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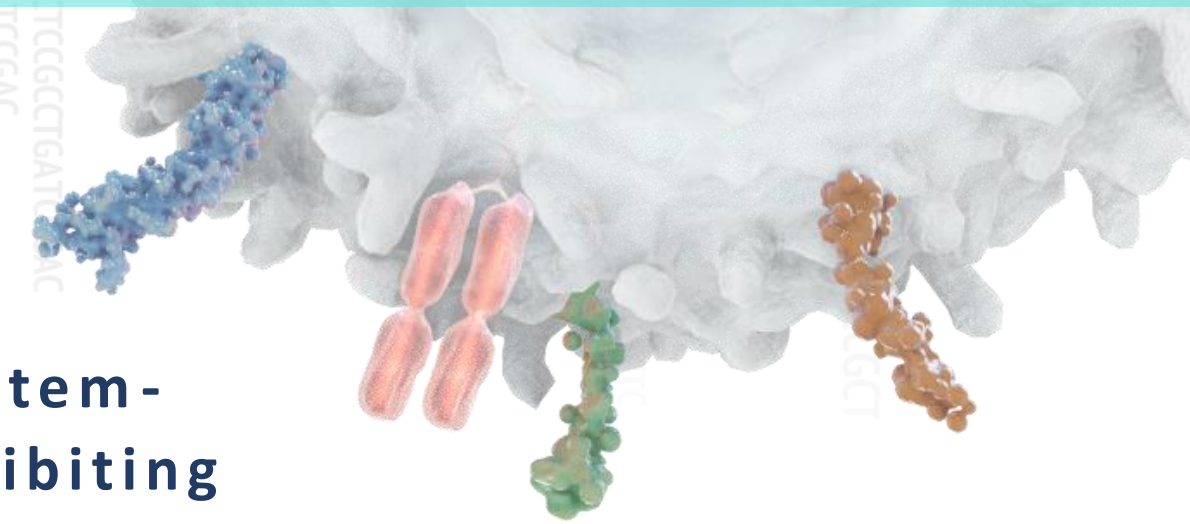

PVRIG, a novel T cell checkpoint, is preferentially expressed in TLS on stem-like memory T cells, potentially inhibiting their expansion

SITC 37th Annual Meeting

Eran Ophir, SVP Research & Drug Discovery

November 2022

SITC 2022

NOVEMBER 8-12 BOSTON MASSACHUSETTS

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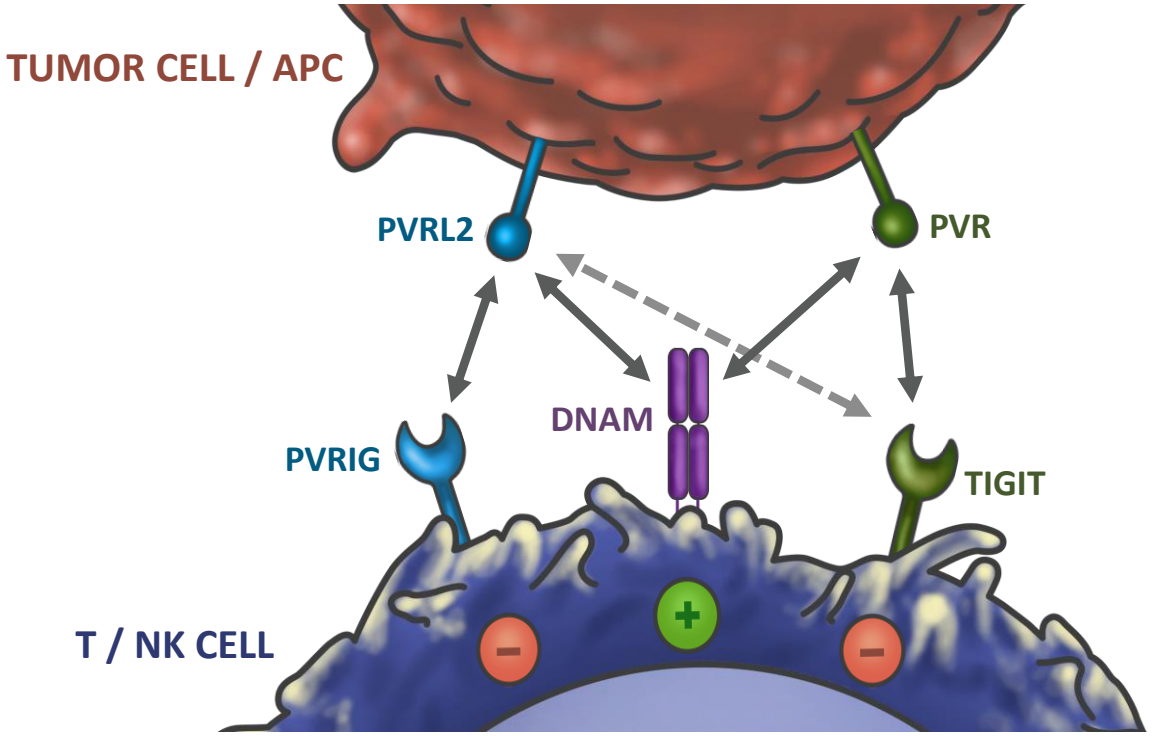
Disclosure

Employee of Compugen LTD

DNAM-1 axis plays an essential role in tumor immunology



- DNAM-1 axis – two parallel dominant complementary inhibitory pathways (PVRIG & TIGIT)
- TIGIT and PVRIG deliver direct inhibitory signals into T and NK cells
- TIGIT/PVRIG has higher affinity to PVR/PVRL2 than DNAM-1 (decoy effect)
- PVRL2 and PVR expressed on PD-L1 positive and negative tumors; PVRL2 broadly expressed on Dendritic cells subtypes

Alteber *et al.* Cancer Discov. 2021

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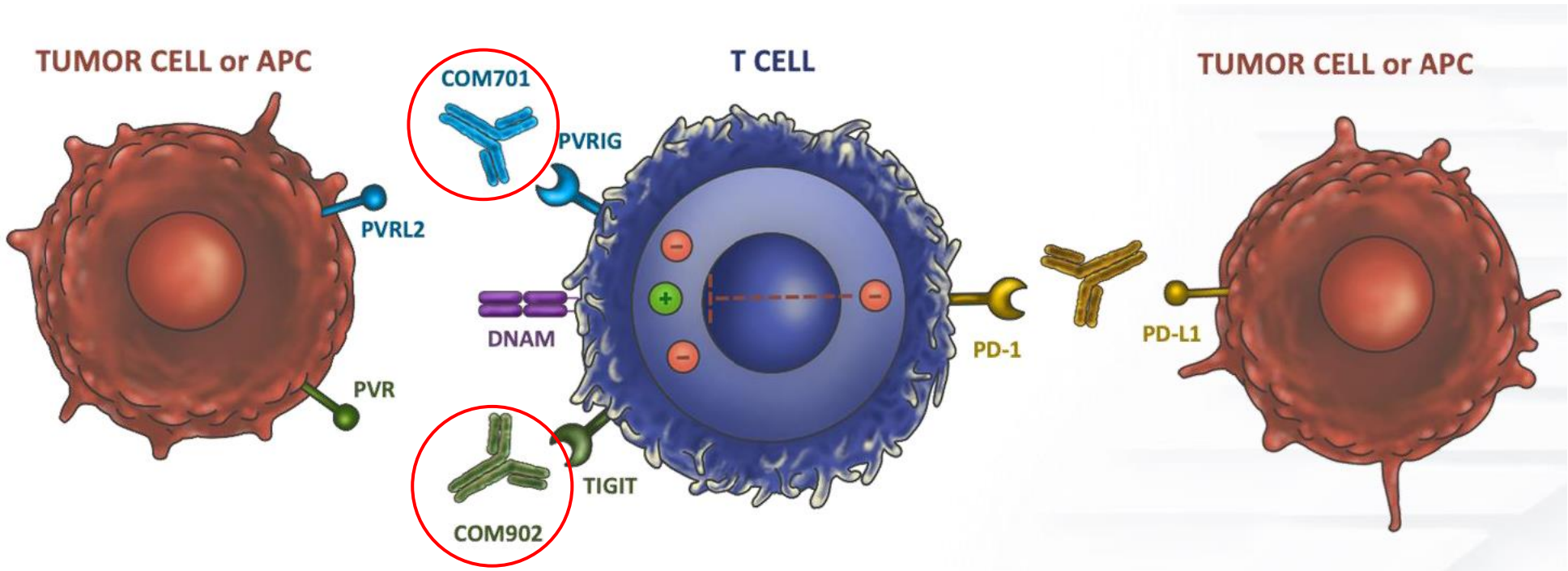
Potential intersection between PVRIG/TIGIT and PD-1 pathways supports combination approach to overcome immunotherapy resistance



