Immune modulation and baseline biomarker correlation with clinical benefit following treatment with COM701+nivolumab+/-BMS-986207 in patients with platinum resistant ovarian cancer

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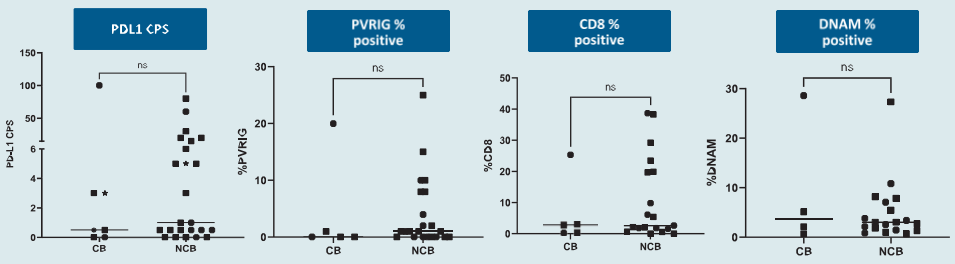
Abstract

Background: COM701 is a first-in-class, T cell checkpoint-inhibitor that binds to PVRIG, blocking its interaction with PVRL2 expressed on tumor and antigen presenting cells. We have reported initial anti-tumor activity of COM701 + nivolumab +/- BMS-986207 (anti-TIGIT) in patients with platinum-resistant ovarian cancer (PROC) [1,2]. Checkpoint inhibitors have limited activity in PROC patients, particularly in patients with reduced PD-L1 and T cell infiltration [3]. Here, we present preliminary biomarker and translational assessment of PROC patients treated with COM701 + nivolumab +/- BMS-986207.
Methods: Pretreatment (n=28) and on-treatment (n=21) biopsies were collected from patients treated with COM701 + nivolumab +/- BMS-986207 Q4W (NCT03667716 and NCT04570839) and subjected to IHC stain with anti-PD-L1, anti-CD8, anti-PVRL2 and anti-PVRIG. Selected biopsies were subjected to ImmunoID NeXT assay. Patient IHC data from both studies were pooled for analysis. In addition, translational assessment of circulating immune cells and cytokines in peripheral blood was assessed at multiple time points.

PVRL2 tumor baseline levels is associated with clinical benefit (CB) in PROC patients treated with COM701+ nivolumab +/- BMS-986207

Clinical responses were independent of PD-L1, CD8, PVRIG and DNAM baseline expression: 3/7 CB patients had baseline PD-L1 CPS<1; median CD8, PVRIG and DNAM pre-levels were similar for both CB and NCB patients (Figure1A). In contrast, higher baseline PVRL2 H-score was associated with response with median PVRL2 score of 290 in CB versus 240 NCB patients (p<0.05, Figure 1B).

A.



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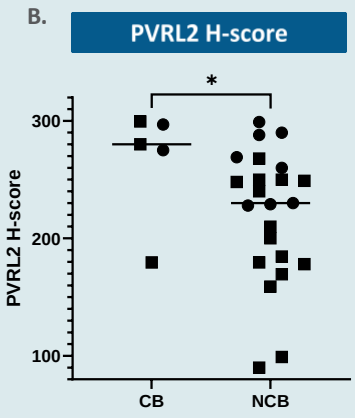


IHC staining of baseline biopsies of PROC patients treated with COM701 + nivolumab +/- BMS-986207 using

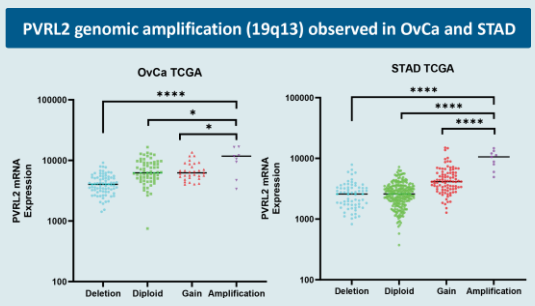
A. Anti-PDL1(clone 28-8, scoring by CPS), CD8 (clone C8/144B), PVRIG (clone 6D8-1) and DNAM (clone 102), for each percent positive cells are reported. Baseline levels of these four markers do not correlate with clinical benefit.

B. Anti-PVRL2 (clone 181H3L2, protocol CGEN001A-C-APD), tumor H-score (sum of IHC intensity multiplied by percent of positive cells in each intensity), shows a higher expression in CB patients at baseline.

CB – Clinical Benefit = CR + PR + SD >=180 days on study, NCB – No Clinical Benefit = PDs + SD <180 days on study, Black square = COM701 + nivolumab + BMS-986207, black dots = COM701 + nivolumab, star = PDL1 CPS from clinical record.

