

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

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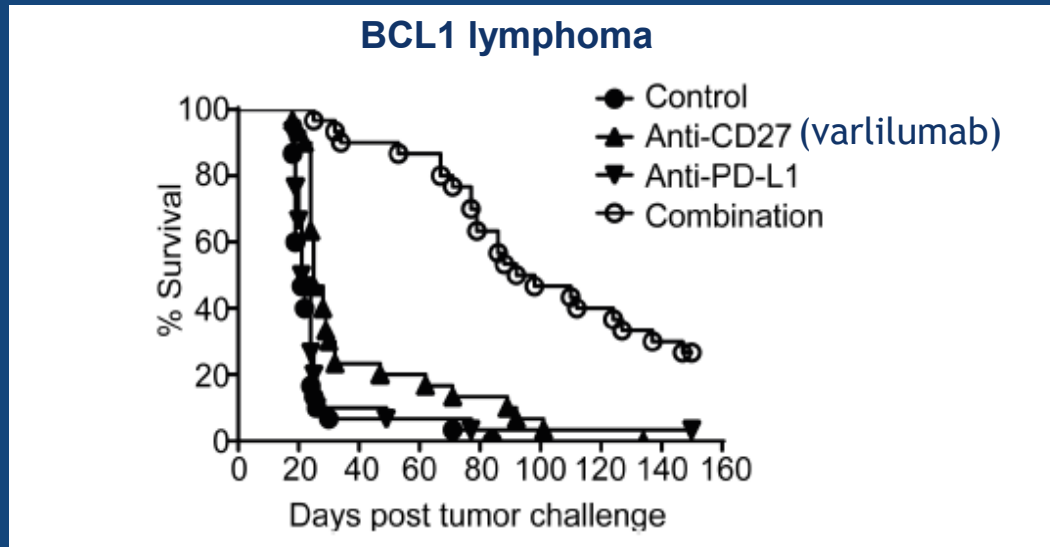
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# Combination of CD27 Costimulation with PD-(L)1 Blockade

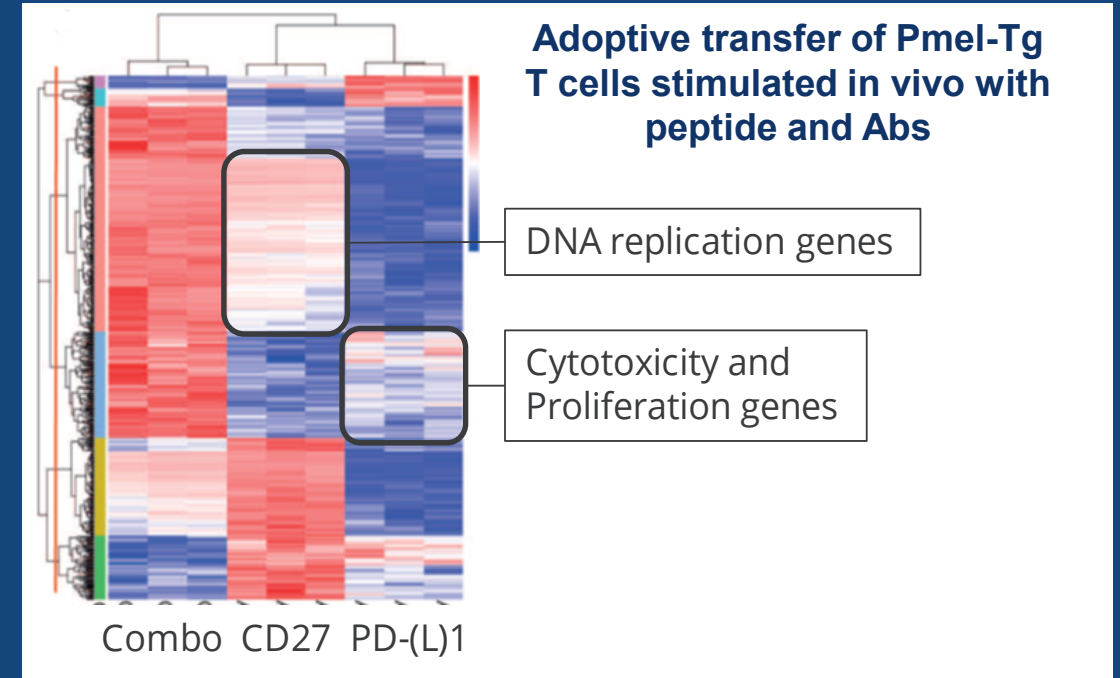
## CD27: Member of the TNF-receptor superfamily

- Single ligand is CD70 (tightly regulated)
- Constitutively expressed on most T cells/subset of B and NK cells<sup>1</sup>
- CD27 activation:
  - Signaling through Traf2, Traf 5
  - Activation of the NF- $\kappa$ B 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<sup>1</sup>



## Cooperative roles of anti-CD27 and PD-(L)1 drives proliferation and cytotoxicity of T cells<sup>1</sup>



## 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)<sup>2, 3, 4</sup>

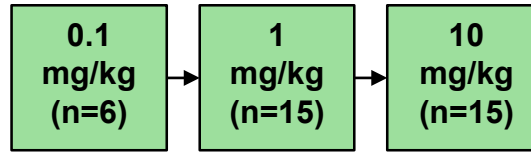
# Phase 1/2 Study of Varlilumab in Combination with Nivolumab

## 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\*

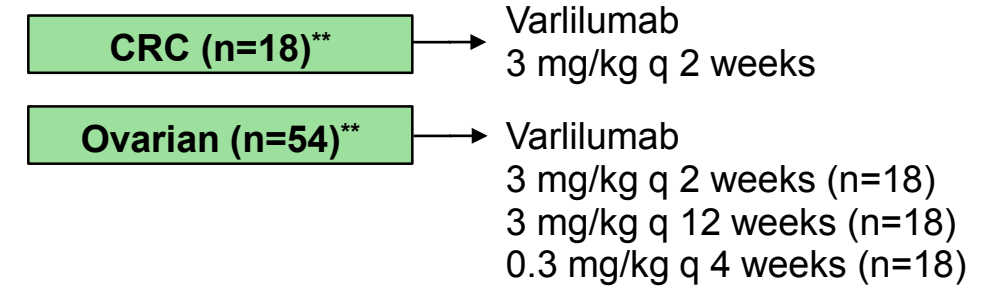
Nivolumab 3 mg/kg q 2 weeks  
Varlilumab escalating doses  
q 2 weeks:



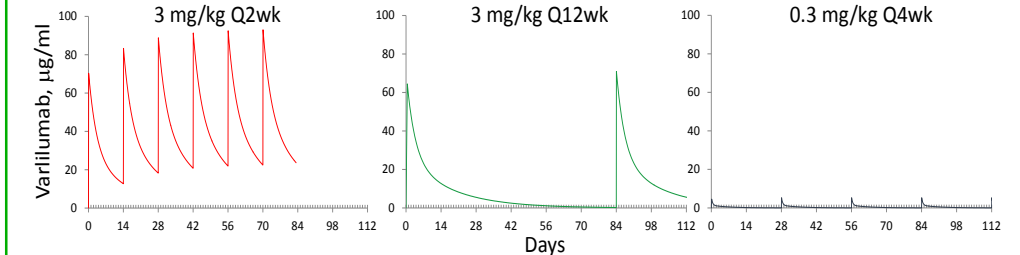
- *Well tolerated, MTD not identified<sup>1</sup>*
- *No clear varlilumab dose response<sup>1</sup>*

## Phase 2 Cohorts\*

Nivolumab flat dose (240 mg) q 2 weeks



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%<sup>2</sup>, MSI-high 31%<sup>3</sup>
- Ovarian: 6-15%<sup>4,5</sup>

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

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

\*\* Planned enrollment

## 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

# Baseline Patient Characteristics

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

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

<sup>1</sup> 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

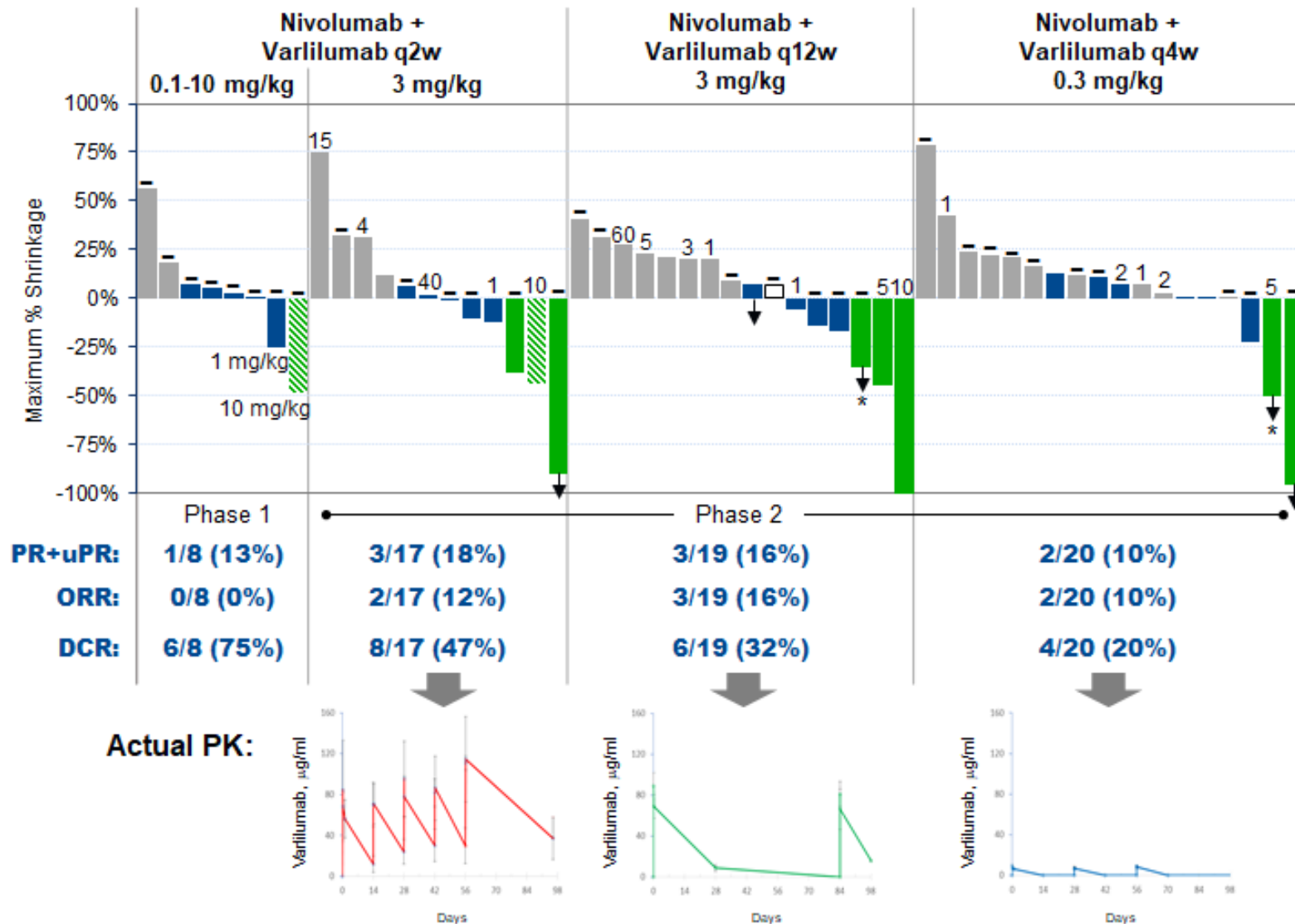
## Treatment-Related Adverse Events

- 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)

