Background

COM701 is a 1st-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 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 (figure 2A). TCGA analysis revealed that ovarian and gastric-tumors have an amplification of PVRL2 rate of ~3–5% which is correlated with higher mRNA expression (figure 2B).

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 (figure 3). 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 (figure 4). 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 (figure 5).

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

Abstract 29 Figure 1

PVRL2 baseline levels correlate with clinical benefit (CB) in PROC patients treated with COM701+ nivolumab +/- BMS-986207. IHC staining of baseline biopsies of PROC patients treated with COM701+ nivolumab +/- BMS-986207 using (A) antiPDL1 (clone 28–8, scoring by CPS), CD8 (clone C8/144B) and PVRIG (clone 6D8–1), for both pretreatment positive cells are reported. Baseline levels of these three markers do not correlate with clinical benefit. (B) antiPVRL2 (clone 181H3L2), tumor H-score (sum of IHC intensity multiplied by percent of positive cells in each intensity), shows a higher expression in CB patients. CB — Clinical Benefit = PRs + SD >=180 days on study, NCB — No Clinical Benefit = PDs + SD <180 days on study, Black square = COM701+ BMS-986207+ nivolumab, black dots = COM701+ nivolumab, star = PDL1 CPS from clinical record.
Abstract 29 Figure 2  PVRL2 genomic amplification observed in one sample from our clinical cohort and across Ovary and Gastric carcinoma in TCGA. (A) 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. Left micrograph X1 magnification of the core biopsy right X20 magnification of the red rectangle. (B) Correlation of TCGA expression (Y axis in RESM units) by category of genomic status of PVRL2 in ovarian (OvCa) and Gastric (STAD) carcinoma. Deletion = one copy deletion, Gain = Two or three copies, Amplification = more than 4 copies. * = p-val <0.05, **** = p-val < 0.0001).

Abstract 29 Figure 3  Increased CD8 T-cell infiltration flowing treatment COM701 + nivolumab +/-BMS-986207 (Triplet and Double treatment 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. And the triplet shows a trend for higher CD8 infiltration post treatment (Medinan change of 2.66 for triplet vs. 1.16 for doublet, nonsignificant). On treatment biopsy taken between C2D1 to C3D1.
Abstract 29 Figure 4  TME Increase in TCR clones following dual and triple blockade in CB patients. Increased T-cells clone number due to infiltration of new T-cell clones and expansion of existing T-cell clones in the TME. (A) Venn 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. On treatment biopsy taken between C2D1 to C3D1.

Abstract 29 Figure 5  Potent immune stimulation in a patient with PR following 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 IFNg signature (upper left graph). The number of clones and T-cell clonality is also increased, as reflected in clone number count and Gini coefficient (right graph), both hallmarks of CD8 anti tumor activity. M1 macrophages deconvolution score increase and M2 macrophage score decreases flowing treatment (lower left graph). Image analysis using HALO® AI modules. RNAseq deconvolution using mySOR algorithm. On treatment biopsy taken between C2D1 to C3D1.

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