PVRL2 genomic amplification observed in a patient with durable partial response following COM701 + nivolumab + BMS-986207 treatment

A.



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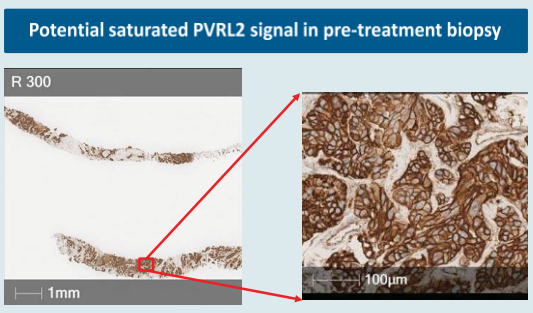


PVRL2 genomic amplification observed in one sample across the clinical cohorts and across Ovary and Gastric carcinoma in TCGA:

A. Correlation of TCGA expression (Y axis in PVRL2 mRNA levels expressed by RESM units) by category of genomic status of PVRL2 in ovarian (OvCa, with 3% of samples showing amplification) and Gastric (STAD, with 5% of samples showing amplification) carcinoma.

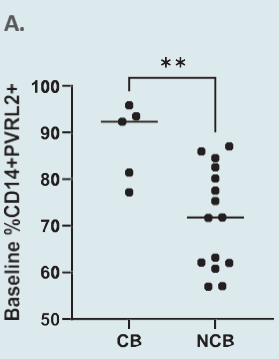
B. One of the responding patients (PR) treated with COM701 + nivolumab + BMS-986207 had an amplification of the PVRL2 genomic locus which is also reflected by a PVRL2 IHC stain with a maximal tumor H-score of 300 (clone 181H3L2, protocol CGEN001A-C-APD). Left micrograph X1 magnification of the core biopsy right X20 magnification of the red rectangle.

Deletion = one copy deletion, Gain = Two or three copies, Amplification = more then 4 copies. * = p-val <0.05, **** = p-val <0.0001)

Higher baseline PVRL2 expression on peripheral monocytes in COM701 + nivolumab + BMS-986207 treated patients showing clinical benefit

Circulating immune cells assessment in peripheral blood, showed higher baseline PVRL2 expression on monocytes in COM701 + nivolumab + BMS-986207 treated patients with clinical benefit

A.



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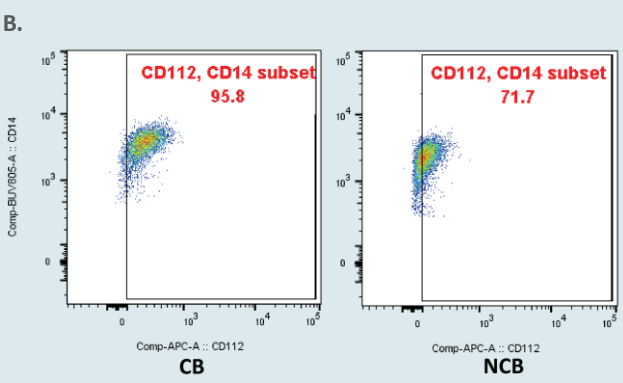


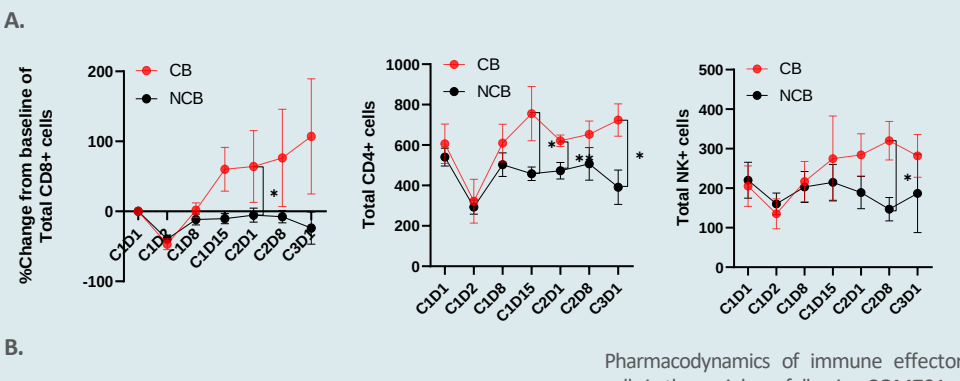
Base line FACS analysis of CD14 positive and PVRL2 positive monocytes.

A. Higher percent of PVRL2 positive monocytes at baseline in COM701 + nivolumab + BMS-986207 treated patients with CB compared to patients with NCB.