Adapted from Alteber *et al.* Cancer Discov. 2021

- **COM701** – High affinity, humanized IgG4 anti-PVRIG mAb, blocks PVRIG/PVRL2 binding interaction
- **COM902** – High affinity, humanized IgG4 anti-TIGIT mAb, blocks TIGIT/PVR binding interaction

Different tumor types may respond to different combinations depending on dominance of the pathways

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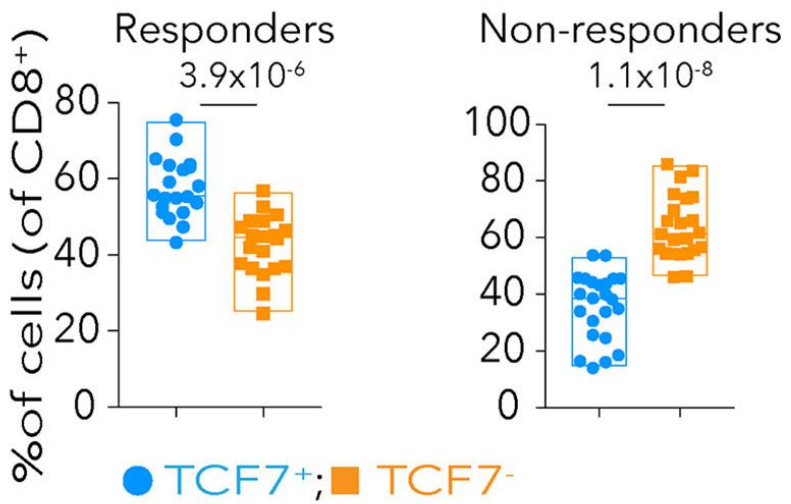
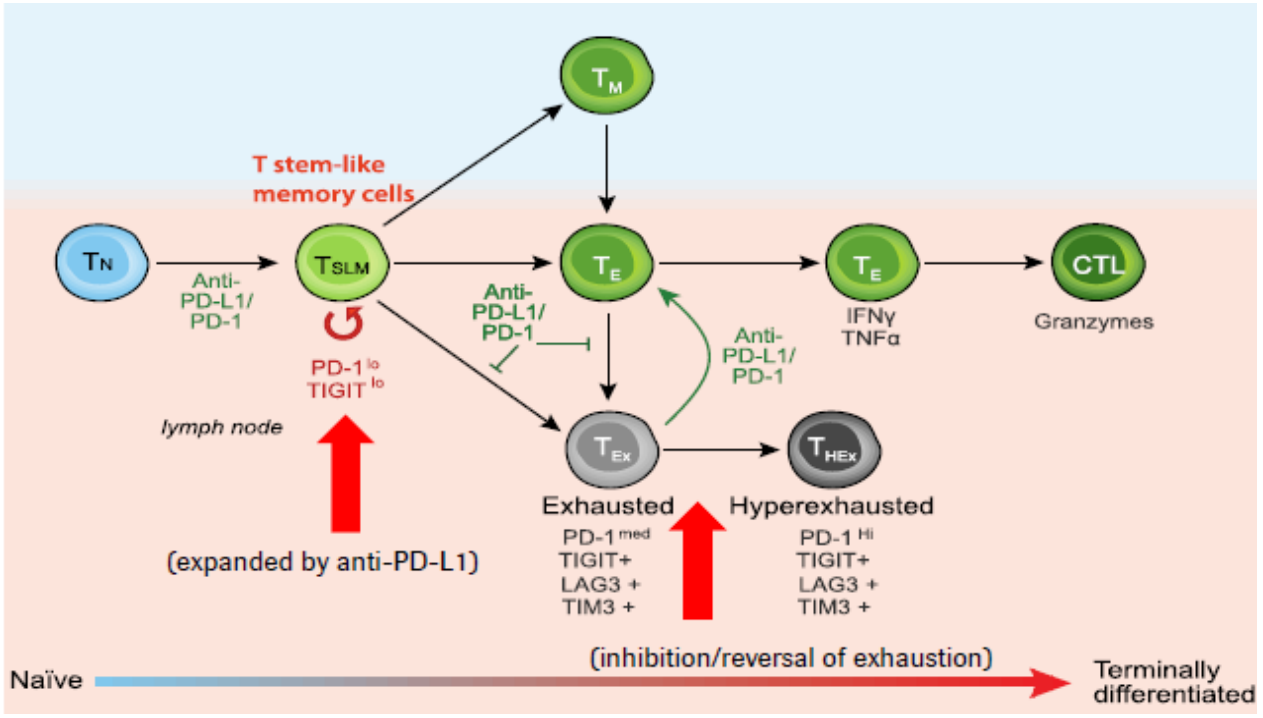
Growing evidence of early differentiated T stem-like memory cells (Tscm) importance in response to checkpoint blockade

The fraction of Tscm cells is predictive of PD-1 response in melanoma



Sadeh-Feldman et al., 2018, Cell

Anti-PD-(L)1 expands a key population of PD-1-positive Tscm cells which also express TIGIT



Modified from Chen and Mellman Nature 2017

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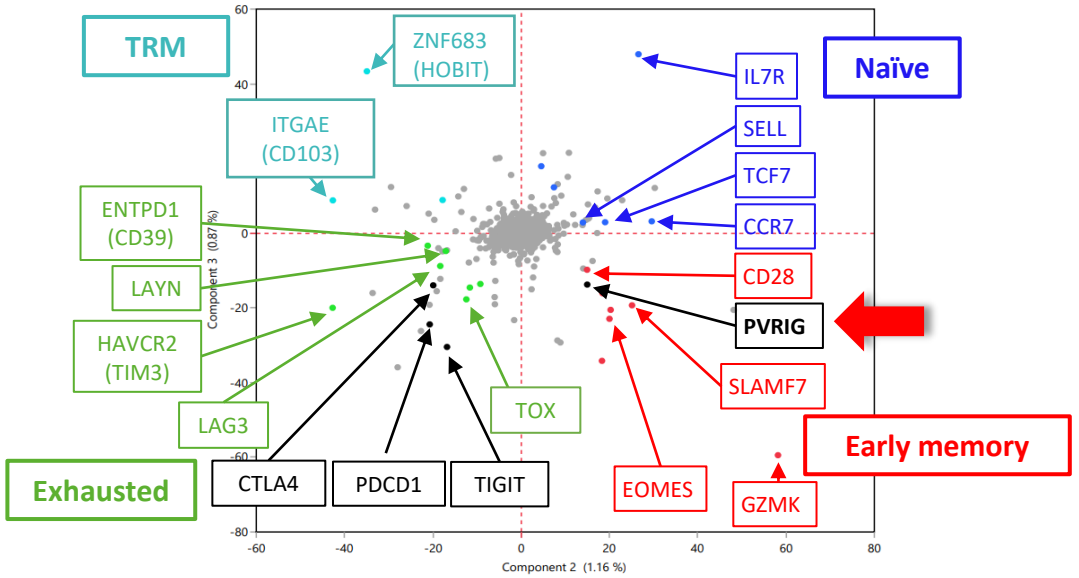
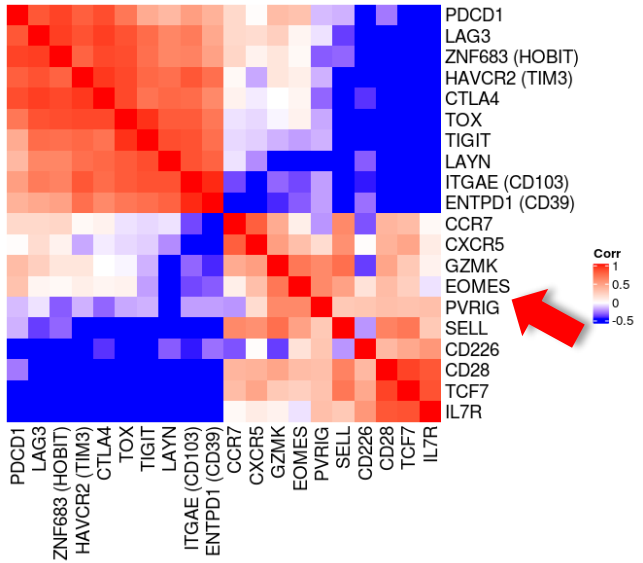
PVRIG uniquely clusters with early differentiated/Tscm genes

