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

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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

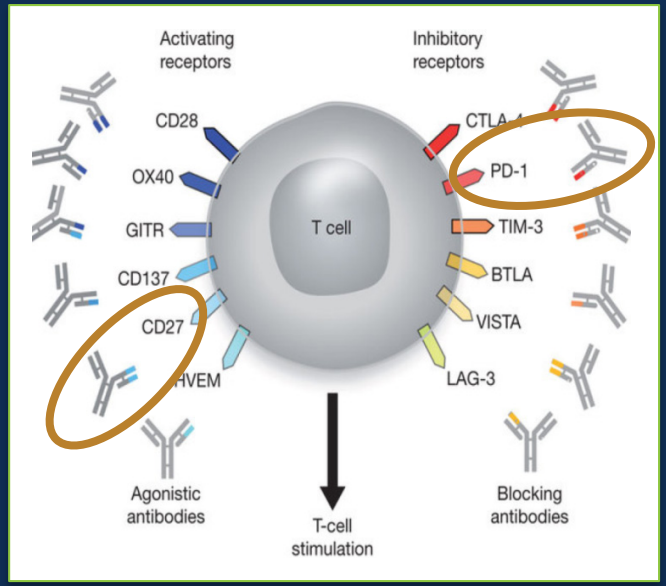
Combination strategies that target T cell costimulation molecules such as CD27 may enhance clinical responses to checkpoint blockade

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

Varlilumab: Fully human IgG1 CD27 agonist mAb

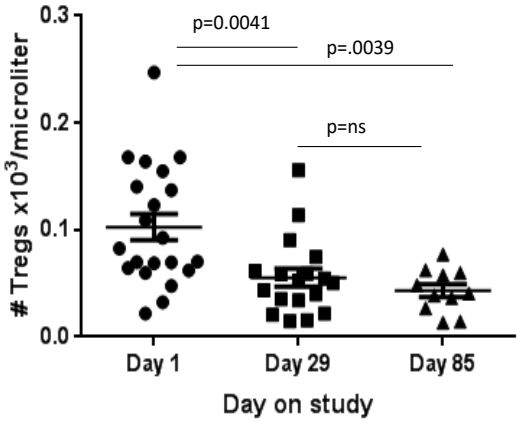
- Strong preclinical data demonstrating single agent and combination activity in tumor models



Varlilumab Clinical Experience: Phase 1 Monotherapy Trial

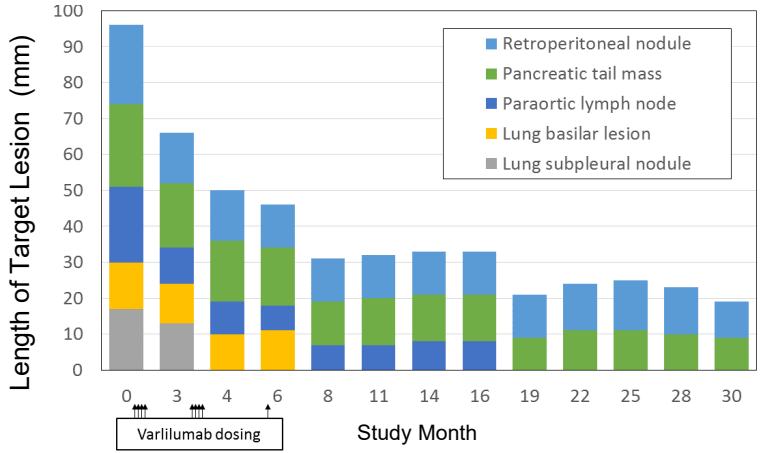
- **Safety profile appears favorable in its class of agonist mAbs**; minimal toxicities; no significant immune-mediated AEs [1, 2, 3]
- **Potent immunologic activity consistent with MOA**[1, 2, 3]
  - Rapid induction of pro-inflammatory IFN-γ driven chemokines, increased expression of T cell activation markers, and marked decrease in T regs without evidence of broad T cell depletion

