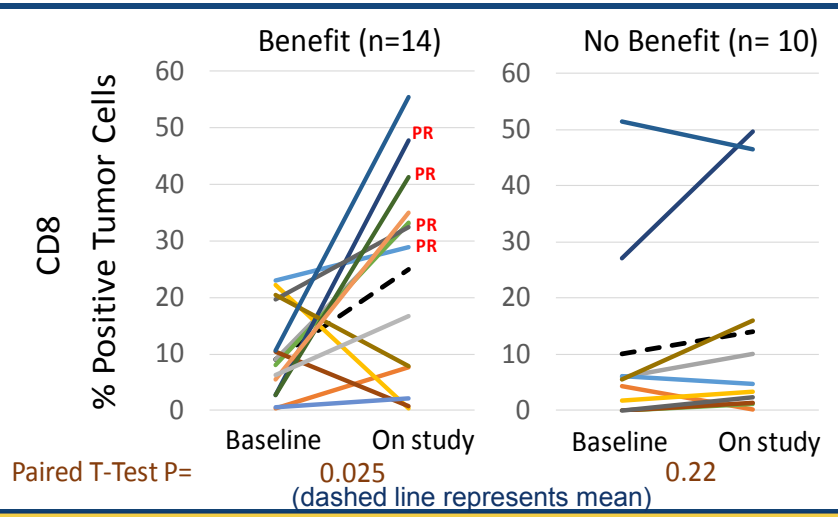
(dashed line represents mean)

Enhanced PD-L1 Expression and CD8 TIL is Associated with Better Outcome in Ovarian Patients

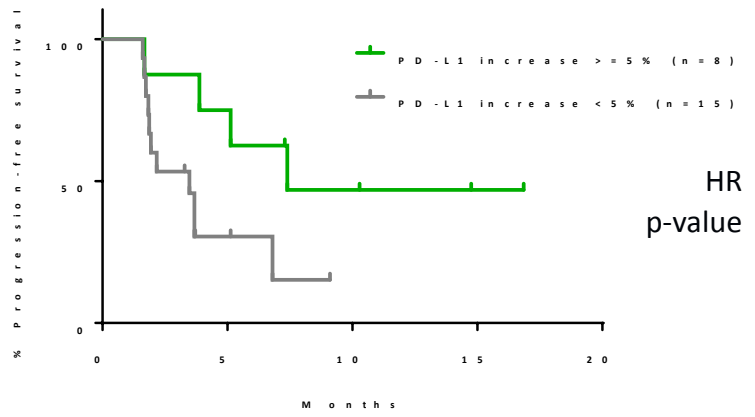
All ovarian patients with paired biopsy samples (Day 29)

Benefit/No Benefit

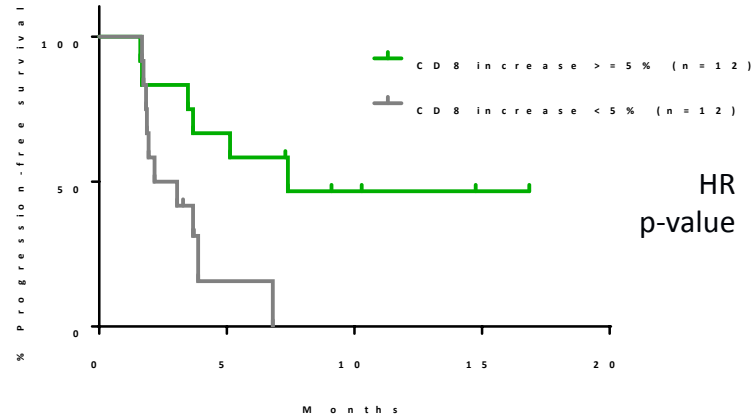




PFS



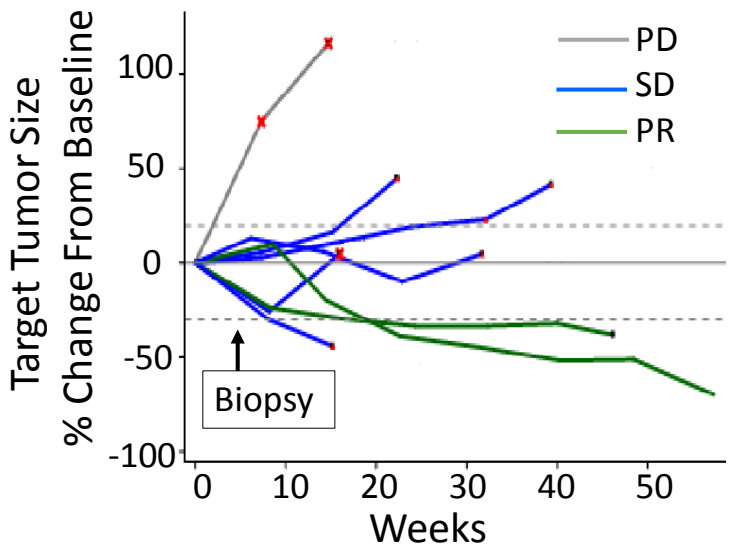
	Median (mos)	PR+uPR
PD-L1 increase >=5% (n=8)	7.4	38%
PD-L1 increase <5% (n=15)	3.5	13%
HR	0.32	
p-value	0.066	

