PVRIG is Uniquely Expressed in Tumor Dendritic Cell-Rich Niches on Stem-Like Memory T Cells and its Blockade may Induce Immune Infiltration and Activation in Non-Inflamed Tumors

Zoya Alteber[1], Gady Cojocaru[1], Roy Granit[1], Inbal Barbiro[1], Assaf Wool[1], Masha Frenkel[1], Amit Novik[1], Adi Shuchami[1], Yu Liang[1], Vered Daniel Carmi[1], Rob Foreman[2], Natalya Petrenko[2], Jiang He[2], Henry Adewoye[3], Pierre Ferre[1], Zurit Levine[1], Eran Ophir[1]

[1]Compugen Ltd, Holon, Israel, [2]Vizgen Inc, Cambridge, MA, [3]Compugen USA Inc., South San Francisco, CA

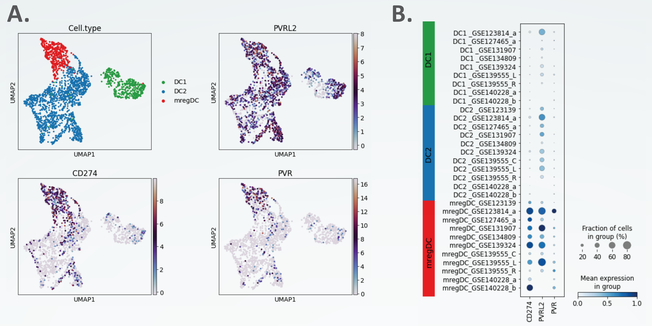
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Overview

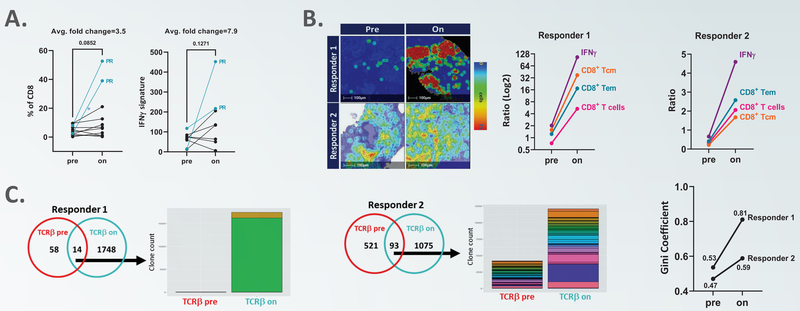
- Tumors with low T cells infiltration respond poorly to checkpoint inhibition.
- Stem-like memory T cells (T_{SCM}) have been identified as a T cells subgroup which possesses strong proliferative capacity that could expand and differentiate following interactions with dendritic cells (DCs).
- PVRIG is a novel T and NK cell regulatory receptor that interacts with PVRL2 on antigen presenting cells and on tumor cells.
- Here we show that in contrast to other T cell checkpoints, PVRIG is uniquely expressed on T_{SCM}, and PVRL2 on DCs in tumor immune aggregate niches.
- PVRIG blockade could therefore enhance T_{SCM}-DC interactions and efficiently drive T cells to tumors.
- COM701 is a first-in-class antibody inhibitor of PVRIG/PVRL2 interaction being tested in clinical trials. Translational data from patients with poorly infiltrated tumors treated with COM701 as monotherapy or in combination with PD-1 and TIGIT blockers, showed increased tumor T cell infiltration, TCR clonality, and intra-tumoral T cells expansion, associated with clinical benefit. Thus, PVRIG-blockade has the potential to show efficacy in patients with low-infiltrated tumors.
- Preliminary data show that PVRL2 baseline levels on tumor and peripheral CD14$^+$ cells correlate with clinical benefit in platinum resistant ovarian cancer (PROC) patients treated with COM701+nivolumab±BMS-986207 (anti-TIGIT).

PVRL2 is prevalently expressed on DC subsets in the TME



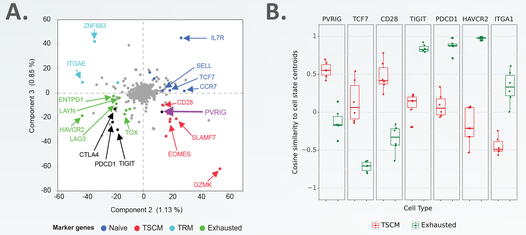
A. Expression profile of PVR/PVRL2/CD274(PD-L1) in major DC subsets in Basal Cell Carcinoma patients (GSE123814). **B.** Percent of cells and average level of expression of PD-L1/PVRL2/PVR in major DC subsets across multiple scRNA cancer studies as indicated.