PCA Analysis of scRNA of CD8+ T cell genes, NSCLC



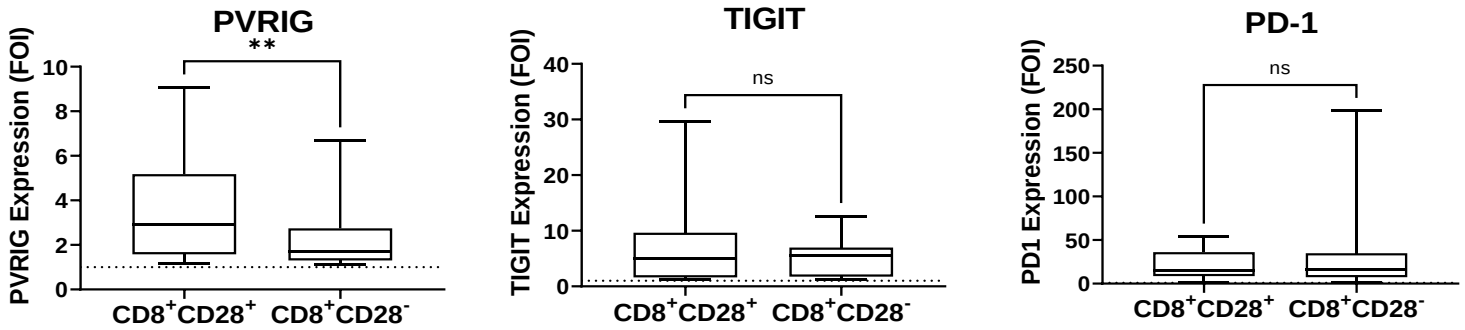
GSE99254_NSCLC Dataset internally analyzed

Unsupervised correlation analysis of scRNA, CRC



GSE108989_CRC Dataset internally analyzed

PVRIG, TIGIT and PD-1 protein expression



Internal FLOW cytometry Data (n=11, CRC, Ovarian and Bladder cancers)

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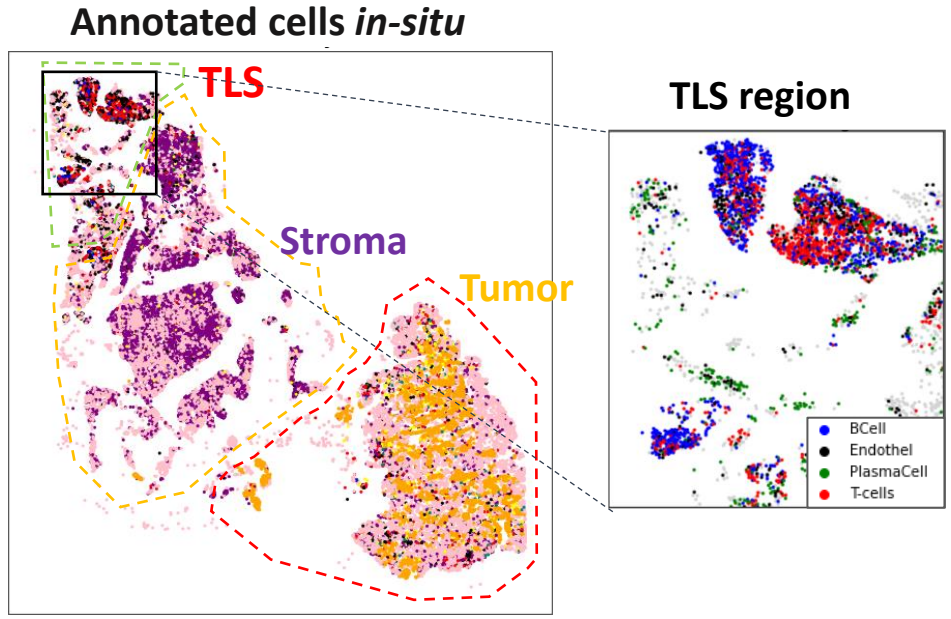
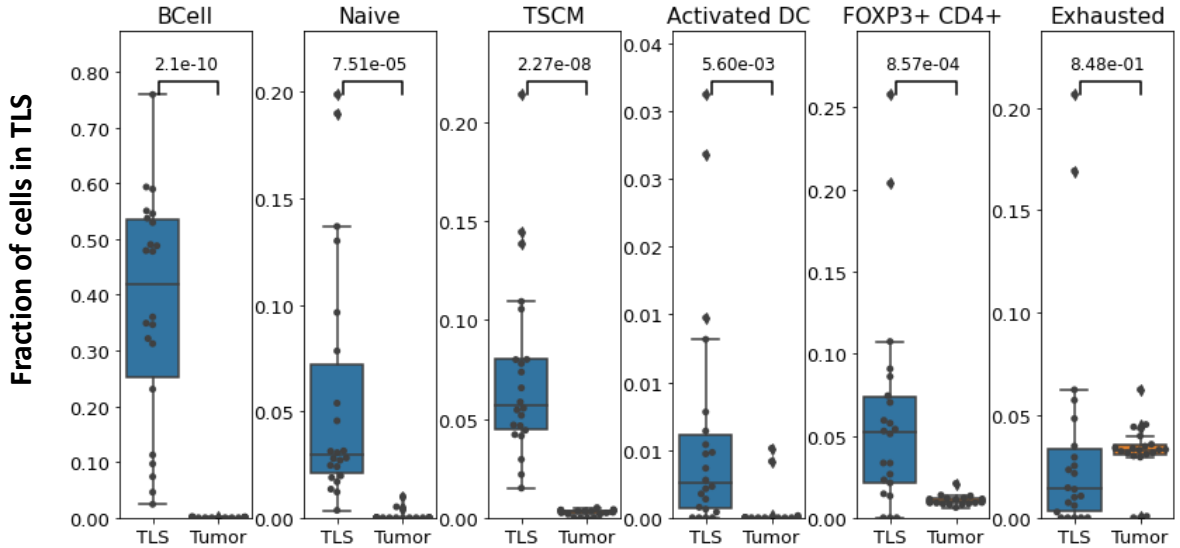
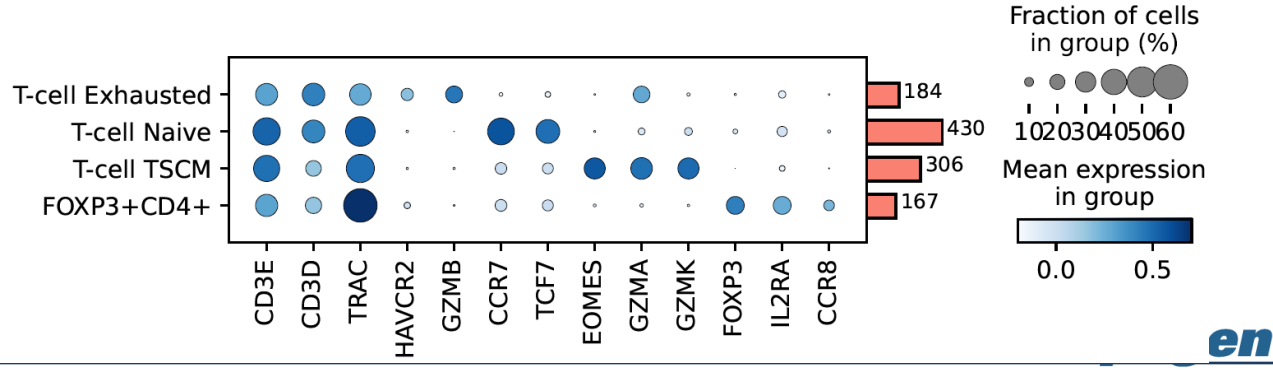
Spatial transcriptomic analysis of TLS regions shows enrichment of Tscm and DCs while exhausted cells localize to the tumor

