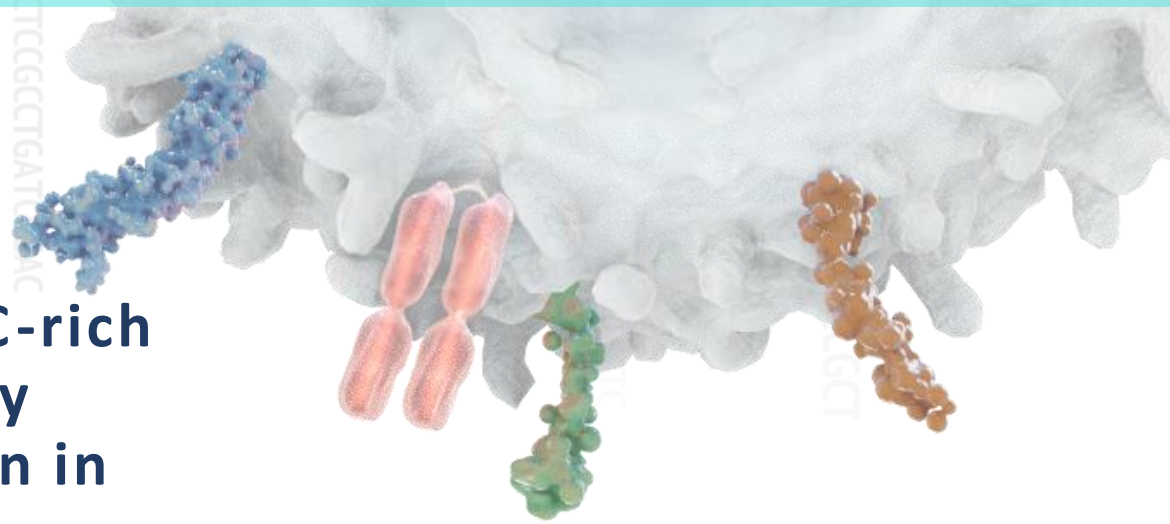
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PVRIG is uniquely expressed in tumor DC-rich niches on T_{SCM} cells, and its blockade may induce immune infiltration and activation in non-inflamed tumors