Increased TME immune activation and TCR clonality in MSS-CRC patients who responded (PR) to COM701+nivolumab therapy



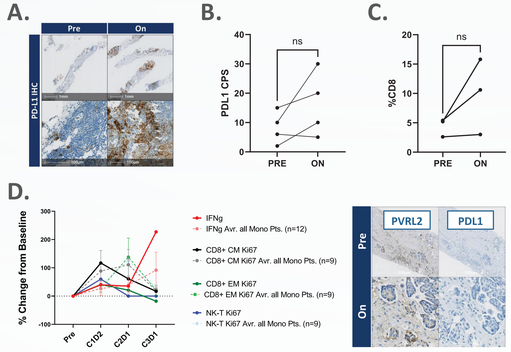
A. An increase in CD8$^+$ cell percentages (IF) and IFNγ signature (RNAseq), in patients with MSS-CRC treated with COM701+nivolumab. Patients with clinical responses are indicated in blue. **B-C.** Pre- and on-treatment biopsies from two MSS-CRC patients, responding to COM701+nivolumab treatment. Increased IFNγ, $CD8_{EM}$, $CD8_{CM}$ and CD8$^+$ T cell mRNA signatures (**B**), increased number of clones and increased clonal expansion as was determined by Gini coefficient (**C**), in the TME post COM701+nivolumab therapy. RNA and TCR sequencing were obtained using Personalis®, ImmunoID NeXT analysis. Gini coefficient, reflects clonal diversity: the higher the index, the lower the diversity, indicating a very few T cell clones are expanding and constitute most of the T cell clones in the TME.

PVRIG clusters with early differentiation/T_{SCM} genes, unlike other immune checkpoints that cluster with exhausted genes, in CD8$^+$ T cells in the TME



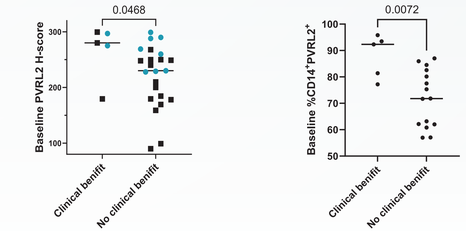
A. Unsupervised PCA analysis of scRNA dataset containing CD8$^+$ T cells from NSCLC tumors (GSE99254, additional 10 datasets were tested and showed similar results). **B.** Association of selected genes with T_{SCM} and Exhausted state. Y-axis represents the cosine-similarity of each gene to the centroid of the marker genes of the corresponding cell state across 6 scRNA datasets representing different solid tumors.

COM701 monotherapy induces TME immune modulation in patients with ovarian cancer



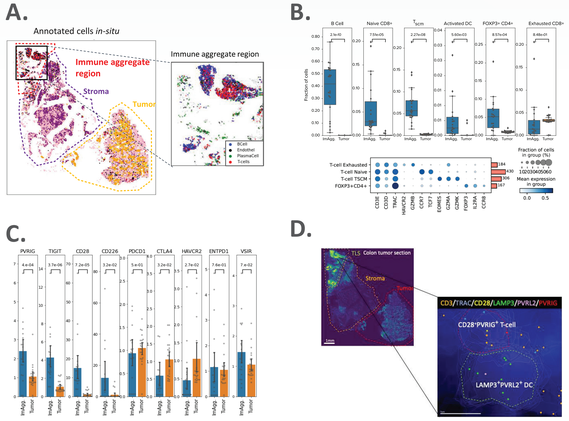
A. Monotherapy with COM701 increased PD-L1 expression (IHC) in a patient with ovarian cancer. **B. and C.** PD-L1 CPS score (3/4) and CD8$^+$ cell percentages (IF, 2/3) were increased in on-treatment compared to pre-treatment biopsies of patients. 4 patients were evaluated for PD-L1 CPS, and 3 patients for percent of CD8, with best clinical response defined as SD. **D.** Serum IFNγ levels, Ki67$^+$CD8$^+$ T_{CM}, Ki67$^+$CD8$^+$ T_{EM} and Ki67$^+$NKT cells (left) in peripheral blood were increased in a patient with primary peritoneal ovarian cancer, positive for PVRL2 and negative for PD-L1 expression (right), clinically responding to COM701 monotherapy (PR, bold lines), compared to the averaged measured parameters in patients treated with COM701 monotherapy (dashed lines).