In-situ MERFISH analysis of tertiary lymphoid structures (TLS) in TME of CRC patients







- TLS - Tertiary Lymphoid structures are the intra-tumoral niches in which local T cell activation occur
- TLS are predictive of response to immunotherapy

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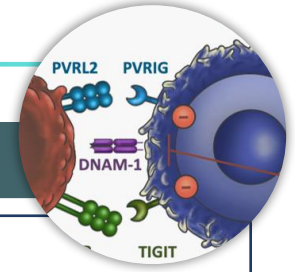
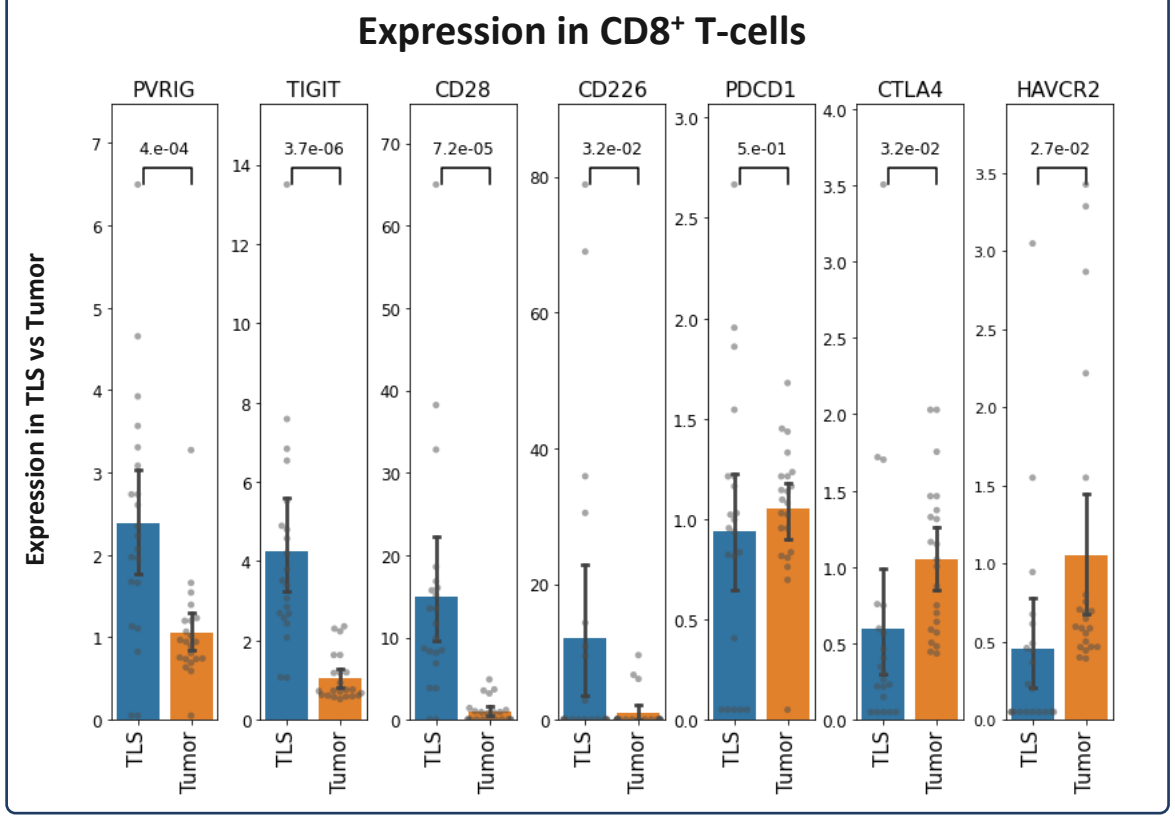
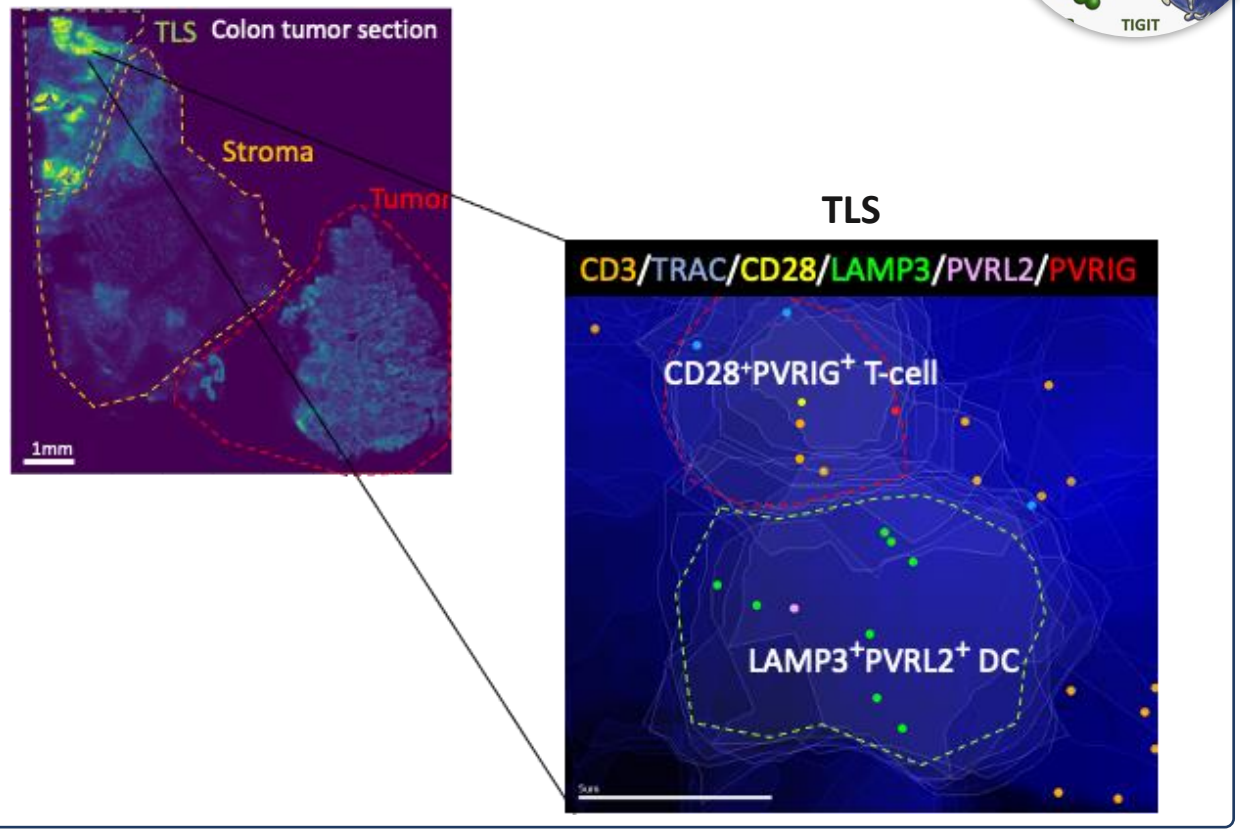
PVRIG and other genes of the DNAM-1 axis are dominantly expressed in TLS region



In-situ MERFISH analysis of tertiary lymphoid structures (TLS) in TME of CRC patients