Decrease in Tregs with Varlilumab



- **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 varlilumab (0.3 mg/kg). Remains in remission at 33.1+ months without further anticancer therapy
    - Patient with RCC achieved a PR with varlilumab (3 mg/kg). PR persists at 2.5 years without further anticancer therapy (see graph below)
    - Patient with RCC completed 5 cycles of varlilumab (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

Durable Partial Response for a Patient with RCC

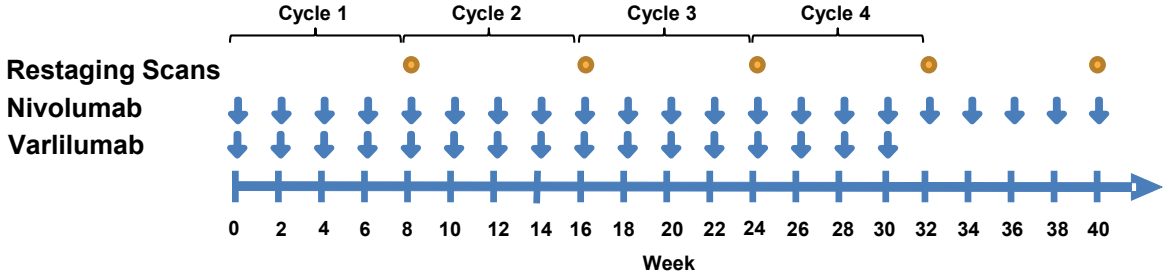


[1] Bullock, et al. SITC 2014
[2] Infante, et al. ASCO 2014
[3] Burris, et al, JCO 2017

Phase 1/2 Study of Varlilumab in Combination with Nivolumab

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



- 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

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)

Baseline Patient Characteristics

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

[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: ≥ 1% tumor cells staining positive, using the BMS developed PD-L1 IHC method at a central lab

Varlilumab & 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 varlilumab with nivolumab
- 3 patients discontinued the study due to treatment related AEs
- 3 patients with treatment-related* SAEs (all 10 mg/kg varlilumab):
  - 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 varlilumab and nivolumab

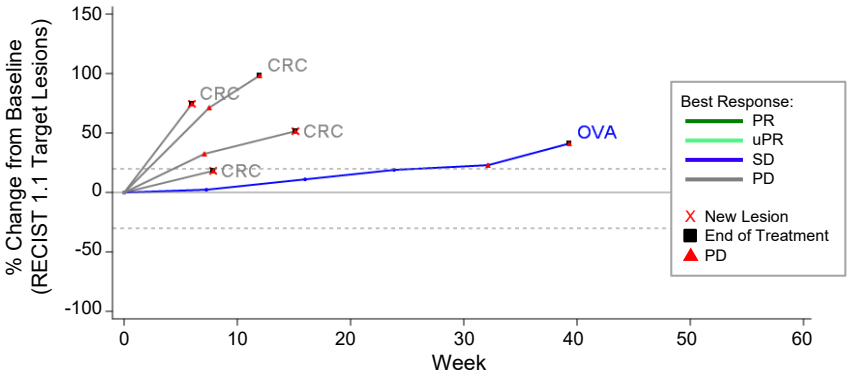
Treatment-Related Adverse Events

	All Phase 1 (n=36)	
	Any Severity	Grade ≥ 3
Any treatment-related adverse event	31 (86%)	10 (28%)
Infusion related reaction	10 (28%)	0
Fatigue	10 (28%)	0
Lymphopenia	9 (25%)	6 (17%)
Pruritus	8 (22%)	0
Rash	11 (19%)	1 (3%)
Nausea	7 (19%)	0
Arthralgia	5 (14%)	0
Pyrexia	4 (11%)	0
Vomiting	4 (11%)	1 (3%)
ALT increased	4 (11%)	2 (6%)*
AST increased	3 (8%)	1 (3%)*
Lipase increased	2 (6%)	2 (6%)
Acute kidney injury	1 (3%)	1 (3%)*
Amylase increased	1 (3%)	1 (3%)
Autoimmune hepatitis	1 (3%)	1 (3%)*
Blood alkaline phosphatase increased	1 (3%)	1 (3%)*
Blood bilirubin increased	1 (3%)	1 (3%)*