Higher baseline PVRL2 expression in PROC patients showing clinical benefit in response to COM701+nivolumab±BMS-986207



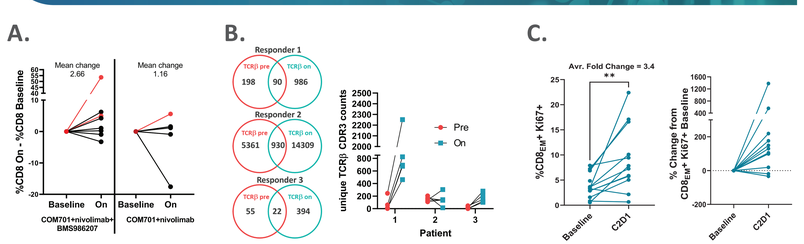
Higher PVRL2 expression in baseline biopsies from patients with PROC treated with COM701+nivolumab±BMS-986207 (clone 181H3L2, protocol CGEN001A-C-APD, Black square = COM701+nivolumab+BMS-986207, blue dots = COM701+nivolumab, **A**), and on peripheral blood monocytes (flow cytometry, **B**) from patients with PROC treated with COM701+nivolumab+BMS-986207, demonstrating clinical benefit. Clinical benefit = CR+PR+SD>180 days on study; No clinical benefit = PD+SD<180 days on study, responses are defined by RECIST 1.1.

T_{SCM} cells that express PVRIG are enriched in immune aggregate regions in TME of CRC patients



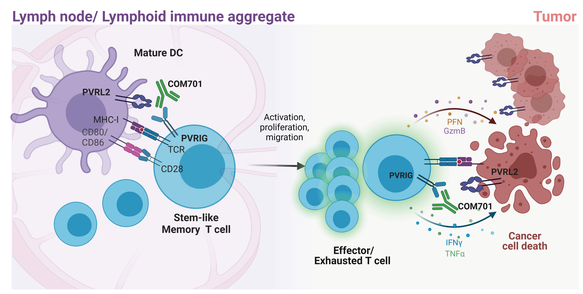
A. Spatial map of single cells clusters obtained from MERFISH analysis. **B.** Cell composition in 21 identified immune aggregate structures or randomly sampled tumor regions. CD8$^+$ T_{SCM} and naïve T cells localize to immune aggregate regions, while exhausted cells localize to the tumor region. (Bottom) Gene expression of selected cell-state markers in a single immune aggregate structure. **C.** PVRIG, TIGIT, and CD226, show dominant expression in immune aggregate regions, whereas other immune checkpoints, such as PD-1, CTLA4, and TIM3 are expressed more in the tumor bed. **D.** CD28$^+$CD8$^+$ T cell expressing PVRIG intimately interacts with LAMP3$^+$PVRL2$^+$ DC in the immune aggregate structure of a CRC patient.

PVRIG blockade by COM701+nivolumab±BMS-986207 induces immune modulation in patients with PROC



A. Increase in CD8 infiltration in patients with PROC (8/13) on-treatment as indicated compared to baseline biopsy. Red dots indicate patients with clinical benefit (CR + PR + SD>=180 days on study). **B.** Increase in number of clones and increased clonality in patients (3) with clinical response (PR) to COM701+nivolumab±BMS-986207. **C.** Increase in percent and ratio of peripheral Ki67$^+$CD8$^+$ T_{EM} from 12 patients treated with COM701+nivolumab.

Summary



The novel T cell checkpoint, PVRIG, is uniquely expressed on T_{SCM} cells in the tumor microenvironment, whereas its ligand PVRL2, is expressed on intra-tumoral DCs. The blockade of PVRIG/PVRL2 interaction by COM701 antibody may induce potent T cell proliferation and infiltration and induce anti-tumor immunity in immune-excluded tumors.