

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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Background

COM701 is a 1st in-class, T-cell checkpoint-inhibitor that binds to PVRL2, 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 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.

Results

Patients with PR or SD>180 days (per RECIST) were defined as having clinical benefit (CB) versus NCB patients (PD or SD<180).

Clinical responses were independent of PD-L1, CD8 and PVRIG baseline expression: 3/7 CB patients had baseline PD-L1 CPS<1; median CD8 and PVRIG pre-levels were similar for both CB and NCB patients (Figure 1A). In contrast, higher baseline PVRL2 H-score was correlated with response with median PVRL2 score of 290 in CB versus 240 NCB patients (p=0.05, Figure 1B). Examining tumor structural genomic-variants (by exome-DNAseq) revealed one responding patient (PR) with a genomic PVRL2-amplification

and baseline PVRL2 H-score of 300 (figure2A). TCGA analysis revealed that ovarian and gastric-tumors have an amplification of PVRL2 rate of ~3-5% which is correlated with higher mRNA expression (Figure2B).

Investigating immune modulation, CD8 increase was shown in 8/13 patients with paired biopsies, with a prominent increase in CB patients and trend for stronger CD8 increase in patients treated with triple versus dual blockade (Figure3). Paired TCR sequencing of three CB patients demonstrated an increase in the number of TCRb clones, where the most dominant on-treatment clones were present pretreatment and expanded in the TME following treatment (Figure4). CD8 increase demonstrated by IHC and mRNA (deconvolution-score) in a patient with PR, was accompanied by an increase in T-cell clone numbers and clonality and increase in M1 macrophages, while M2 macrophages mRNA-signature decreased (Figure5).

Conclusions

These results demonstrate the efficacy of COM701 treatment combinations in terms of clinical responses and immune modulation, regardless of the tumor baseline inflammatory status. In addition, the preliminary correlation 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.

References:

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



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COM701 Translational Abstract