B. Representative dot plots for each CB and NCB are shown.

Pharmacodynamic activation of the immune system following COM701 + nivolumab +/- BMS-986207 treatment, which is associated with clinical benefit

A.



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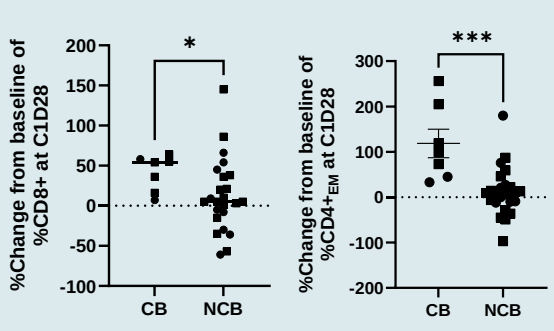


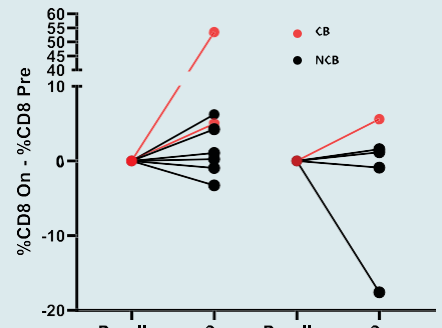
Pharmacodynamics of immune effector cells in the periphery following COM701 +nivolumab +BMS-986207.

A. Increased total number of CD8, CD4 and NK cells in COM701+nivolumab + BMS-986207 treated patients with CB.

B. Increased percent of CD8 and CD4 effector memory (EM) CD45RA-CCR7- T cells at C1D28 in COM701+nivolumab + BMS-986207 or COM701+nivolumab treated patients with CB. Black square = COM701+ nivolumab + BMS-986207, black dots = COM701 + nivolumab

Increased tumor CD8 T cells infiltration following COM701 + nivolumab +/- BMS-986207 treatment

%CD8 change on treatment



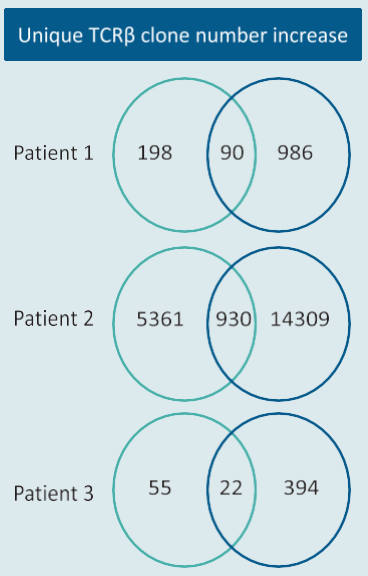
	Baseline	On	Baseline	On
	Triplet		Doublet	
Mean difference	2.66		1.16	

Increased tumor CD8 T cell infiltration following treatment COM701 + nivolumab +/-BMS-986207, respectively. CD8 IHC stain (clone C8/144B) measured as percent positivity of total cells. 8/13 patients increased CD8 post treatment. Most prominent increase in patients with clinical benefit. COM701 + nivolumab + BMS-986207 shows a trend for higher CD8 infiltration post treatment (Median change of 2.66 for triplet vs. 1.16 for doublet, nonsignificant). on-treatment biopsy taken between C2D1 to C3D1.

TME increase in TCR clones following doublet and triplet blockade in patients demonstrating clinical benefit

Paired TCR sequencing of three CB patients demonstrated an increase in the number of TCRβ clones, where the most dominant on-treatment clones were present pre-treatment and expanded in the TME following treatment

A.



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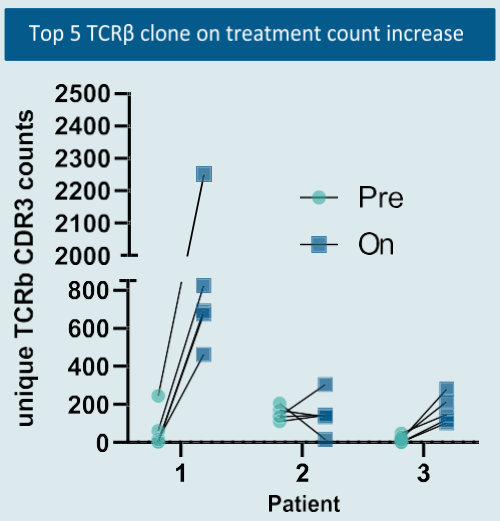