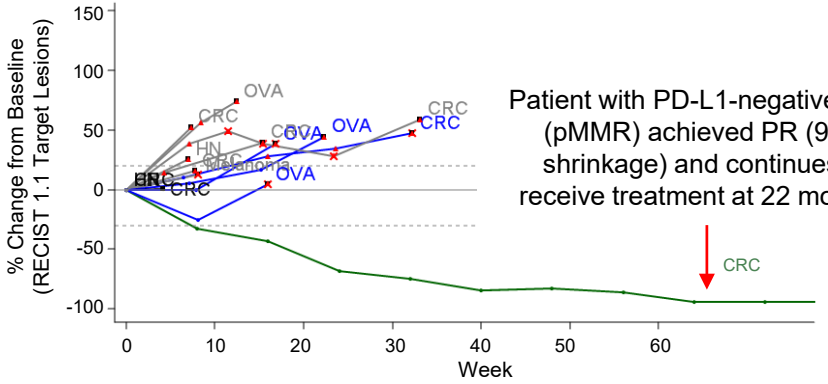
Table includes adverse events assessed as related to either varlilumab or nivolumab for ≥ 10% of patients overall, or at grade ≥ 3 severity any patient.
* 1 patient had all AEs (excluding 1 incident of ALT increased)

Tumor Response

0.1 mg/kg varlilumab and 3 mg/kg nivolumab

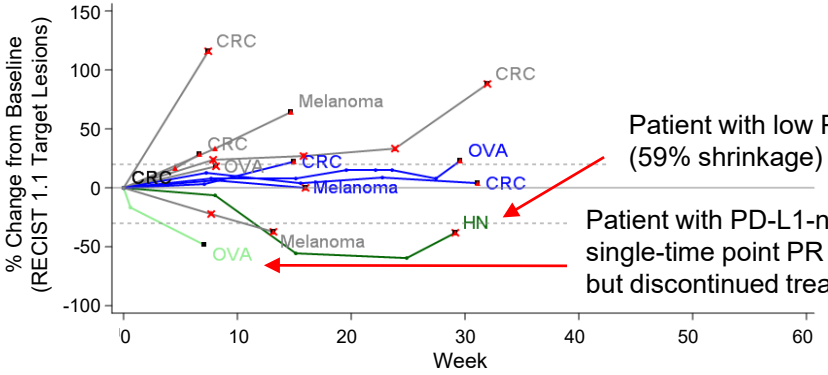


1 mg/kg varlilumab and 3 mg/kg nivolumab



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

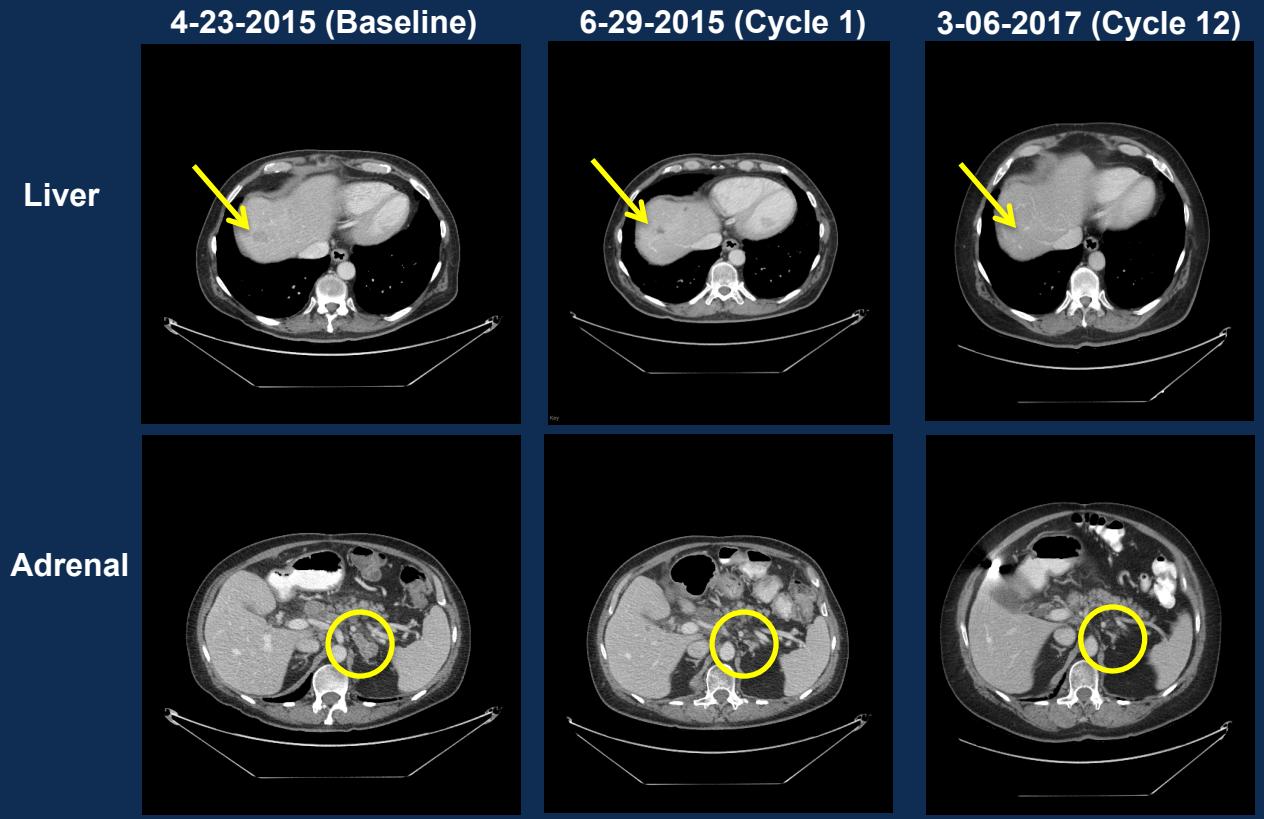
Patient with PD-L1-negative ovarian cancer experienced a single-time point PR (49% shrinkage; uPR) at 1.6 months, but discontinued treatment due to a DLT.