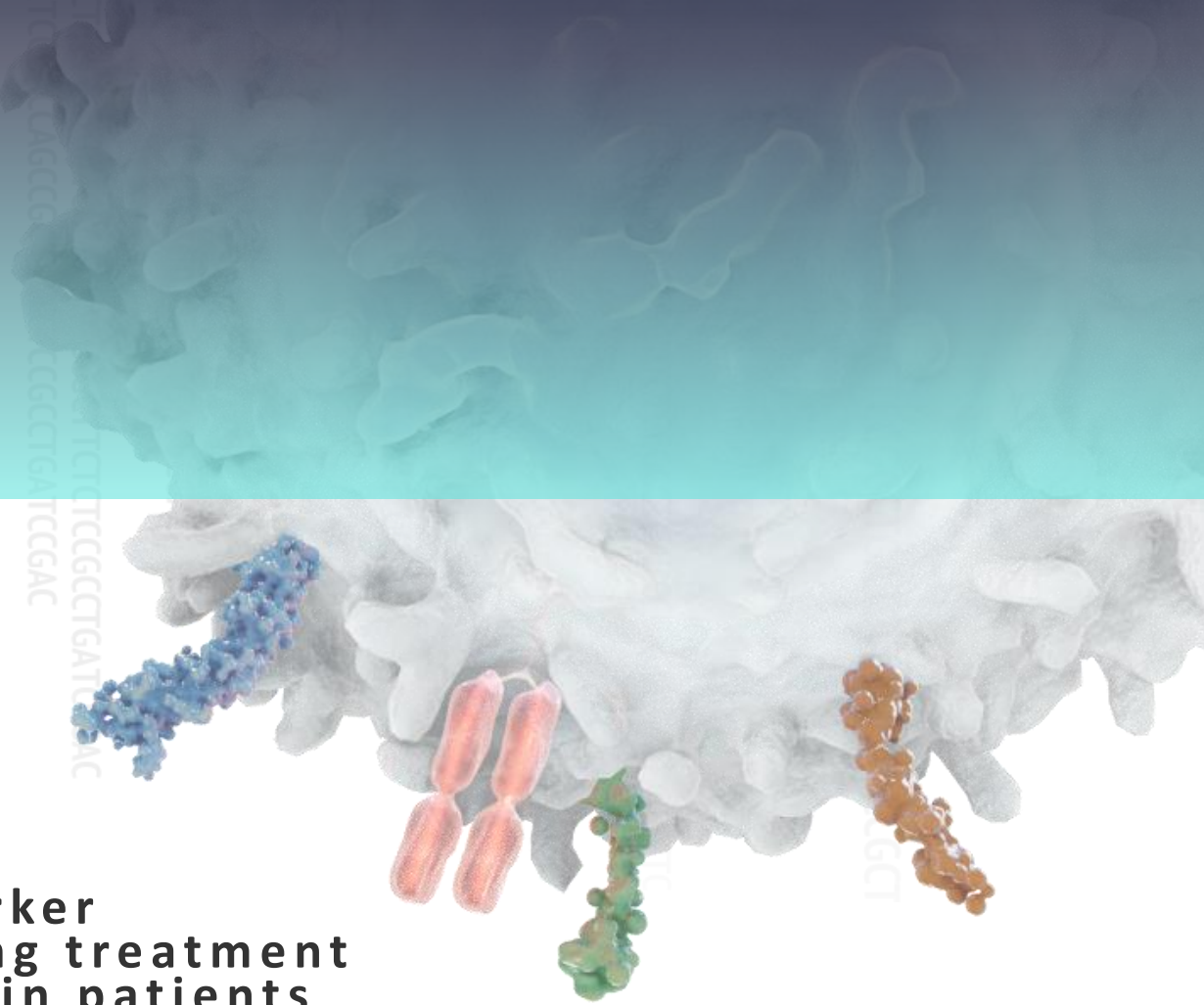