	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

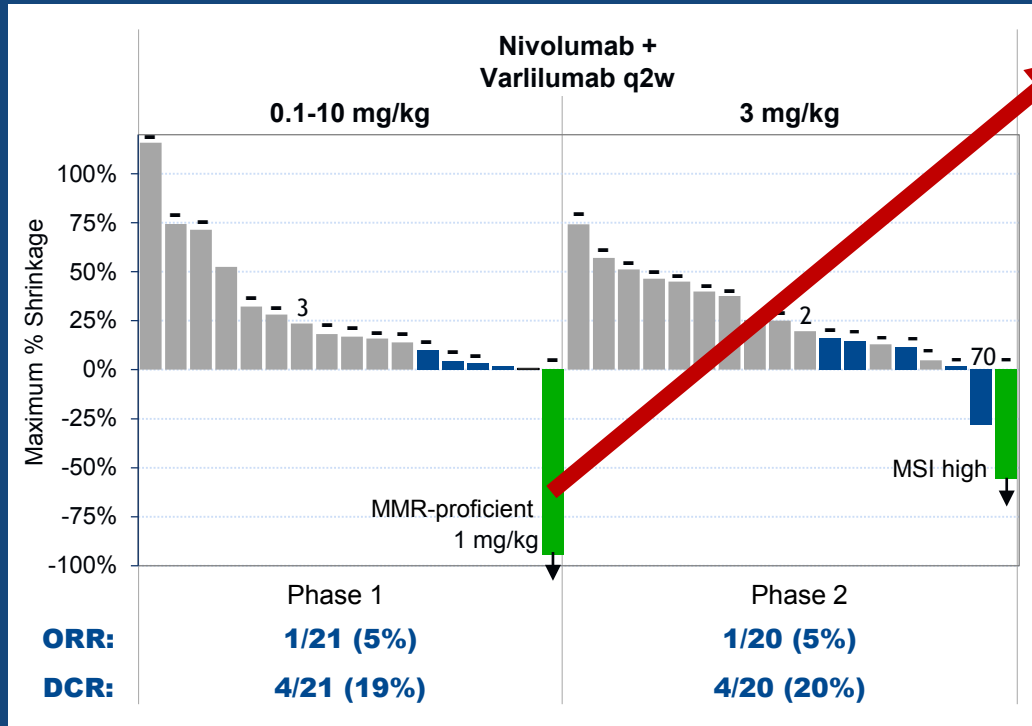
Response rate by PD-L1 status:  
PDL-1 positive: 20% (n=4 of 20; 3 PR, 1 uPR)  
PDL-1 negative: 14% (n=5 of 37; 4 PR, 1 uPR)

**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



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

**Best Response:**

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

**PD-L1 Status:**

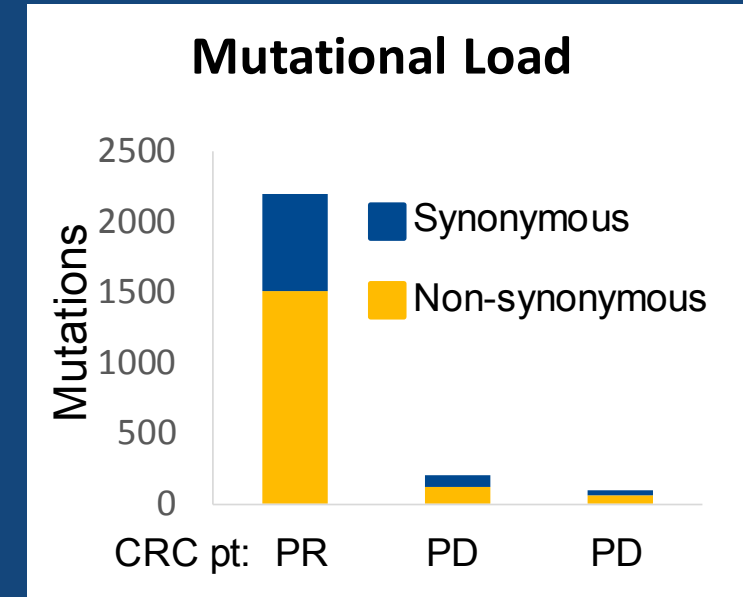
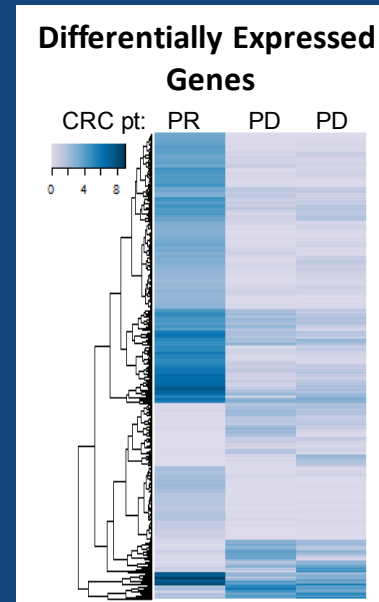
- Negative

Numerical values represent % cells positive

↓ Patient continues treatment

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

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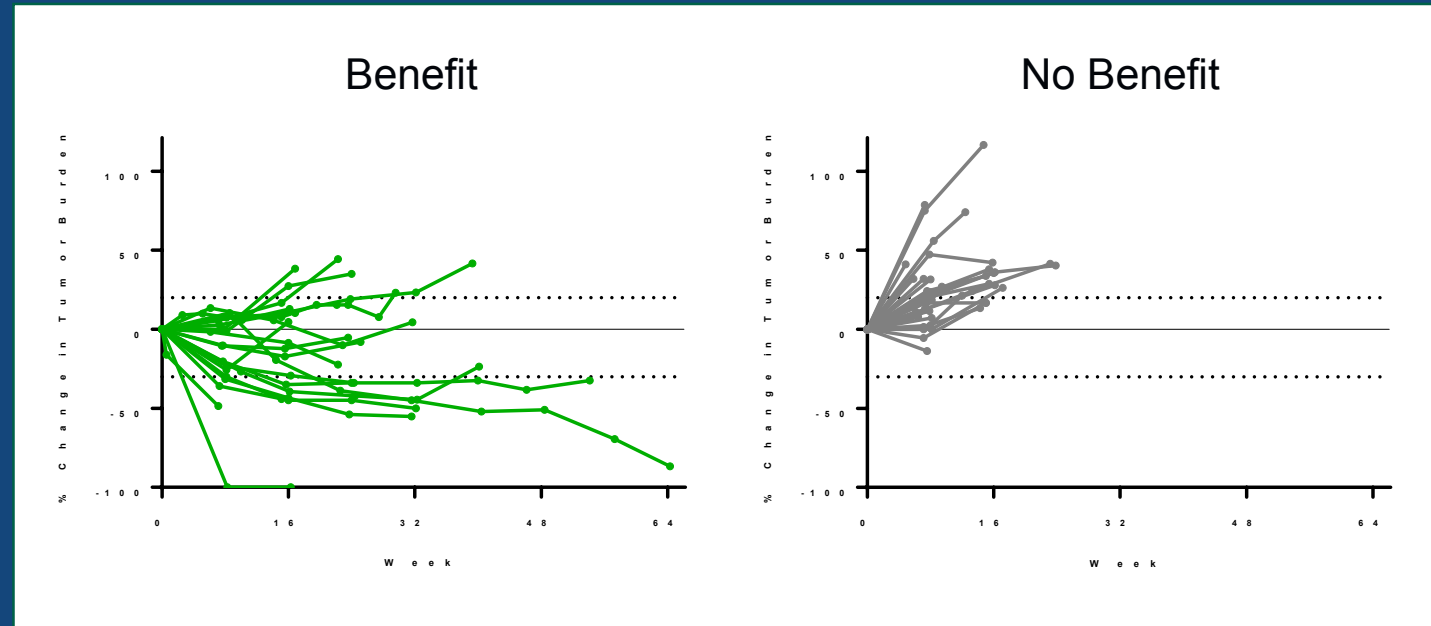
# Analysis of Immune Monitoring and Correlations with Outcome