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

Durable Response in MMR-proficient CRC Patient



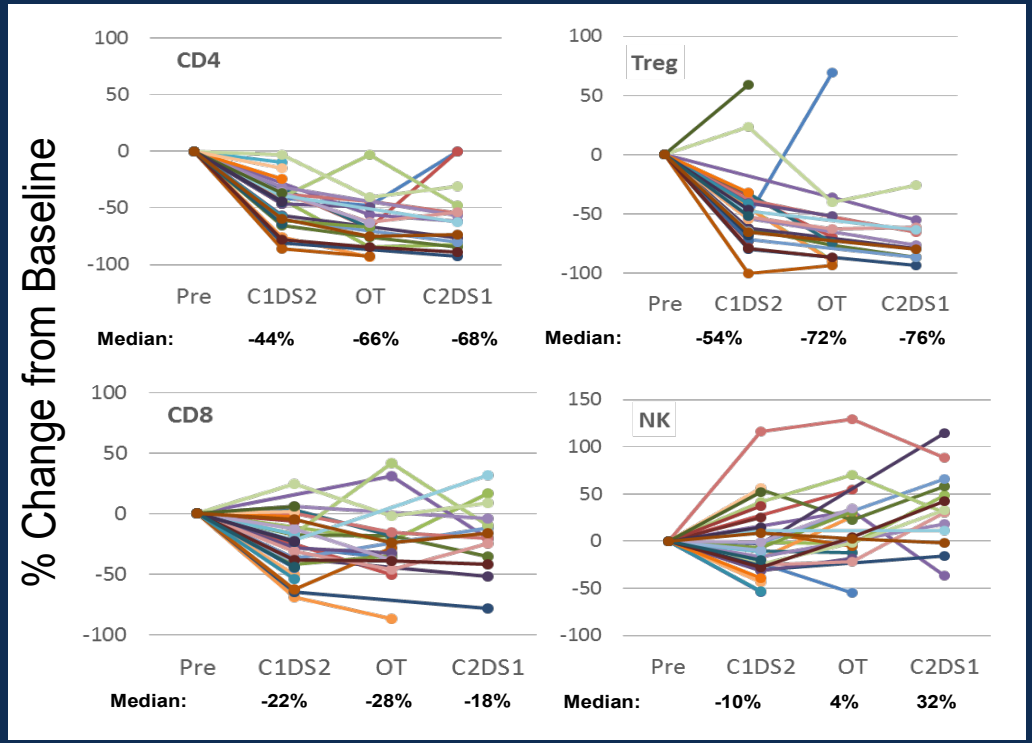
- PD-L1-negative, pMMR colorectal adenocarcinoma with metastatic disease to liver, adrenal gland, abdomen and mesenteric nodule[1]
- 2 prior chemotherapy based regimens (1 with EGFR targeted therapy)
- On study, had a 95% decrease in target lesions, including resolution of 4/5 target lesions. One 6 mm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