KEYSTONE SYMPOSIA

Dr. Zoya Alteber, Director of Research & Drug Discovery

March, 2024

Safe Harbor Statement

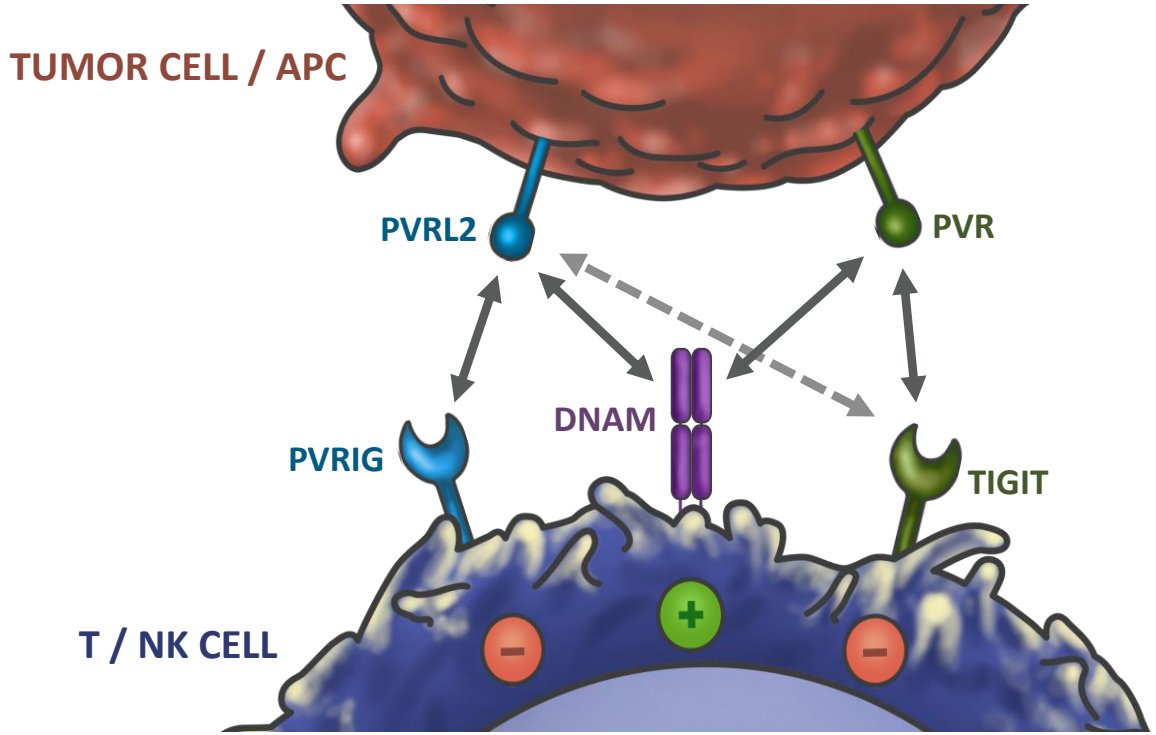
This presentation contains “forward-looking statements” within the meaning of the the Securities Act of 1933 and the Securities Exchange Act of 1934, as amended, and the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by the use of terminology such as “will,” “may,” “expects,” “anticipates,” “believes,” “potential,” “plan,” “goal,” “estimate,” “likely,” “should,” and “intends,” and similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. These forward-looking statements involve known and unknown risks and uncertainties that may cause the actual results, performance or achievements of Compugen to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements, including statements regarding the timing and success of our clinical trials, enrollment of patients, type of clinical trials, presentation of data and our cash position and expenditures. Among these risks: Compugen’s operations could be affected by the outbreak and spread of COVID-19, Compugen’s business model is substantially dependent on entering into collaboration agreements with third parties, and Compugen may not be successful in generating adequate revenues or commercialize its business model or control its expenditures. Compugen also may not meet expected milestones in its development pipeline and may also be unable to enroll patient to its clinical trials or to present data. Moreover, clinical development involves a lengthy and expensive process, with an uncertain outcome and Compugen may encounter substantial delays or even an inability to begin clinical trials for any specific product or may not be able to conduct or complete its trials on the timelines it expects. These and other factors, including the ability to finance the Company, are more fully discussed in the "Risk Factors" section of Compugen’s most recent Annual Report on Form 20-F as filed with the Securities and Exchange Commission (“SEC”) as well as other documents that may be subsequently filed by Compugen from time to time with the SEC. In addition, any forward-looking statements represent Compugen’s views only as of the date of this presentation and should not be relied upon as representing its views as of any subsequent date. Compugen does not assume any obligation to update any forward-looking statements unless required by law. Certain studies and data presented herein have been conducted for us by other entities as indicated where relevant. Intellectual property, including patents, copyrights or trade secret displayed in this presentation, whether registered or unregistered, are the intellectual property rights of Compugen. Compugen's name and logo and other Compugen product names, slogans and logos referenced in this presentation are trademarks of Compugen Ltd. and/or its subsidiary, registered in the U.S.A., EU member states and Israel.

Disclosure

- Compugen ltd. employee

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DNAM-1 axis plays essential role in tumor immunology