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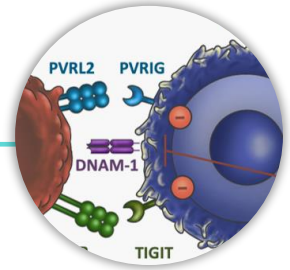
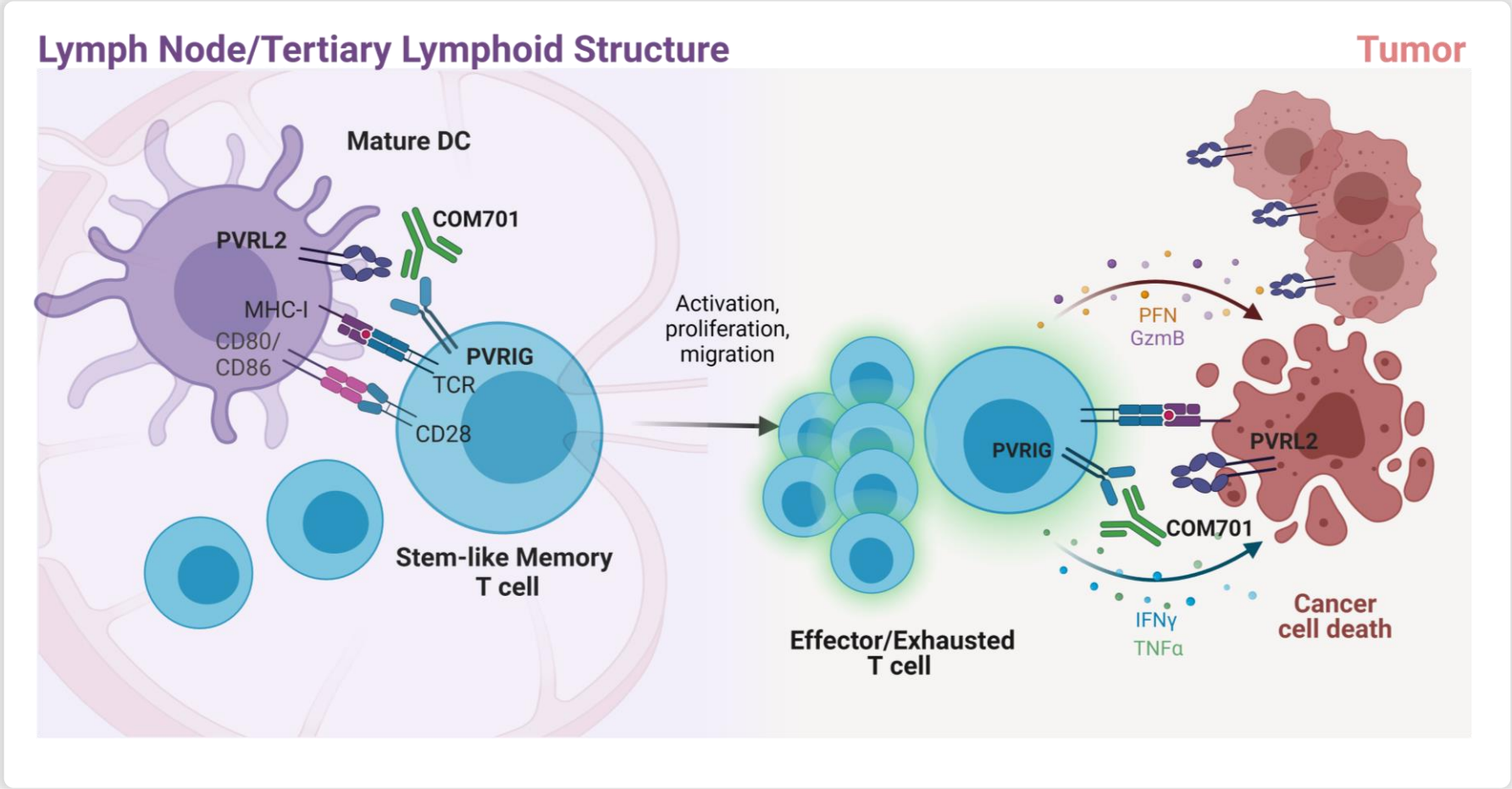
PVRIG+ Tscm interaction with PVRL2+ DCs hypothesis





This hypothesis may support COM701 activity in less inflamed PD-L1^{low} tumor types

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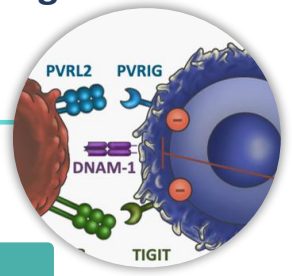
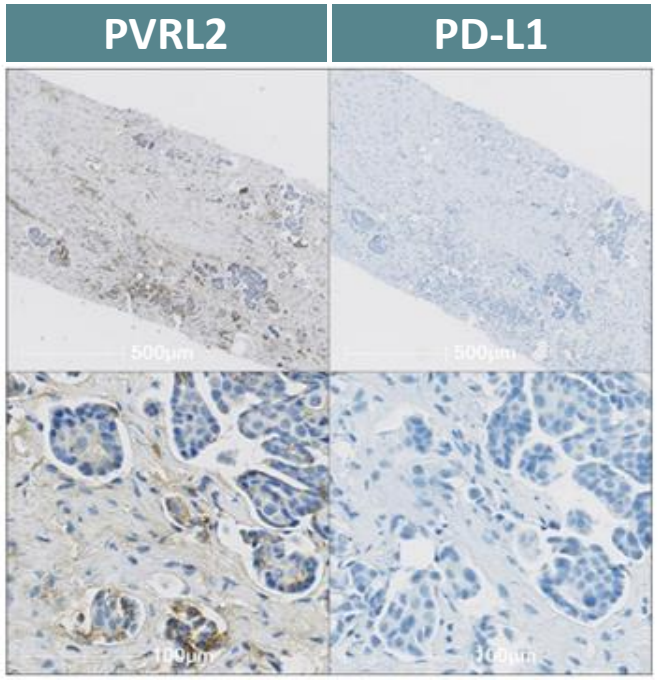
Immune modulation in peripheral blood of a patient with PD-L1^{neg} primary peritoneal cancer responding to COM701 monotherapy

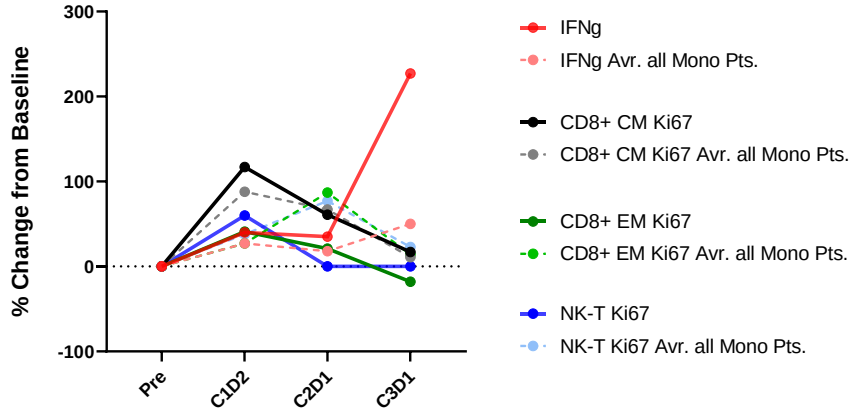


Patient received 3 prior lines of anti cancer therapy



- Pre- treatment archival biopsy (>1 year)
- Negative PD-L1 staining
- PVRL2 expression found on tumor and endothelial cells
- Immune “desert”: no immune cells detected in the biopsy

Increase in IFNγ induction and immune activation in peripheral blood



ASCO, June 2021, Vaena et al., Oral presentation

Confirmed PR in a patient with non-inflamed TME demonstrating immune activation in peripheral blood following COM701 monotherapy