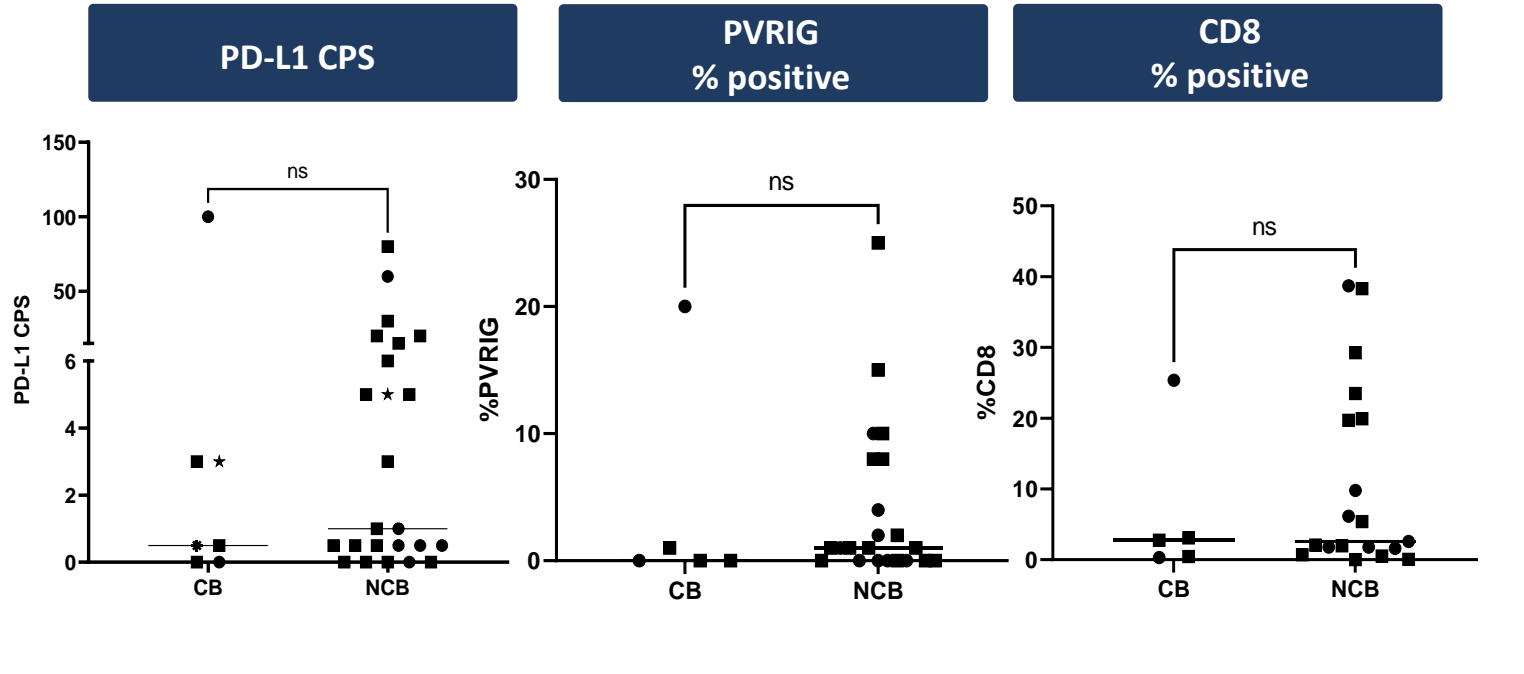