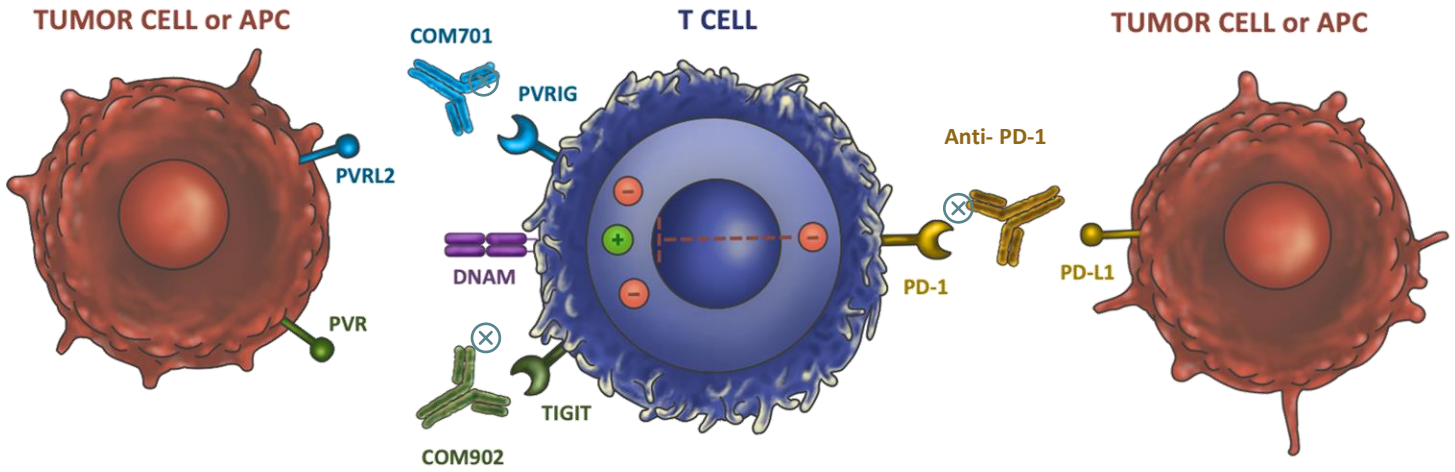
Modified from Alteber et al. Cancer Discov. 2021

- DNAM axis – two parallel and complementary inhibitory pathways (PVRIG & TIGIT)
- PVRIG binds PVRL2 as a functional ligand and TIGIT binds PVR
- TIGIT and PVRIG deliver direct inhibitory signals into T and NK cells
- TIGIT/PVRIG have higher affinity to PVR/PVRL2 than DNAM-1 (decoy effect)

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

Blocking PVRIG may be the missing piece when checkpoint inhibitors fail



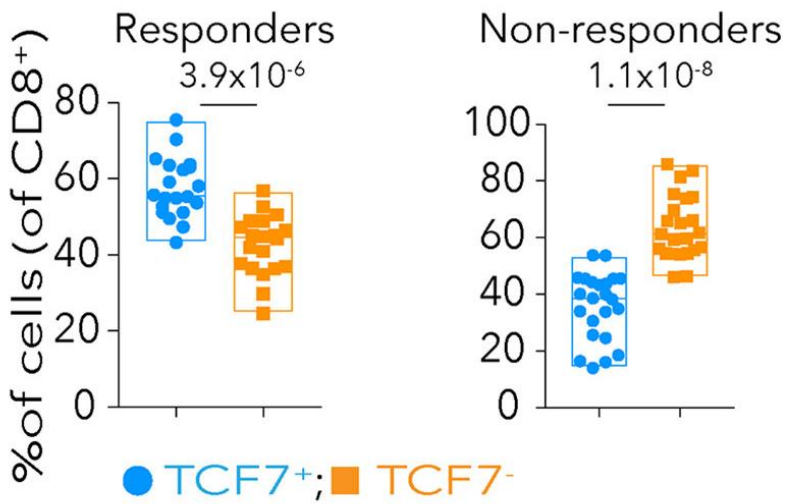
- PD-1 suppresses DNAM-1 co-stimulation
- Potential synergy in blocking PVRIG, TIGIT and PD-1 pathways
- Different tumor types may respond to different combinations depending on dominance of the pathways
- PVRL2 broadly expressed in PD-L1 high and low tumors