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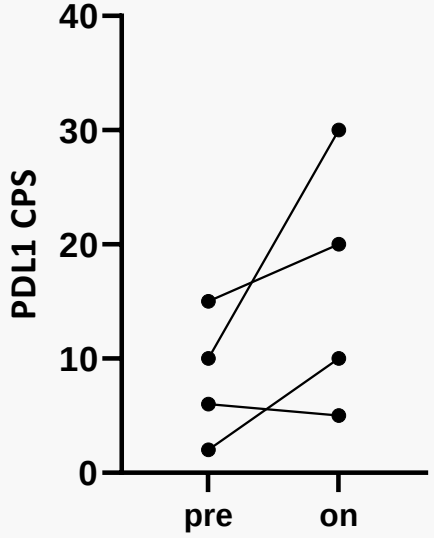
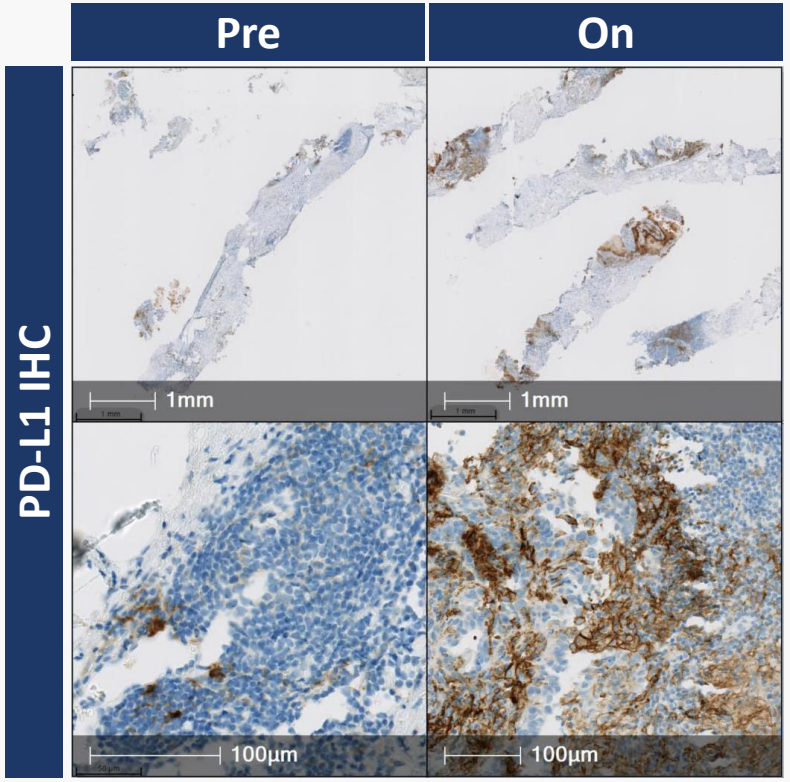
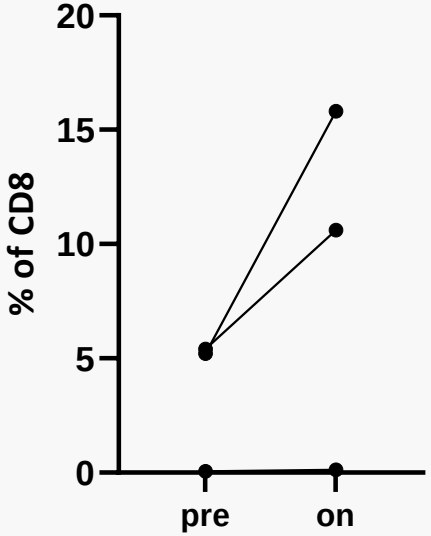
COM701 monotherapy induces TME immune modulation in patients with ovarian cancer

PD-L1 expression





CD8 IF



- 3 out of 4 patients showed an increase in CPS PD-L1
- 2 out of 3 patients showed an increase in % CD8
- PD-L1 upregulation and increased CD8 infiltration indicate on immune activation induced by COM701 monotherapy

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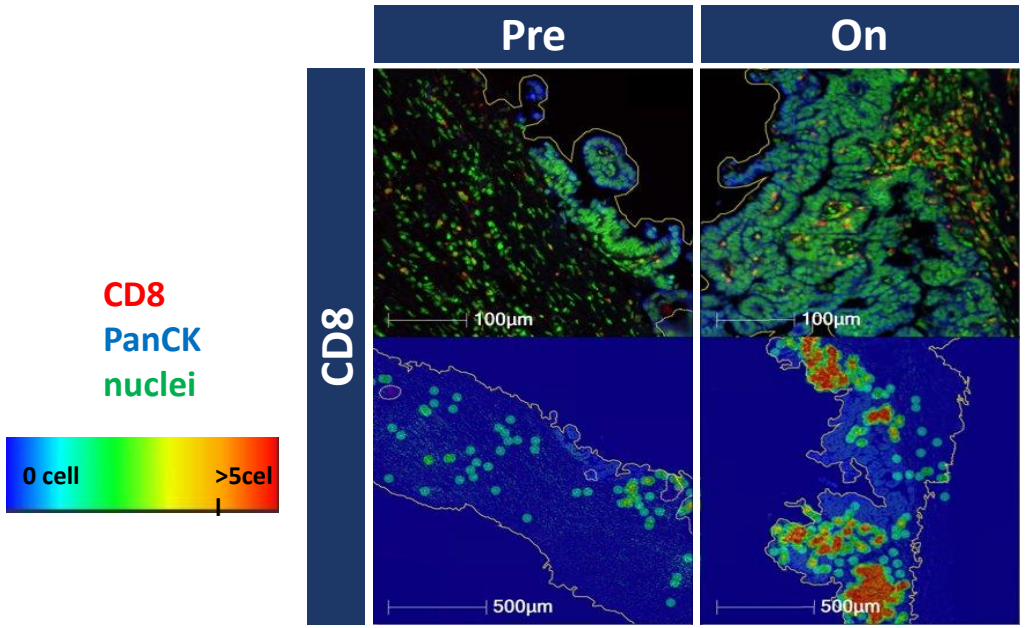
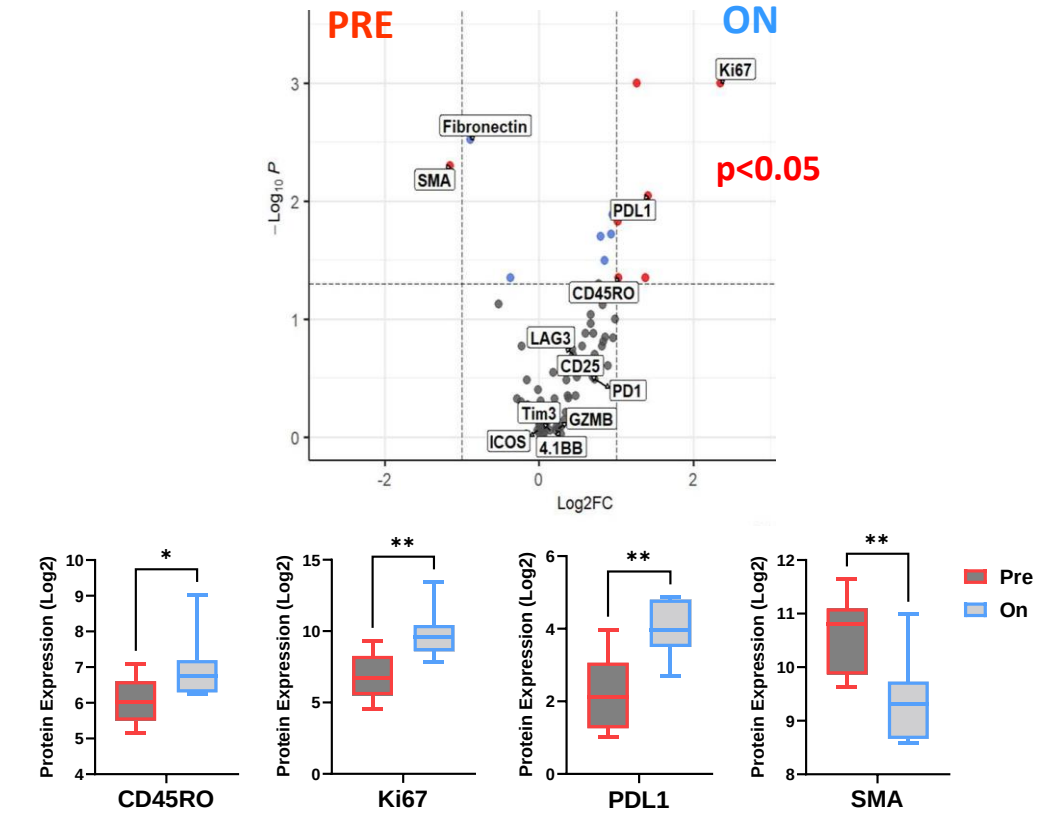
COM701 monotherapy induced immune activation in the TME of patient with ovarian cancer

CD8 distribution in TME



% CD8 cells	5.2	15.8
Maximum CD8 Density (CD8/µm²)	0.005	0.012
Av. Distance Tumor-CD8 (µm)	51.027	23.190

Protein expression in CD8 regions (NanoString, DSP)



Patient with ovarian cancer demonstrating shift from stromal markers towards immune activation in TME following COM701 monotherapy