[1]Expected 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

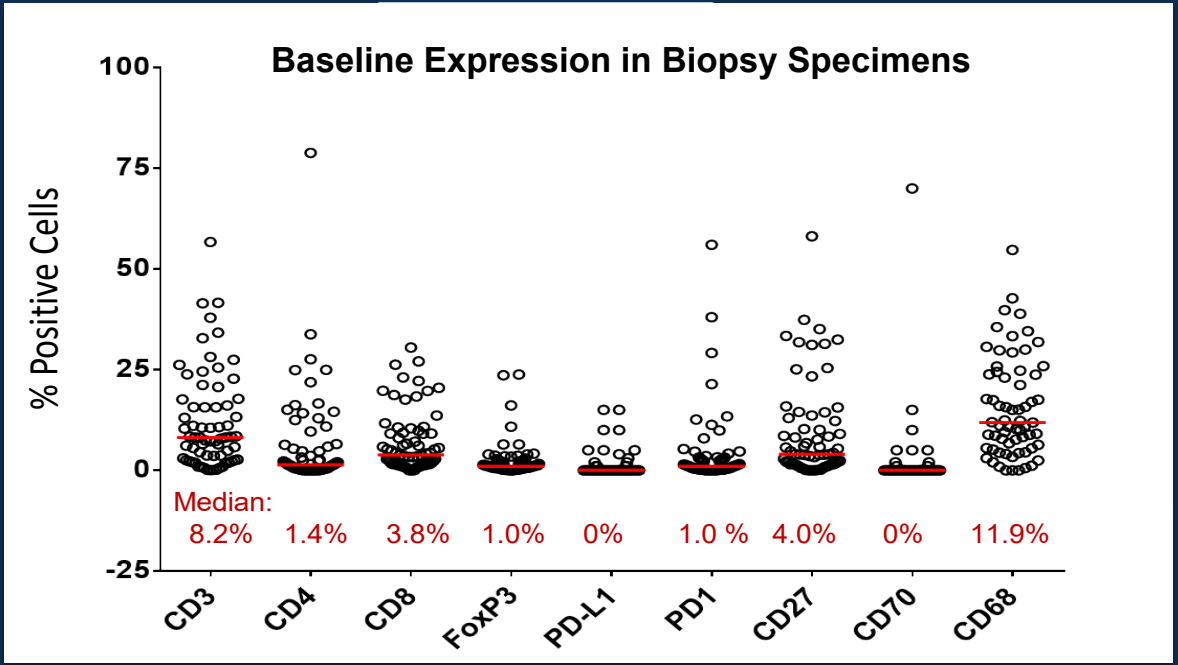
- Peripheral blood analysis
  - Prominent decrease in CD4 and Treg cells observed across all cohorts
  - Serum chemokine changes consistent with varlilumab monotherapy
    - Transient increase in inflammatory chemokines (CXCL10, MCP-1, MIP-1β and MIG) observed across all cohorts



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



Includes patients from Phase 1 (n=28) and Phase 2 (n=37)