Modified from Alteber et al. Cancer Discov. 2021

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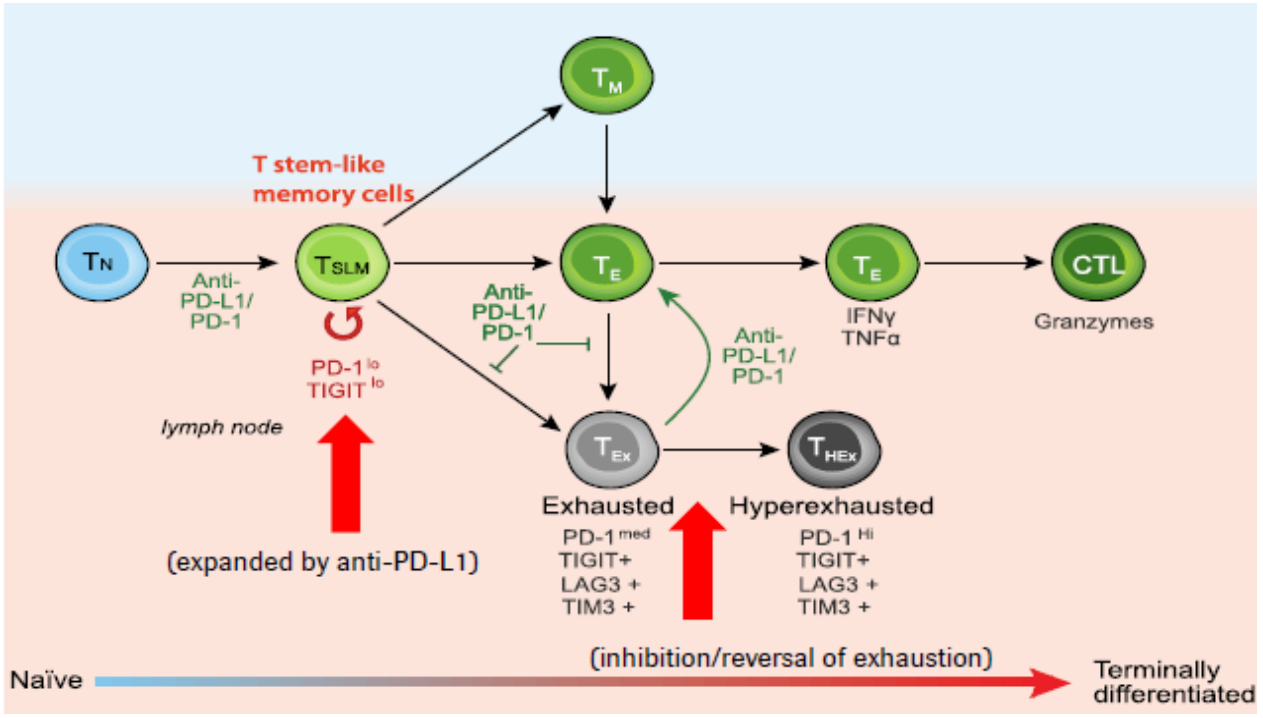
Growing evidence of early differentiated T_{SCM} importance in response to checkpoint blockade

The fraction of T_{SCM} 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^{low} T_{SCM} cells which also express TIGIT^{low}



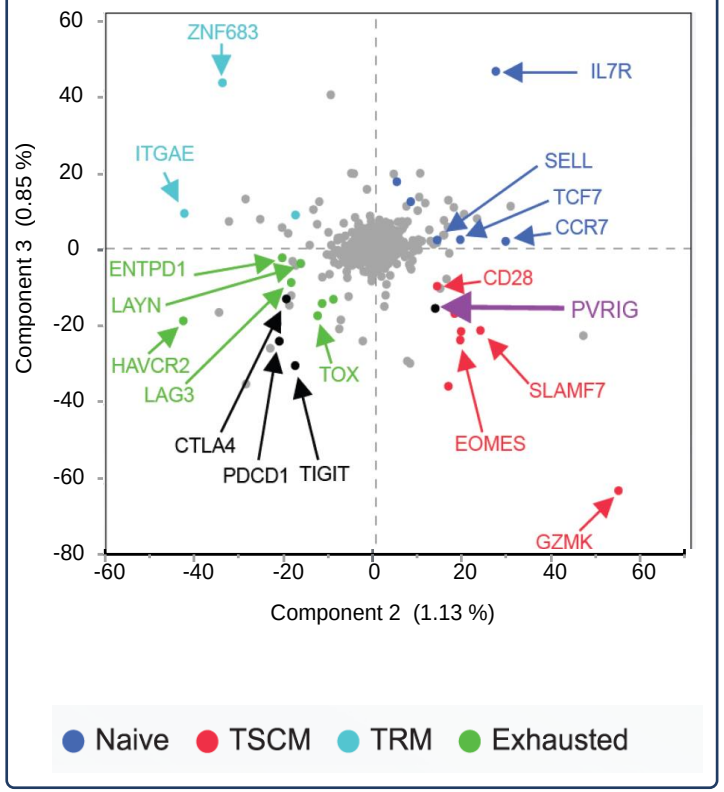
Modified from Chen and Mellman Nature 2017