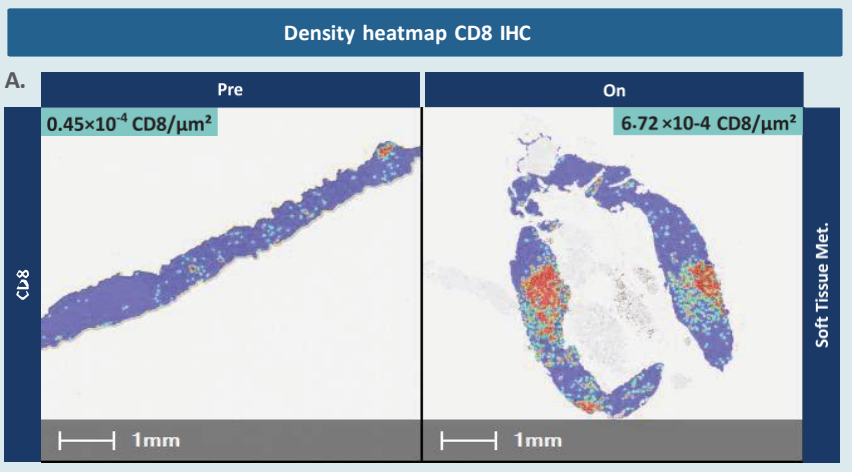
Increased TCR clones following doublet and triplet blockade: increased T cells clone number due to infiltration of new T cell clones and expansion of existing T cell clones in the TME.

A. Vann diagram representing the pre-treatment number of unique clones CDR3 TCRβ (green circle) and on-treatment number of unique clones (blue cycle), the overlap region represents the number of clones shared between Pre and on-treatment.

B. Counts of top 5 unique CDR3 TCRβ clones on-treatment vs. the counts pre-treatment. Most dominant On treatment clones were present pretreatment and expanded in the TME following treatment. on-treatment biopsy taken between C2D1 to C3D1.

Potent immune modulation in a patient with PR following COM701 + nivolumab + BMS-986207 treatment

A.



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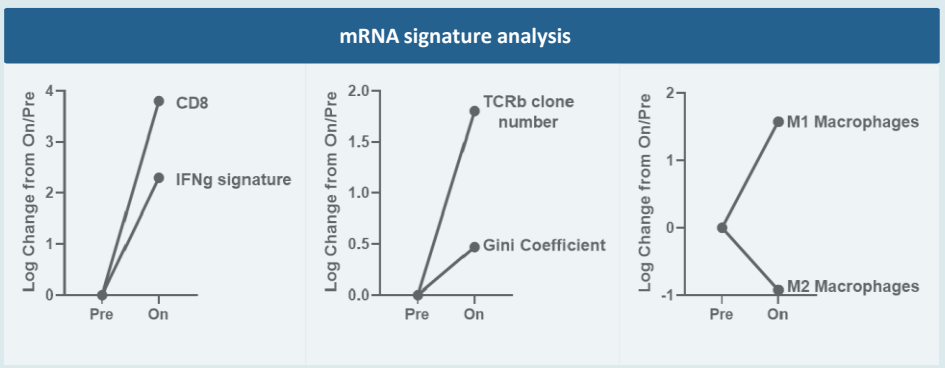

Extensive immune modulation in patient with clinical response (PR) flowing COM701 + nivolumab + BMS-986207 treatment.

A. Density heat map of CD8 infiltration in pre (left) and On (right) treatment biopsy, demonstrates massive infiltration of CD8 T cells flowing treatment, as can be seen also by CD8 density per µm².

B. The CD8 infiltration is also demonstrated by RNAseq data, by CD8 deconvolution score increase as well as by IFNγ signature (upper left graph). The number of clones and T-cell clonality is also increased, as reflected in clone number count and Gini coefficient (middle graph), both hallmarks of CD8 anti tumor activity. M1 macrophages deconvolution score increase and M2 macrophage score decreases following treatment (right graph). Image analysis using HALO® AI modules algorithm. RNAseq deconvolution using mySOR. on-treatment biopsy taken between C2D1 to C3D1.

References: 1. Abstract #159P; ESMO-IO 2022, **2.** Abstract #158P; ESMO-IO; 2022, **3.** J Clin Oncol. 2021 Nov 20;39(33):3671-3681

CONCLUSION

These results demonstrate the activity of COM701 treatment combinations in terms of clinical responses and immune modulation both in the TME and the periphery. This is in accordance with previous cytokine data showing notably an increase in IFNγ in PROC patients treated with COM701+nivolumab+BMS-986207 [1]. Clinical benefit is observed regardless of the tumor baseline inflammatory status. In addition, the preliminary association between the expression of the PVRIG ligand, PVRL2, and clinical benefit may suggest the potential of baseline PVRL2 as a biomarker to enrich for responding patients to COM701-containing treatment regimen.