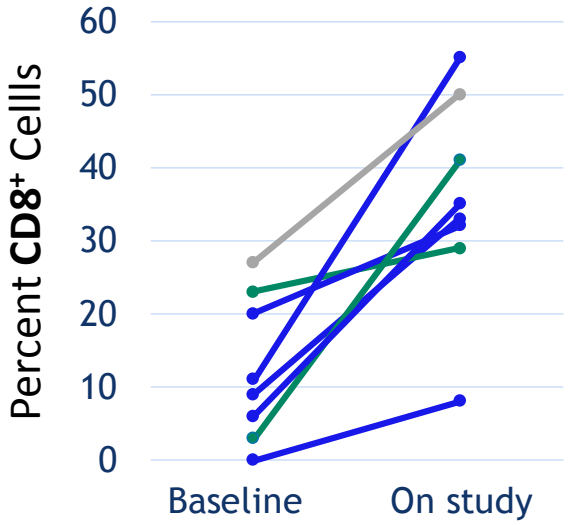


	Median (mos)	PR+uPR
CD8 increase >=5% (n=12)	7.4	42%
CD8 increase <5% (n=12)	2.6	0%
HR	0.24	
p-value	0.015	

Expression of TIM-3, LAG-3 Does Not Distinguish Refractory Ovarian Patients

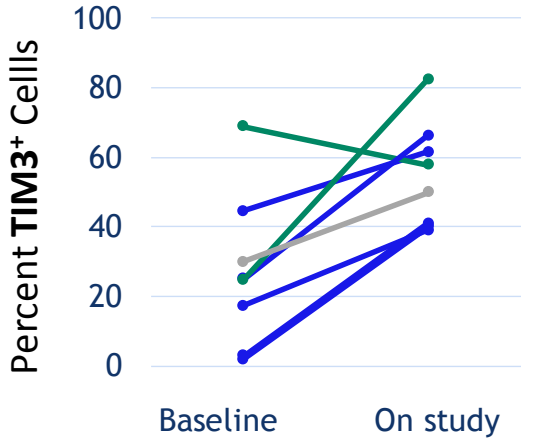
Analysis on ovarian patients with ↑CD8 TIL but varying clinical outcome

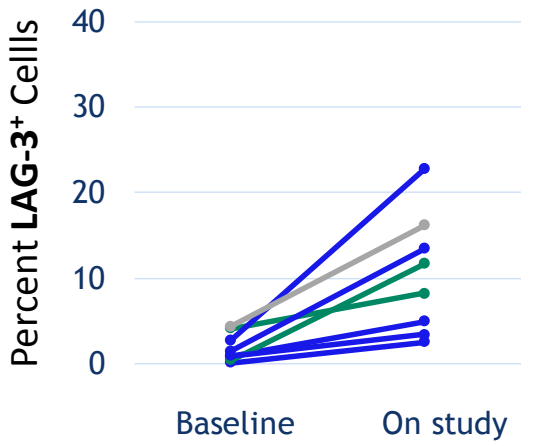




The inhibitory/exhaustion markers TIM-3 and LAG-3 increased in correlation with CD8 T cells independent of outcome

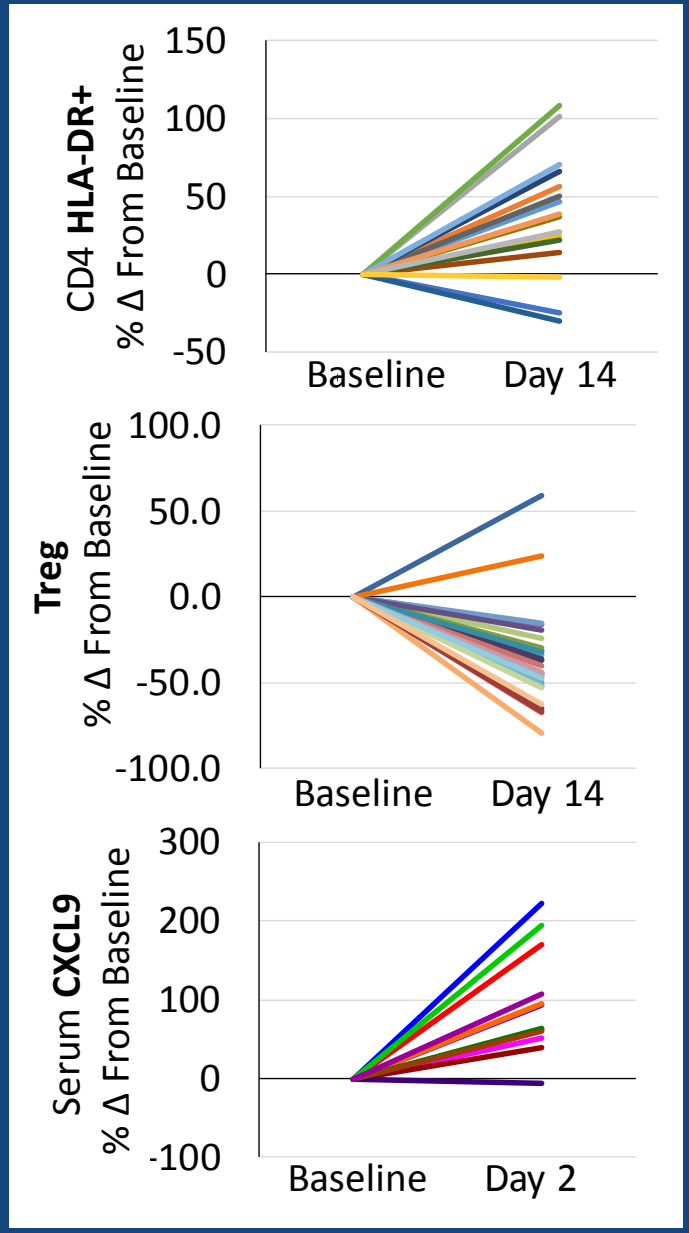
Expression of exhaustion markers





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 varlilumab 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

- Varlilumab and nivolumab combination therapy was generally well tolerated at all varlilumab 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 varlilumab 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 varlilumab/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