T_{SCM}: T stem-like memory cells

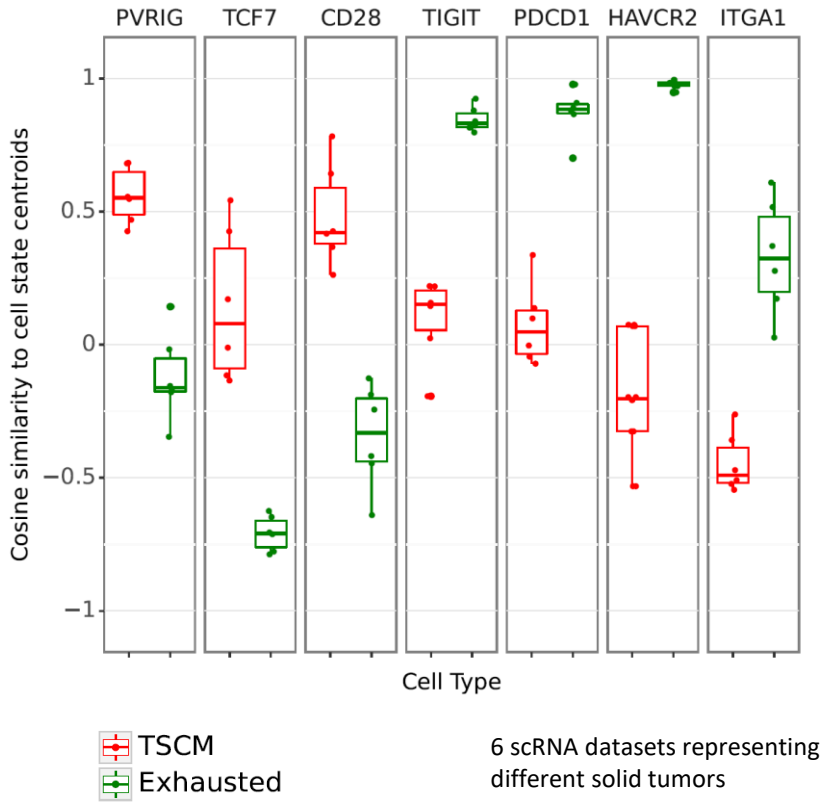
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PVRIG uniquely clusters with early differentiated/T_{SCM} genes