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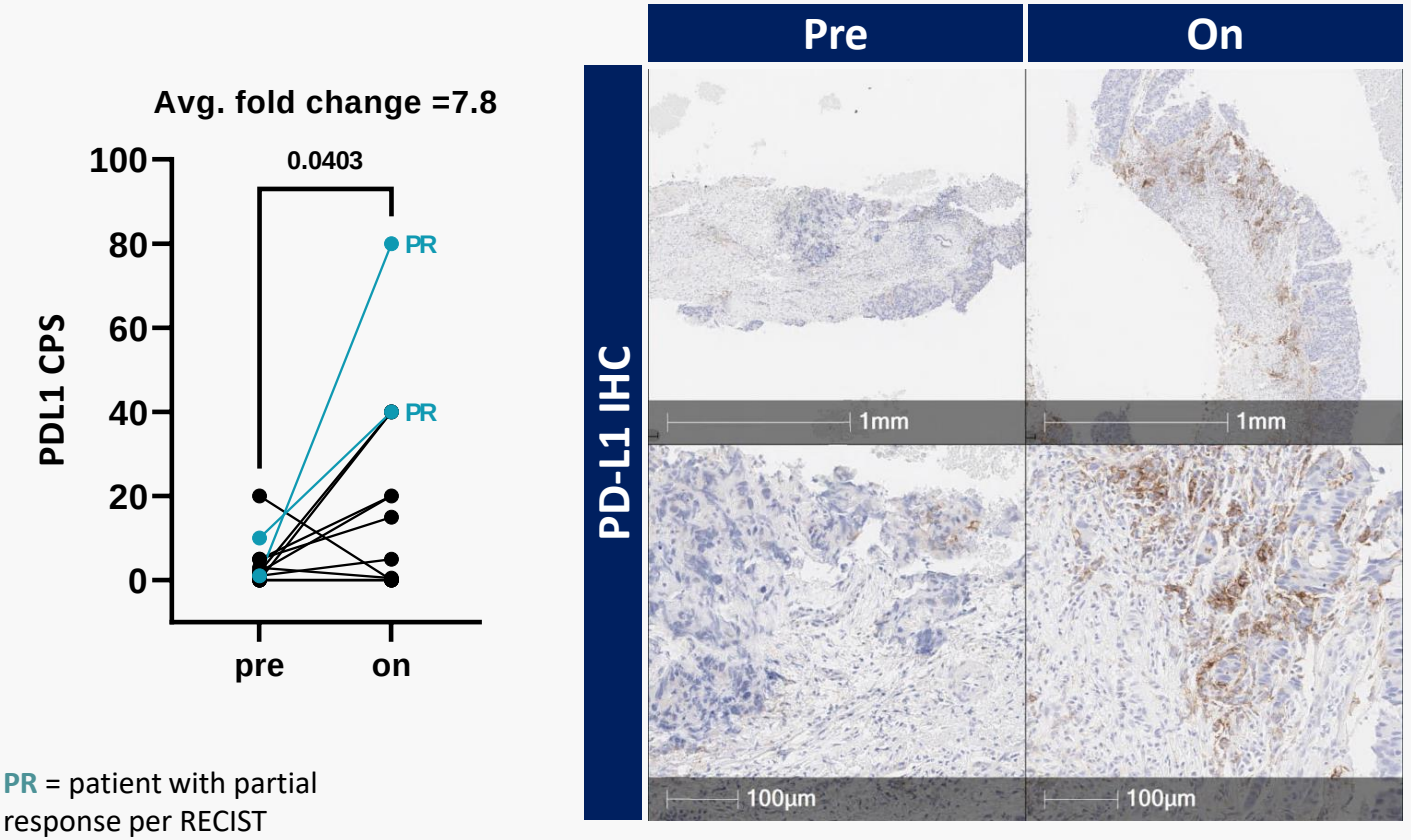
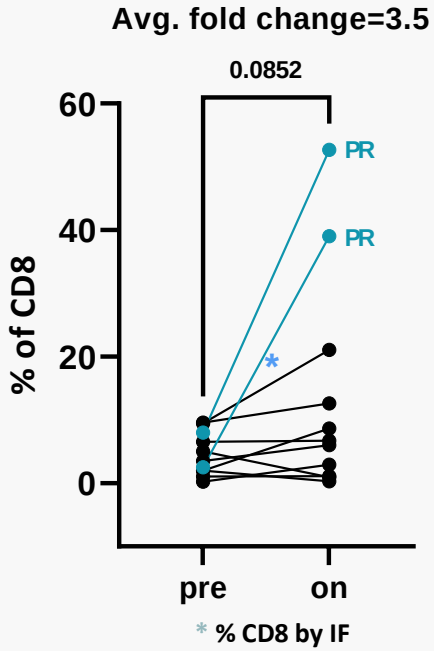
COM701+ nivolumab combination induces TME immune modulation in patients with MSS-CRC

PD-L1 expression

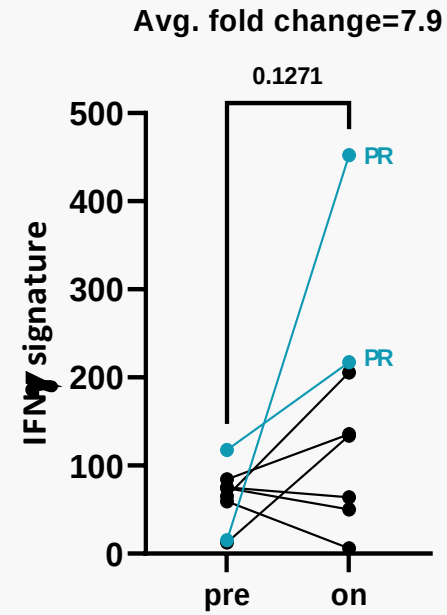


PR = patient with partial response per RECIST

CD8 IHC



IFNγ signature



PR = patient with partial response per RECIST

- 9/13 patients showed an increase in CPS PD-L1
- 7/11 patients showed an increase in % CD8
- 5/8 patients showed an increase in IFNγ signature

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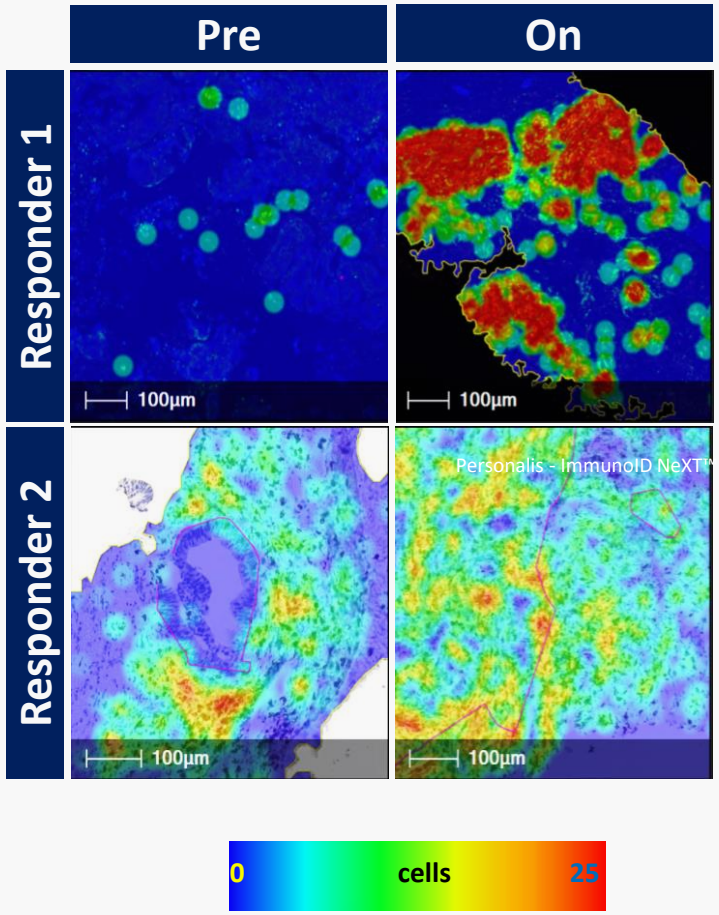
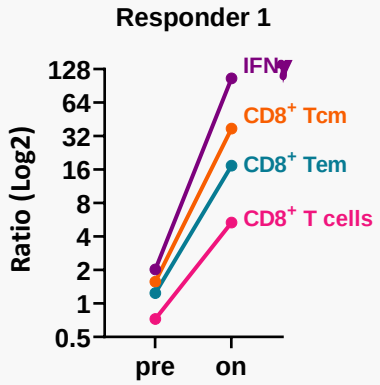
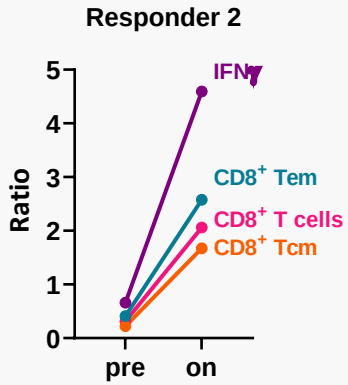
Extensive TME modulation in MSS-CRC patients partially responding to COM701+ nivolumab