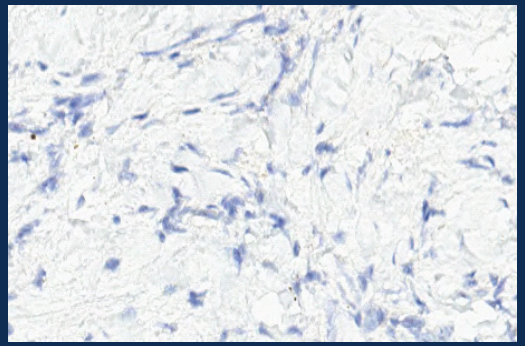
- T cell infiltrates and PD-L1 expression increased significantly during treatment in some patients
- This was particularly evident in a sub-group analysis focused on ovarian patients

Tumor Expression of PD-L1 is Increased in Ovarian Patients

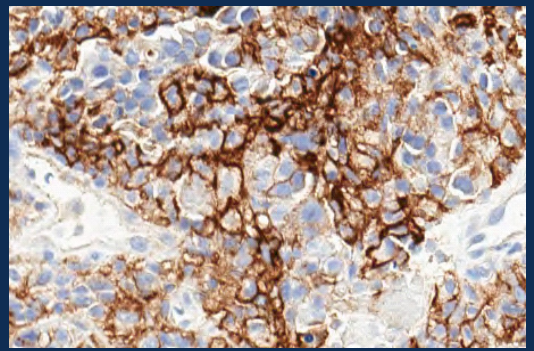
- Baseline biopsies were generally negative or low PD-L1 positive
  - 10 of 26 (38%) had PD-L1 + tumors; range 1%-15% (mean = 5.1%)