PCA analysis of scRNA of $CD8^+$ T cell genes, NSCLC

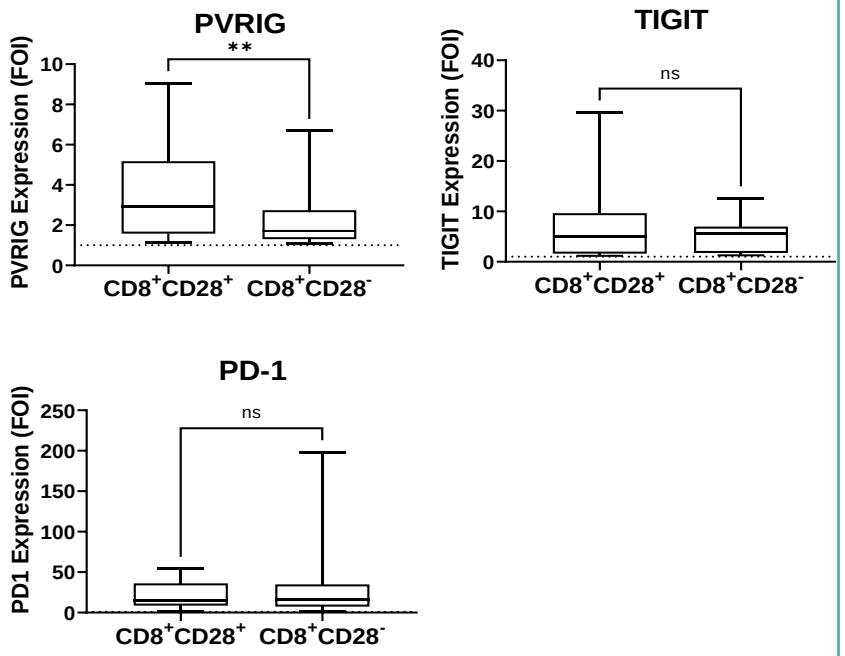


PVRIG is expressed in T_{SCM} cells whereas other immune checkpoints are enriched in exhausted



6 scRNA datasets representing different solid tumors

PVRIG, TIGIT and PD-1 protein expression

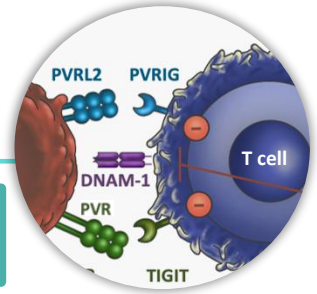


Internal flow cytometry Data (n=11, CRC, Ovarian and Bladder cancers)

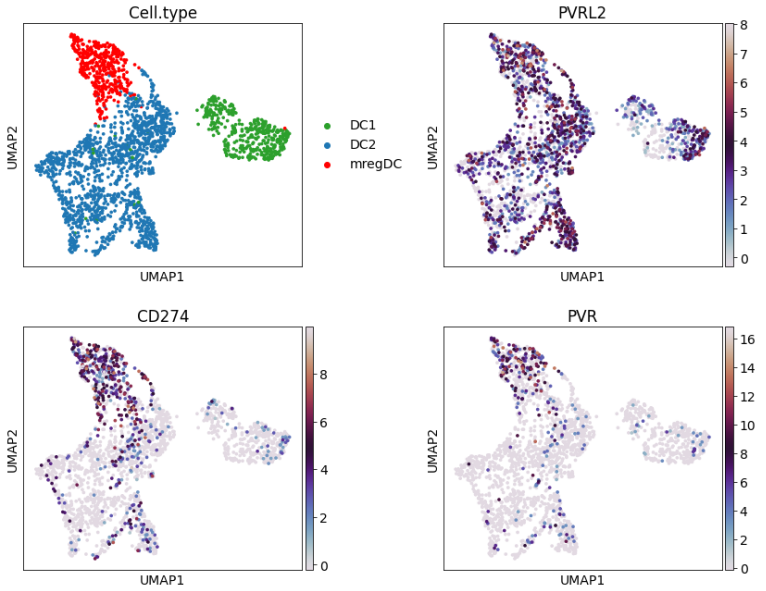
NSCLC: Non small cell lung cancer

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PVRL2 has a dominant expression on dendritic cells