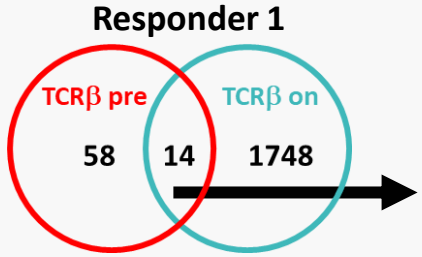
Increased CD8 infiltration and immune modulation

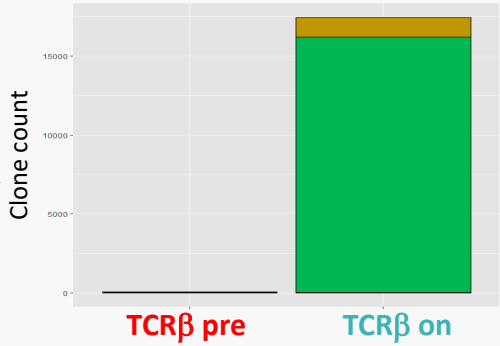




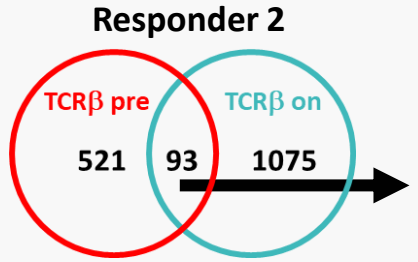


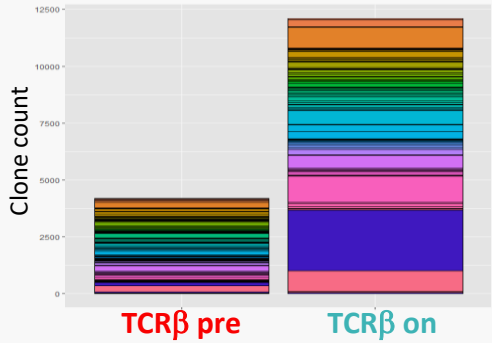
Increased TCR clonality and clonal expansion





Most dominant clone on treatment pre-existed in the TME pre-treatment





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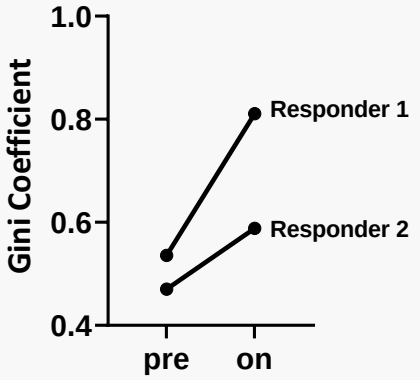

Personalis - ImmunoID NeXT™

COM701 + nivolumab induces infiltration of new clones as well as expansion of pre-existing clones in both MSS-CRC responding patients

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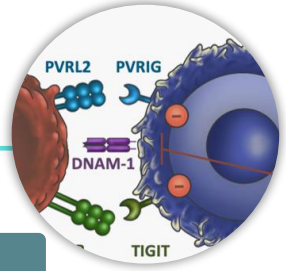
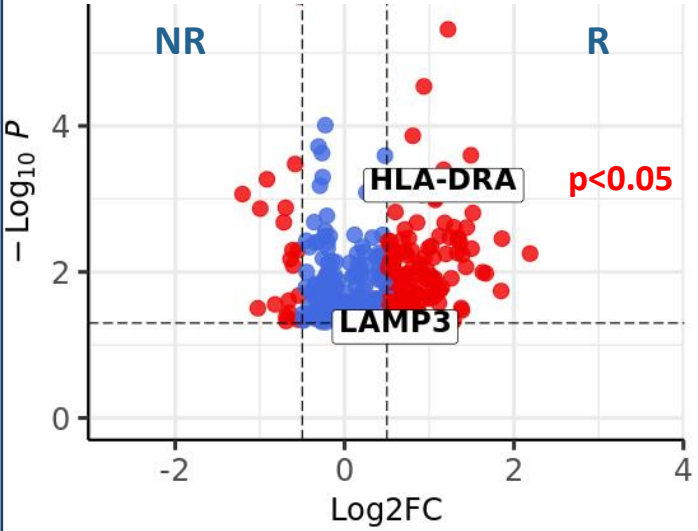
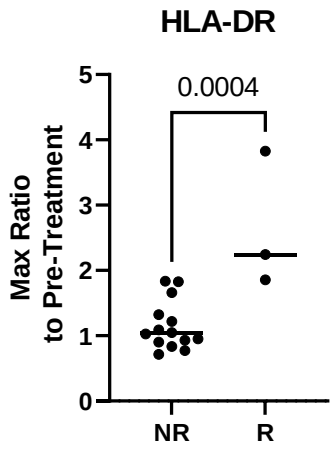
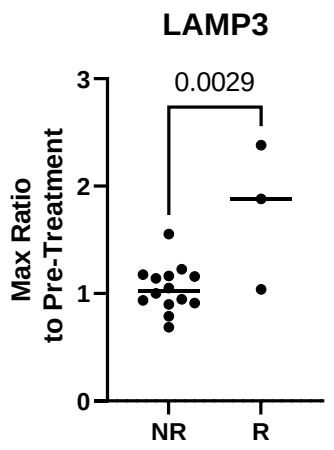
Combination of COM701+nivolumab induced markers of activated DCs in serum of 3 responding patients

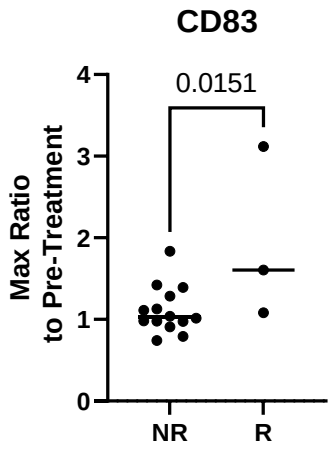


Responders (R) vs non-responders (NR) differential gene expression









Olink® Explore 1536

Induction of activated-DC markers in serum of 3 patients that clinically responded to COM701+nivolumab compared to non-responders

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Summary

- PVRIG has a unique dominant expression on Tscm, its ligand, PVRL2, is expressed also on dendritic cells (DCs)
- Spatial transcriptomic analysis showed that Tscm and DCs preferentially localize to TLS regions while exhausted T cells localize to the tumor
    - PVRIG is dominantly expressed on CD8+ T cells in TLS region
- PVRIG blockade may enhance Tscm activation by DCs in lymph-nodes and TLS, a potential mechanism which could lead to increased T cell expansion and infiltration also into less ‘inflamed’ tumors
- COM701+/- nivolumab induced preliminary anti tumor activity and TME immune-modulation in patients with MSS-CRC and ovarian cancer, typically not responsive to approved CPI
- Translational data analysis of immune-modulation following PVRIG, PD-1 and TIGIT triplet blockade is ongoing
- Further clinical evaluation of PVRIG blockade is being pursued

Acknowledgments:

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Compugen Ltd.
Holon, Israel
Predictive Target Discovery
& Experimental Validation

Zoya Alteber, Roy Granit, Gady Cojocaru, Amit Novik, Niv Sabath, Assaf Wool, Yossef Kliger, Yu Liang, Pierre Ferre, Yaron Turpaz, Zurit Levine

Thank you!

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Natalia Petrenko, Rob Foreman, Jiang He,

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