## 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  $\geq$  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

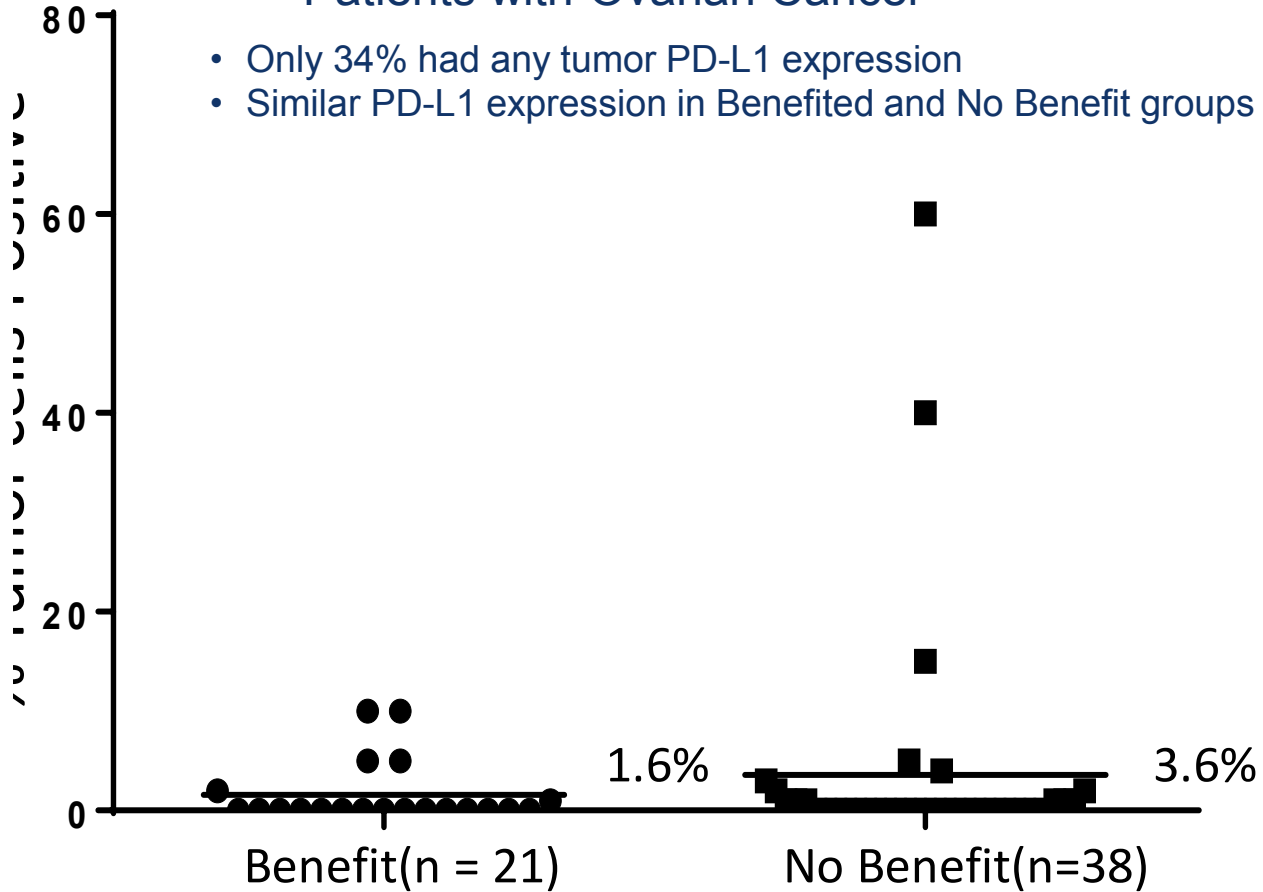




# PD-L1 Expression of Baseline Biopsy Samples

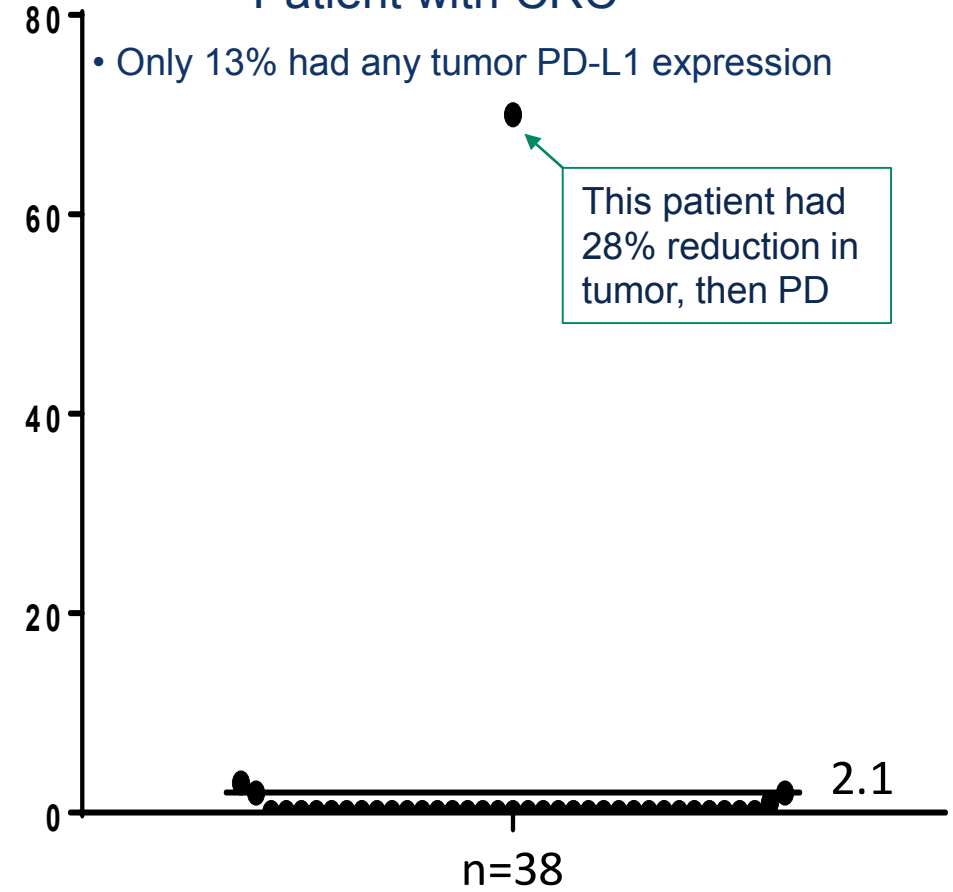
## Patients with Ovarian Cancer

- 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