- 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

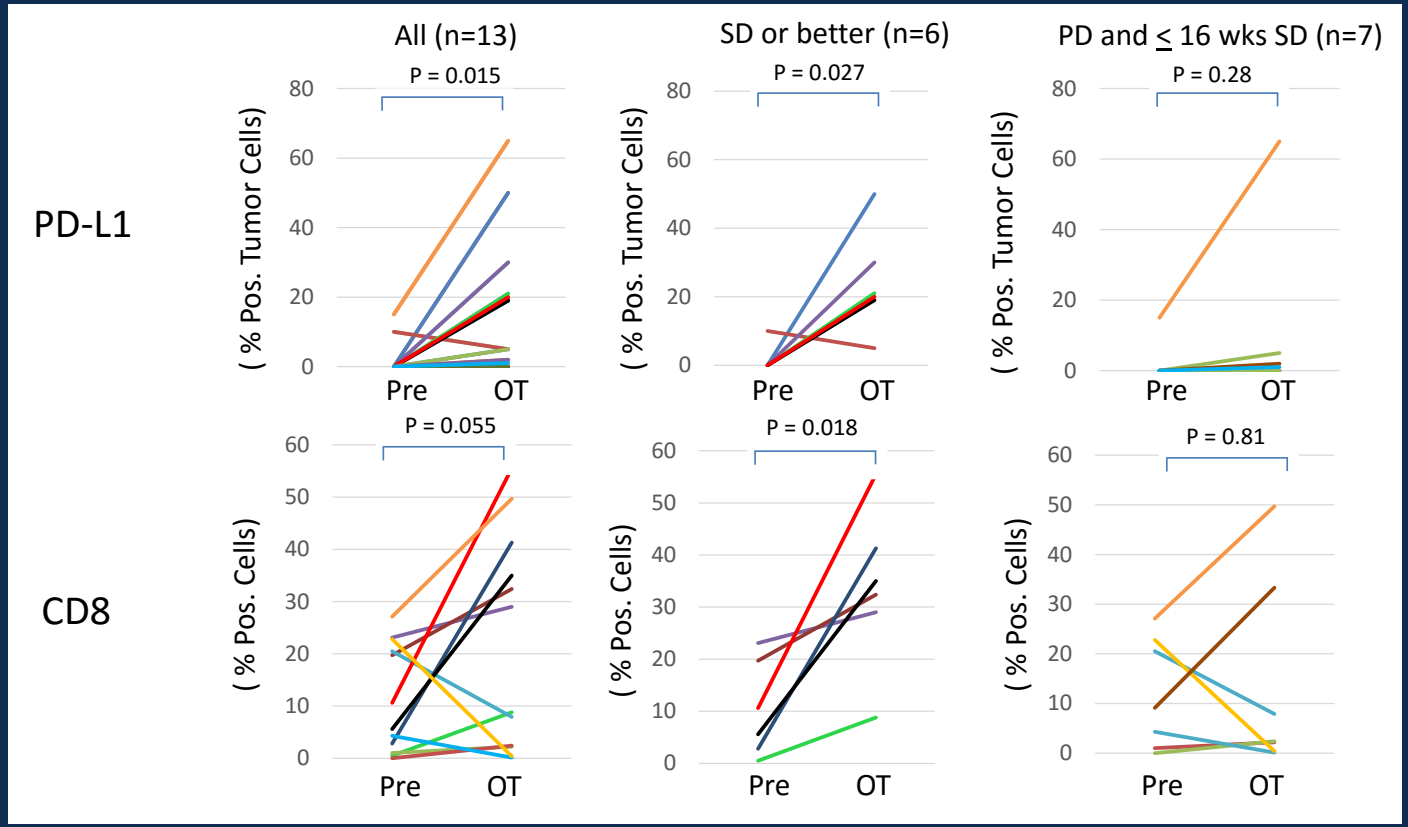


On-treatment



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

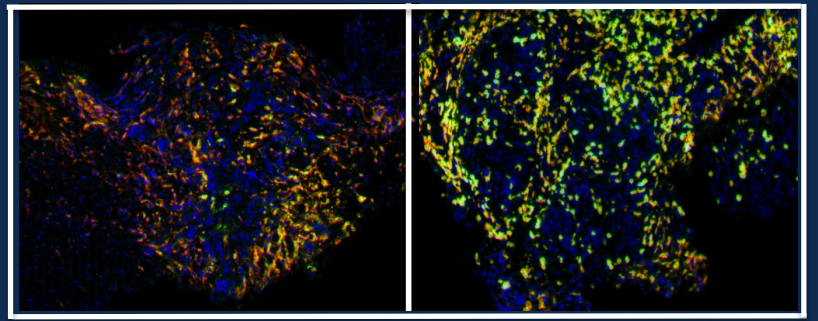
P value: 2-tailed Paired T-Test

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

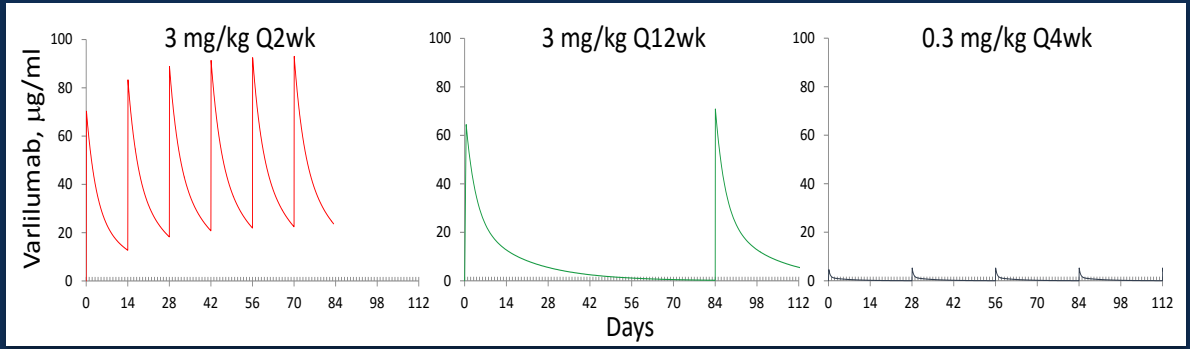
Red = CD3
Green = PD-1

Ovarian Patient with SD



Baseline = 21% PD-1+ **OT = 69% PD-1+**

Continuous saturation or clearance following high or low dose of varlilumab



Planned Phase 2 Cohorts:

- CRC (n=18), GBM (n=20) and RCC (n=25): varlilumab 3 mg/kg q 2 weeks
- Ovarian and SCCHN:
  - Varlilumab 3 mg/kg q 2 weeks (n=18)
  - Varlilumab 3 mg/kg q 12 weeks (n=18)
  - Varlilumab 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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