Figure 1: PVRL2 baseline levels correlate with clinical benefit (CB) in PROC patients treated with COM701+nivolumab or COM701+BMS-986207+nivolumab

A



B

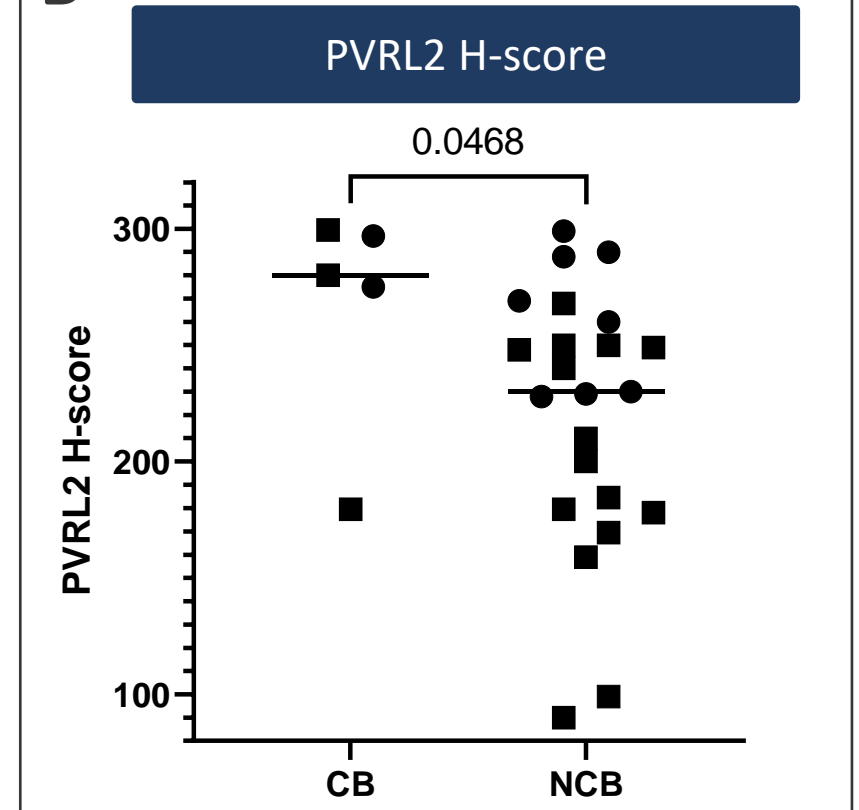


Figure 2: PVRL2 genomic amplification observed in a patient with durable partial response following COM701+BMS-986207+nivolumab treatment