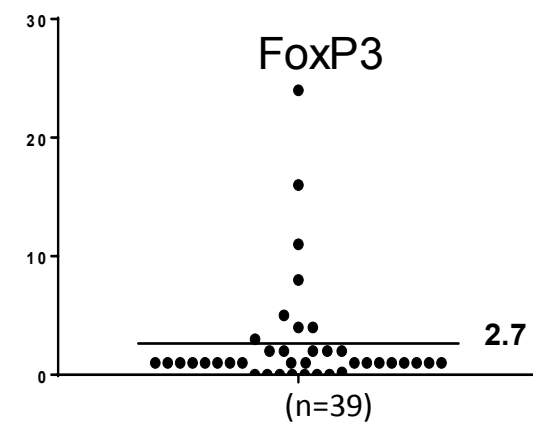
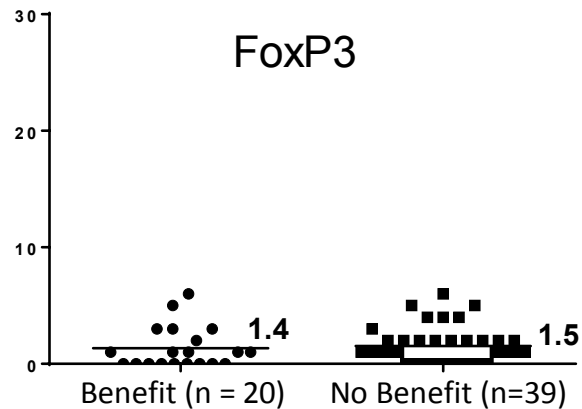
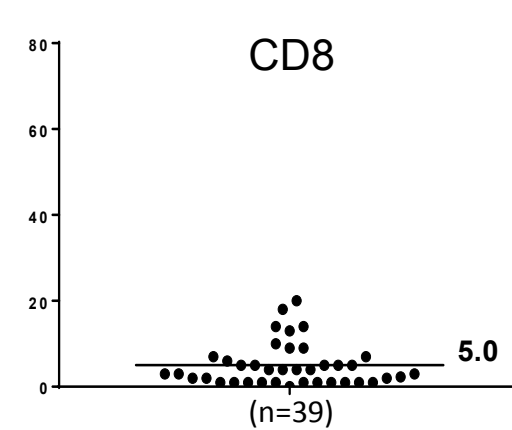
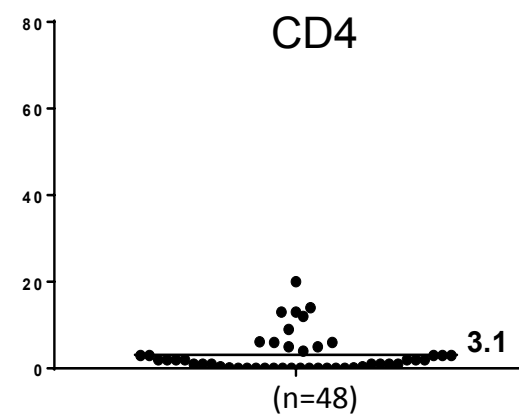
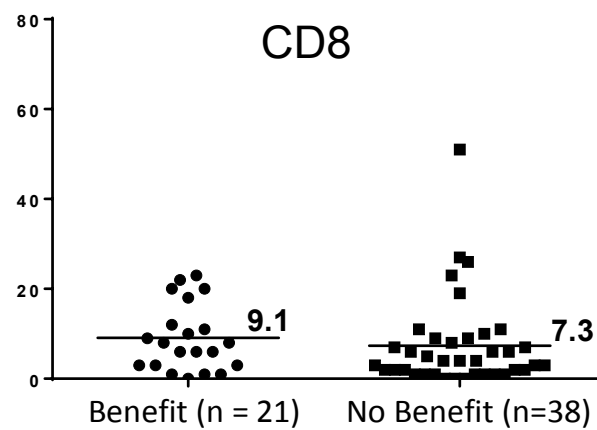
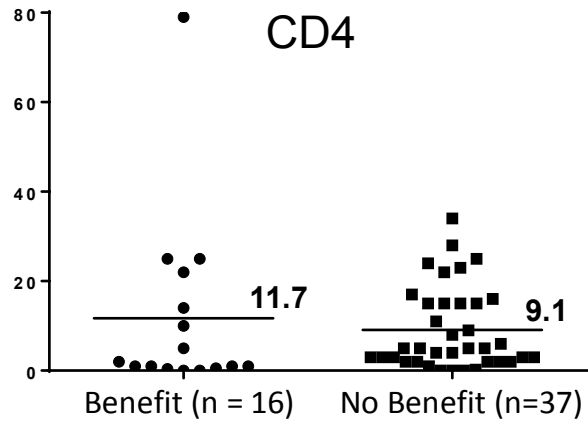
Includes all patients with ovarian cancer and CRC

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  $\geq 1\%$  of tumor cells

# Generally Low TIL Levels in Baseline Biopsy Samples

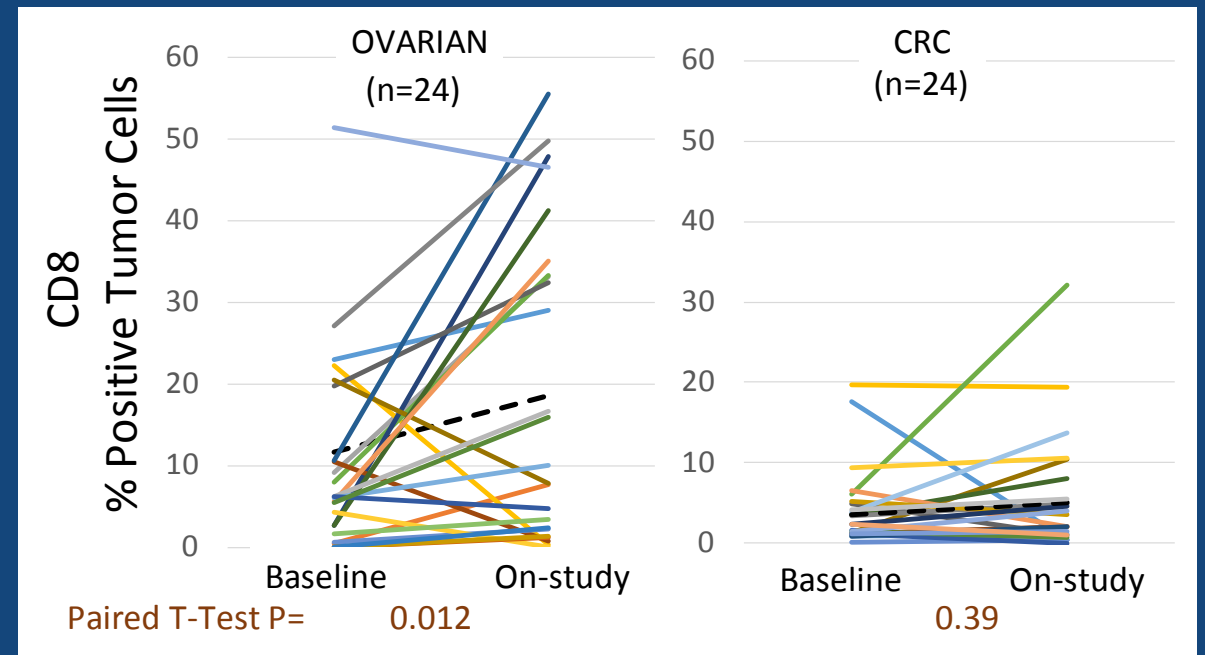
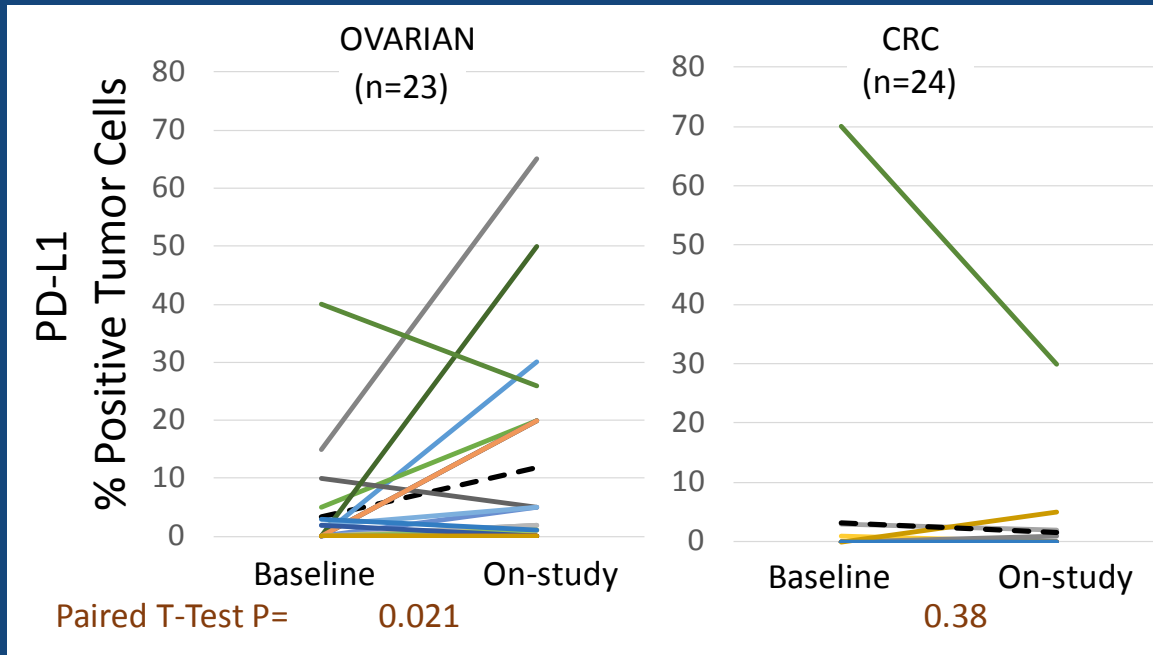
Ovarian Cohort (all pts) - Baseline