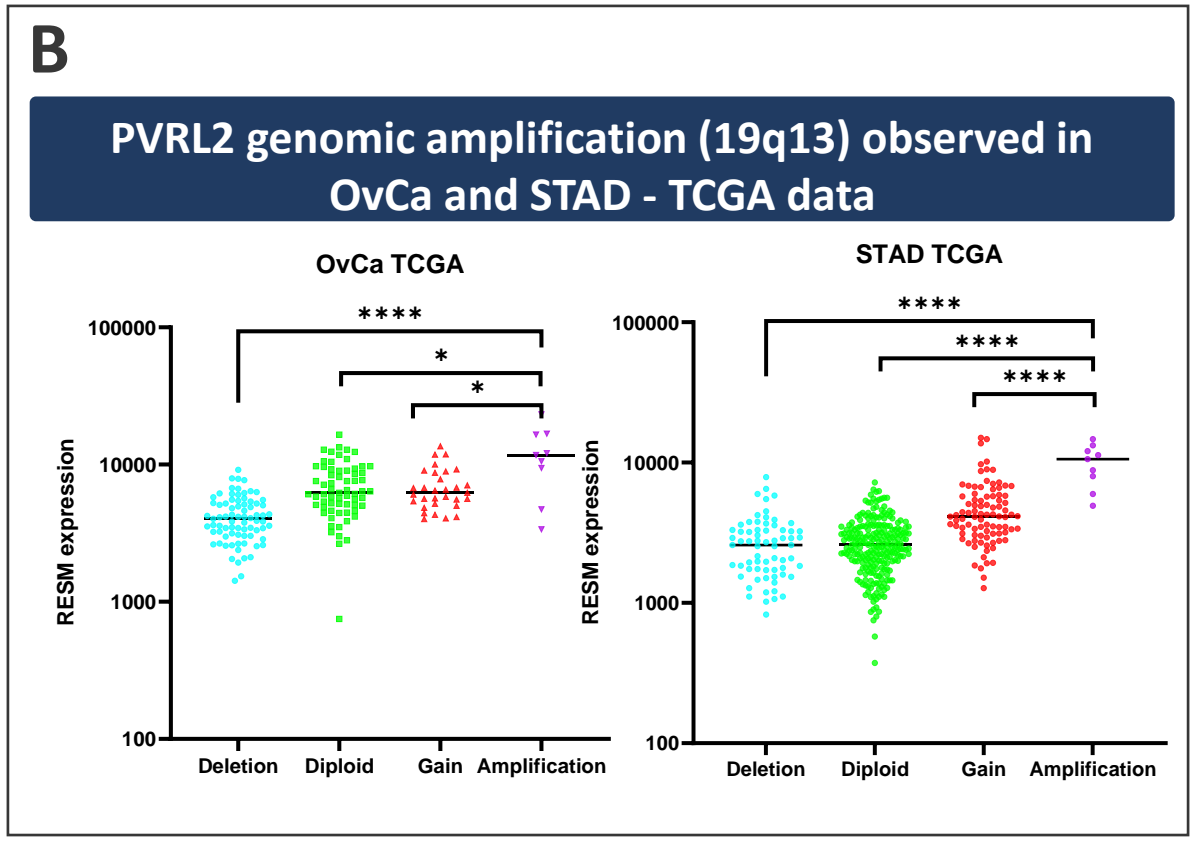
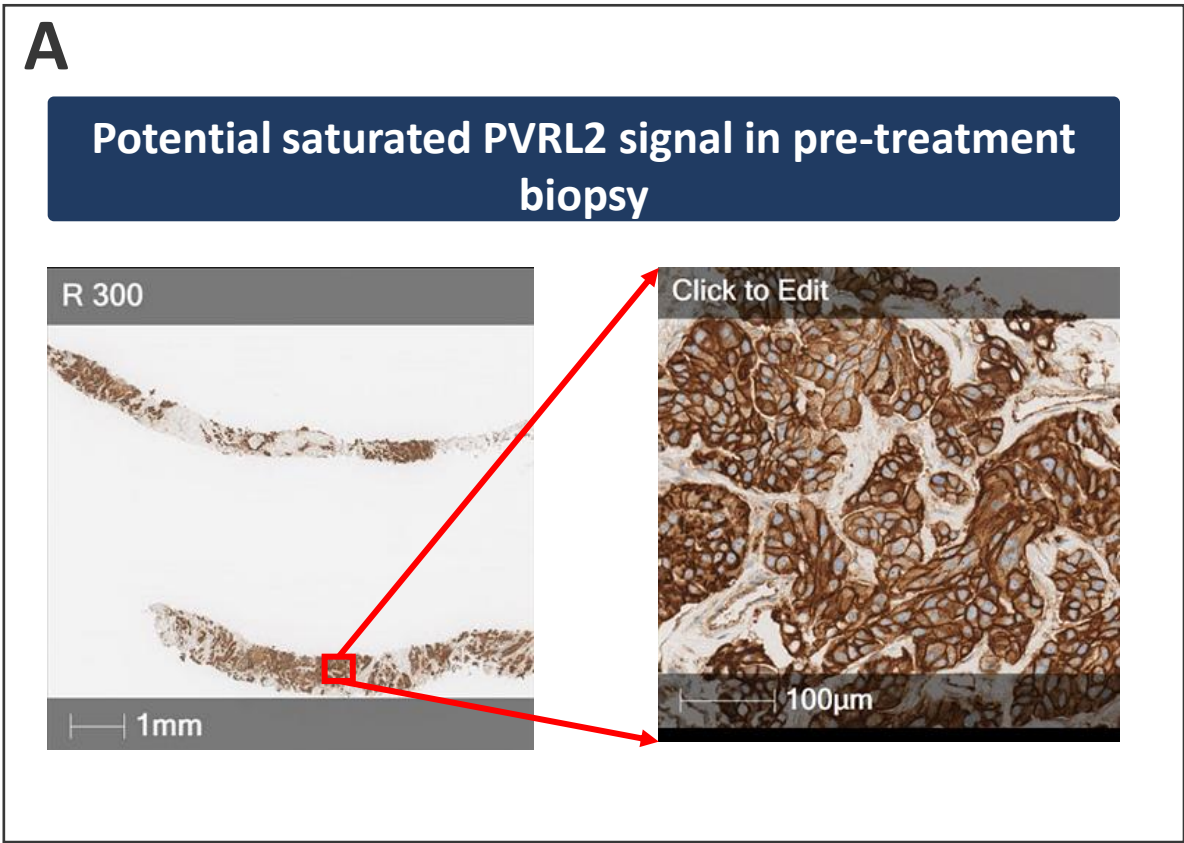