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

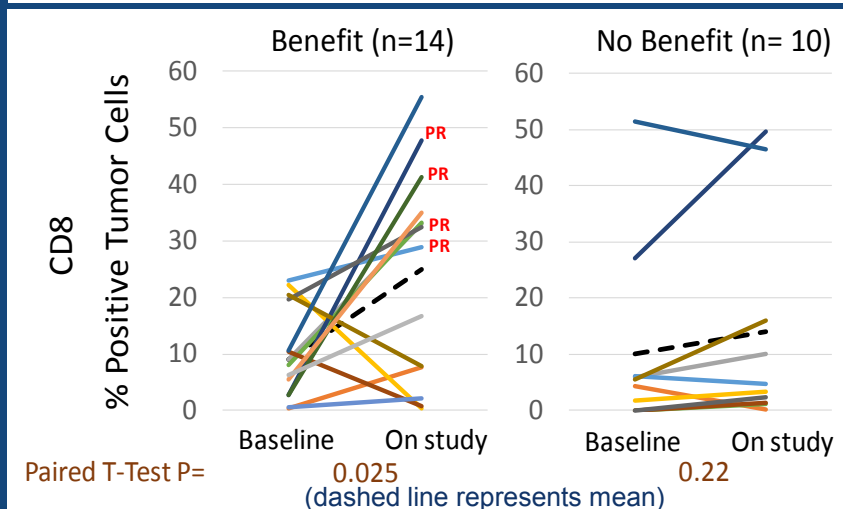
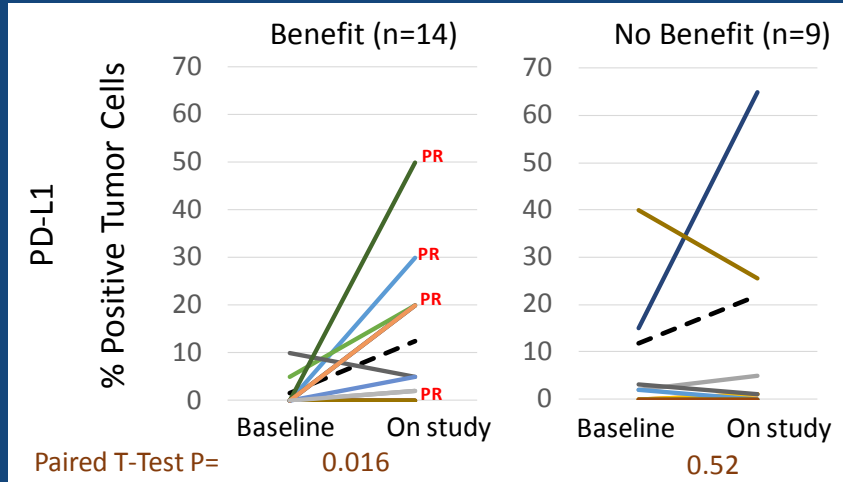


(dashed line represents mean)

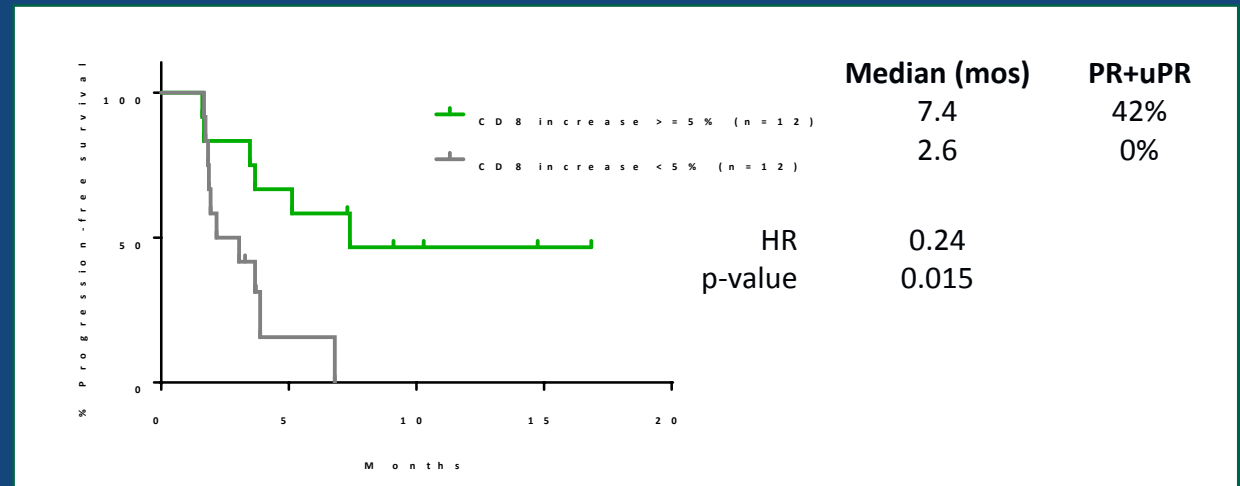
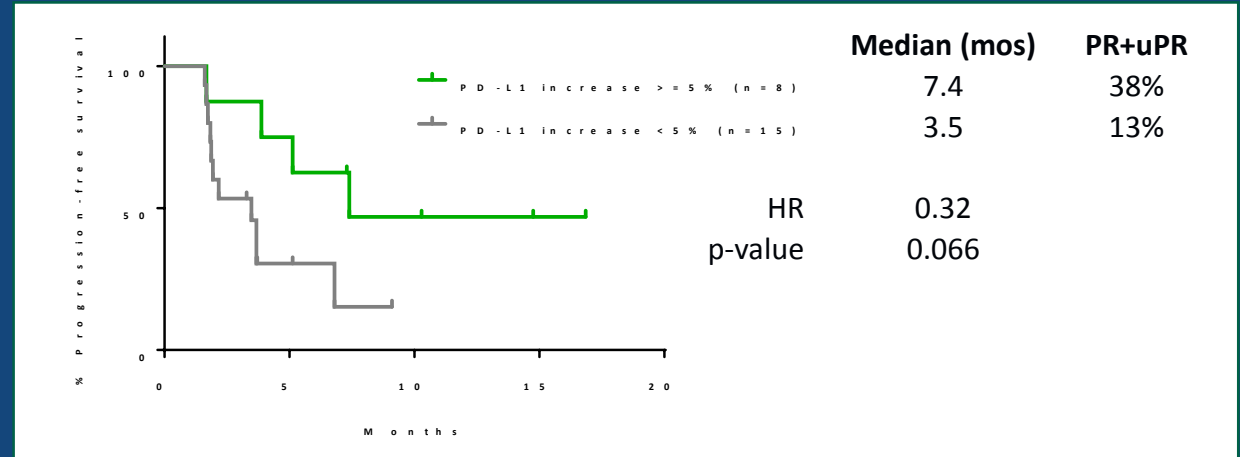
# Enhanced PD-L1 Expression and CD8 TIL is Associated with Better Outcome in Ovarian Patients

All ovarian patients with paired biopsy samples (Day 29)

## Benefit/No Benefit

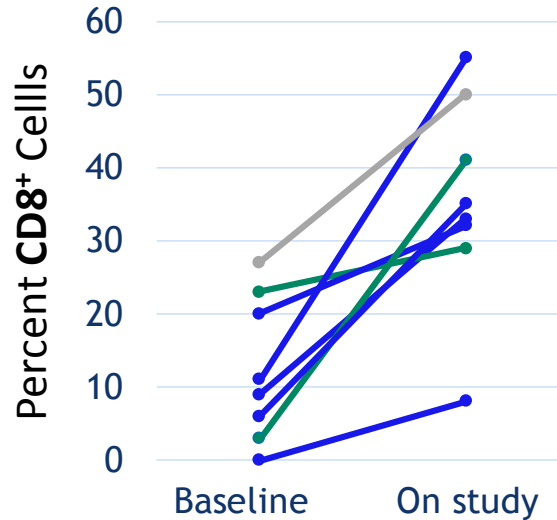
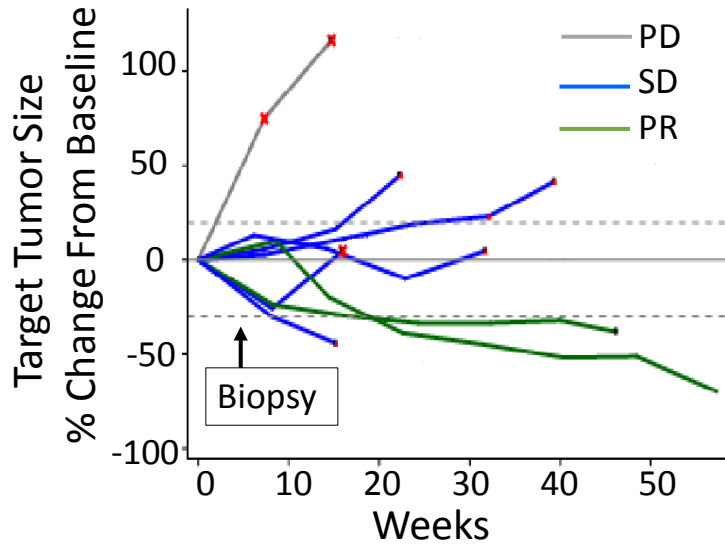


## PFS

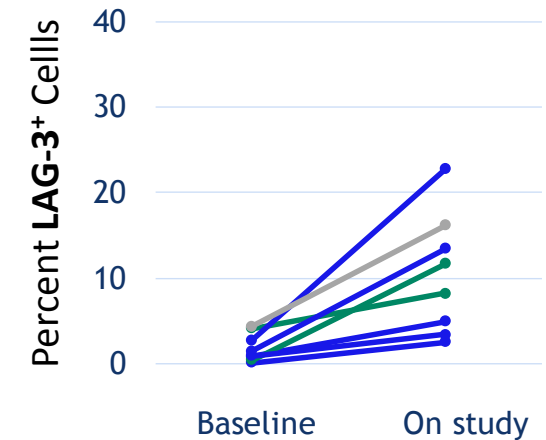
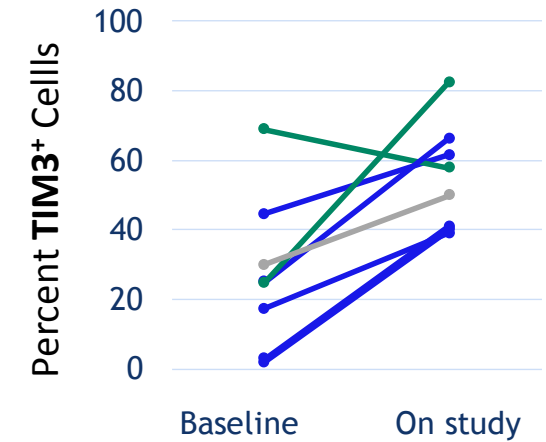


# Expression of TIM-3, LAG-3 Does Not Distinguish Refractory Ovarian Patients

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



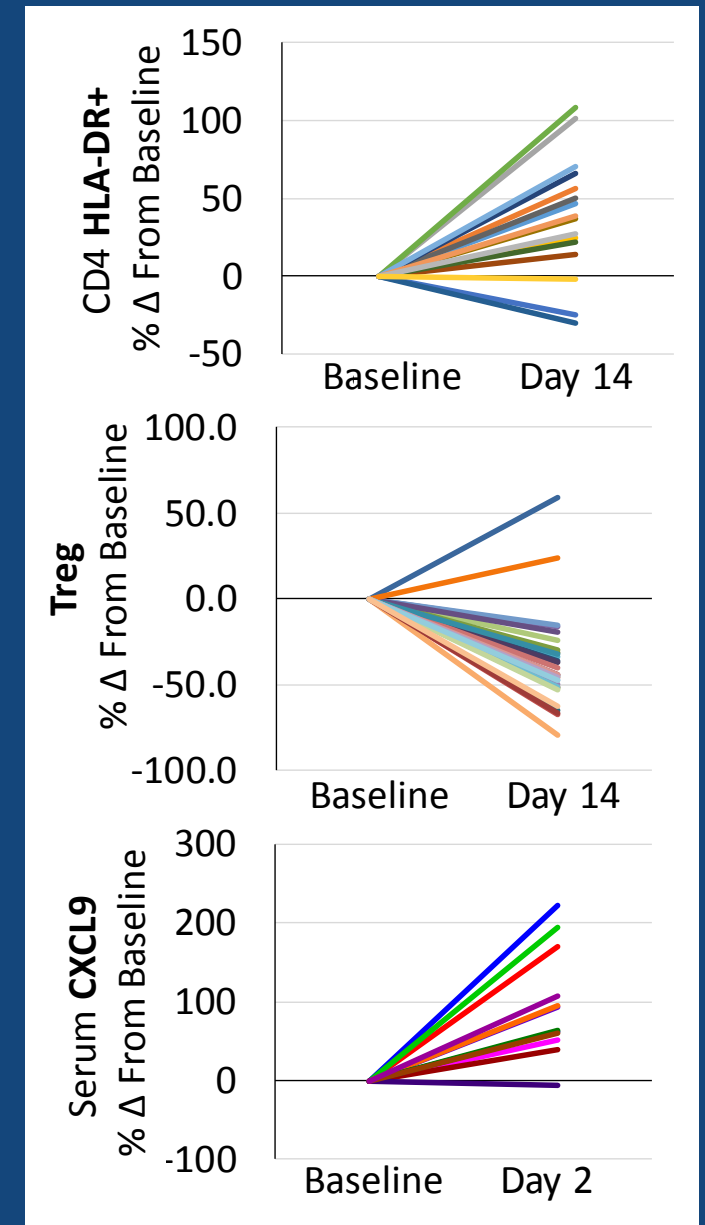
Expression of exhaustion markers



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 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

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