Figure 3: Increased CD8 infiltration following dual and triple blockade

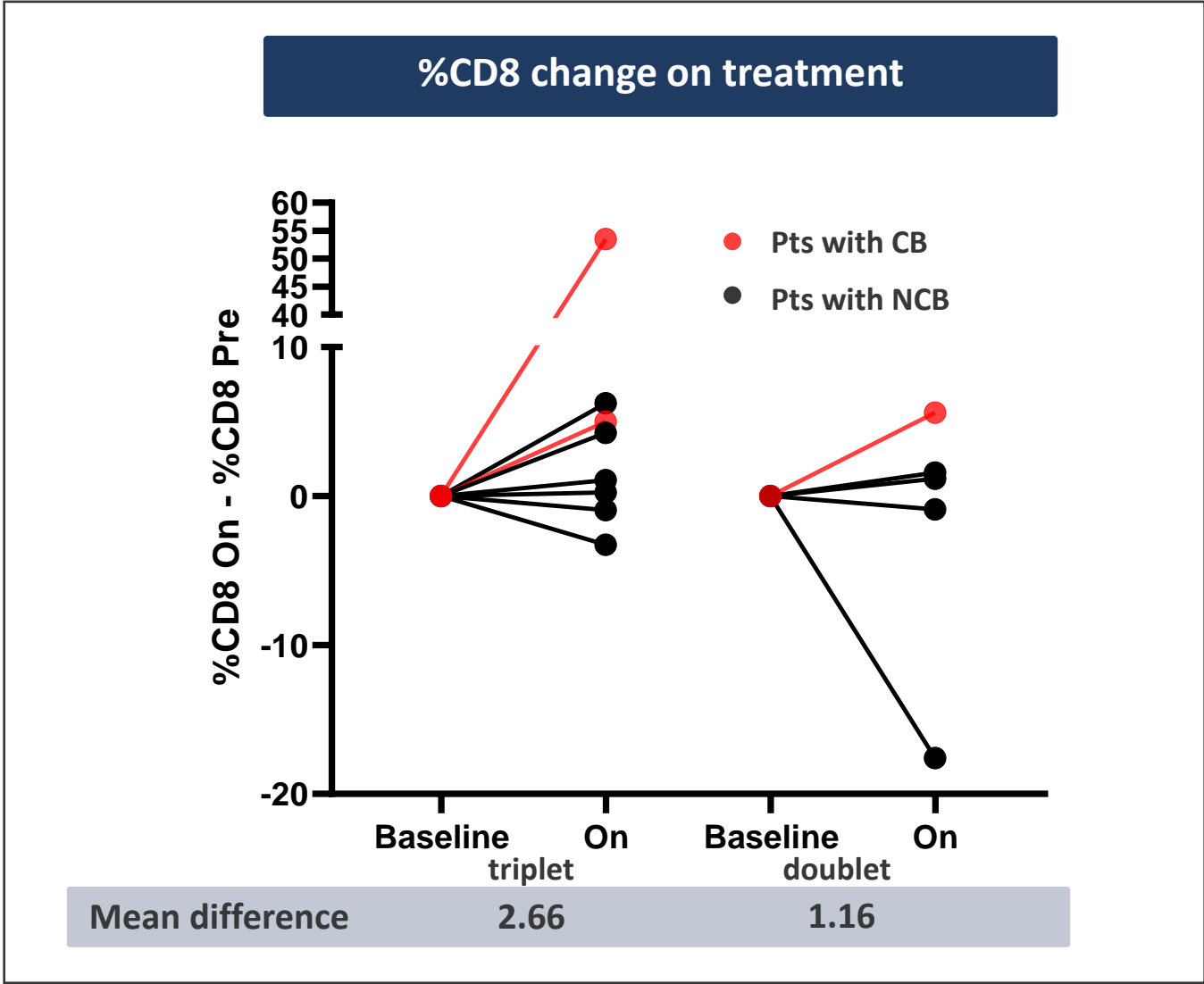


Figure 4: TME Increase in TCR clones following dual and triple blockade in CB patients

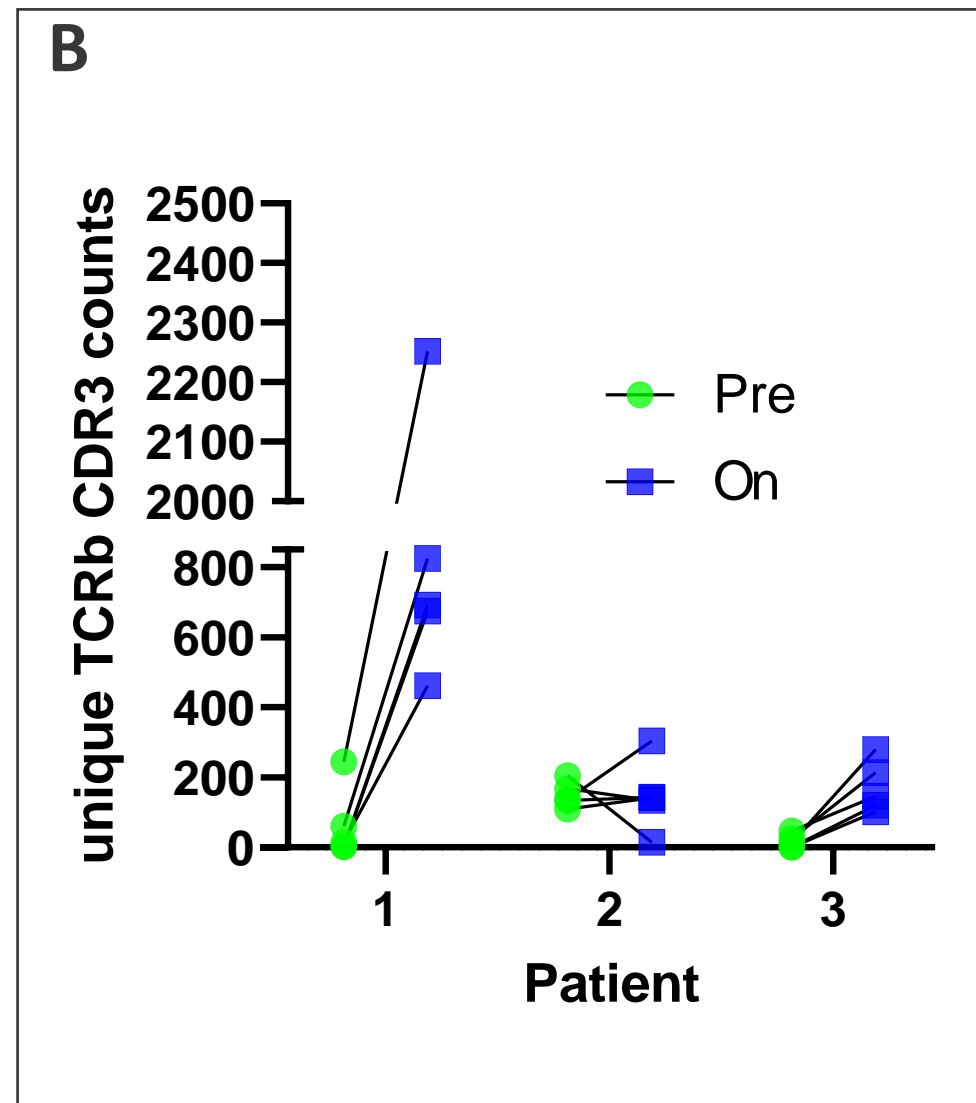
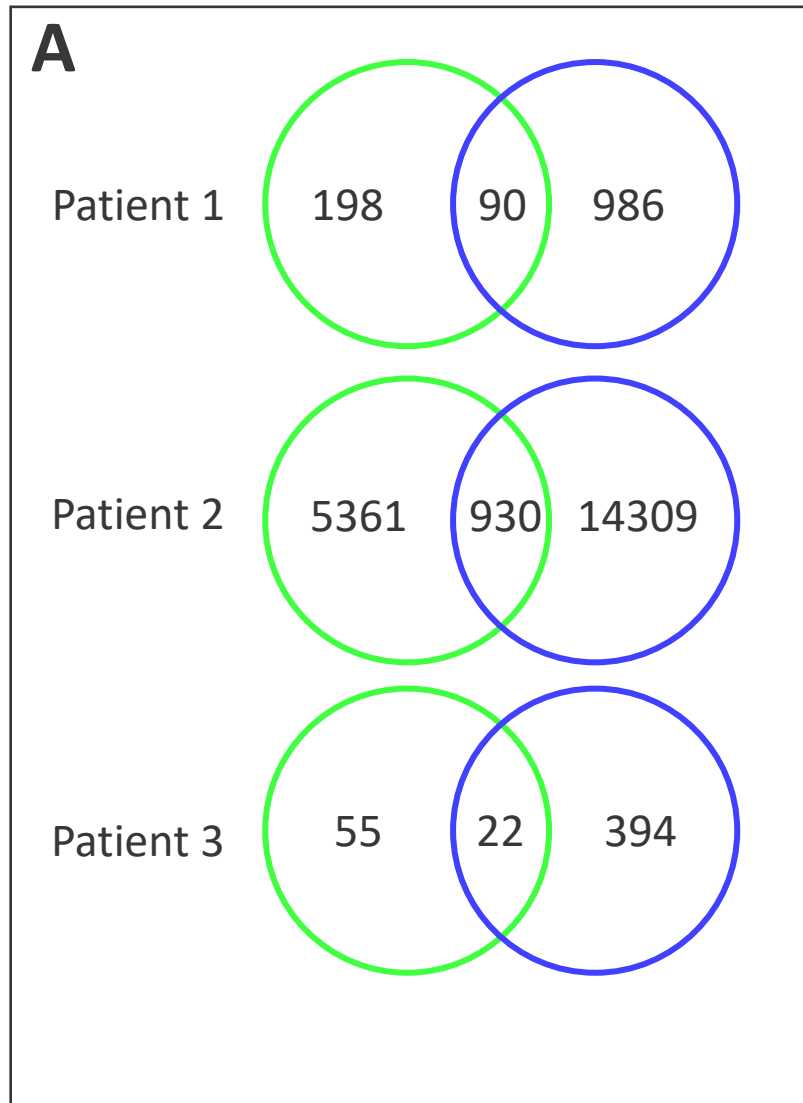


Figure 5: Potent immune stimulation in a patient with PR following COM701+BMS-986207+nivolumab treatment