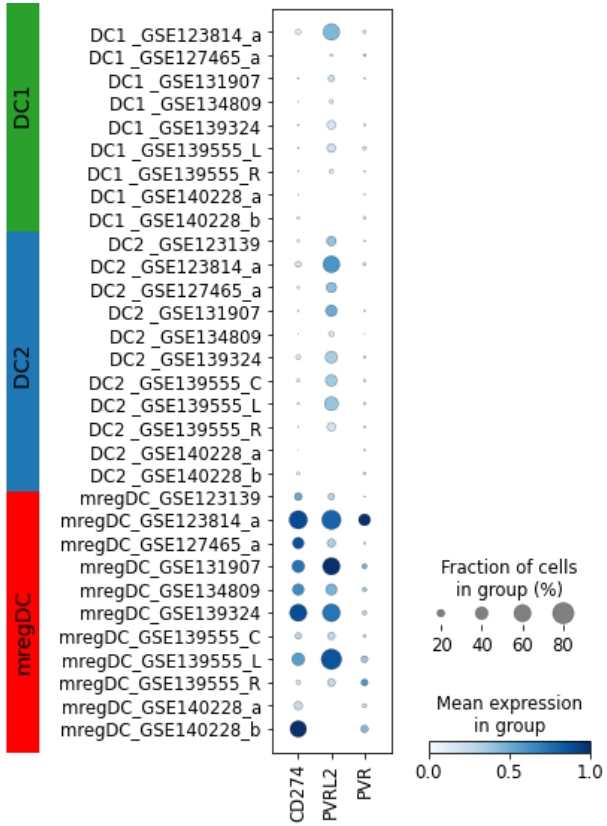


PVRL2 is expressed on DCs

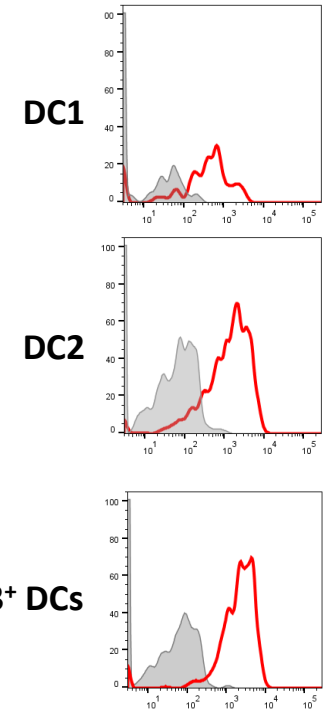


GSE123814 Dataset of SCC/BCC internally analyzed

PVRL2, PD-L1, PVR expression on DCs across multiple scRNA cancer datasets



PVRL2 protein expression on DCs in ovarian cancer



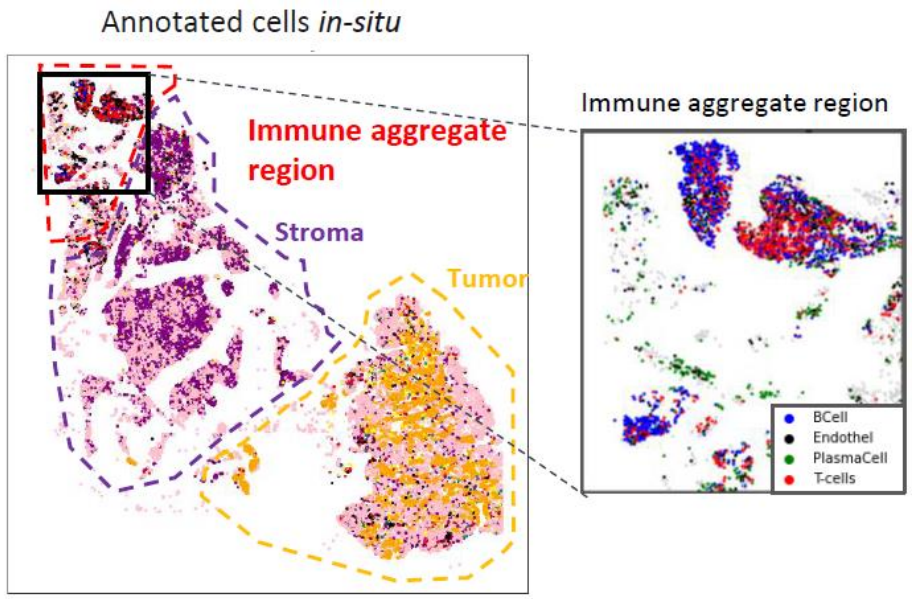
Internal FLOW cytometry Data

PVRIG blockade may enhance T_{SCM} - DC interaction and induce potent T_{SCM} activation

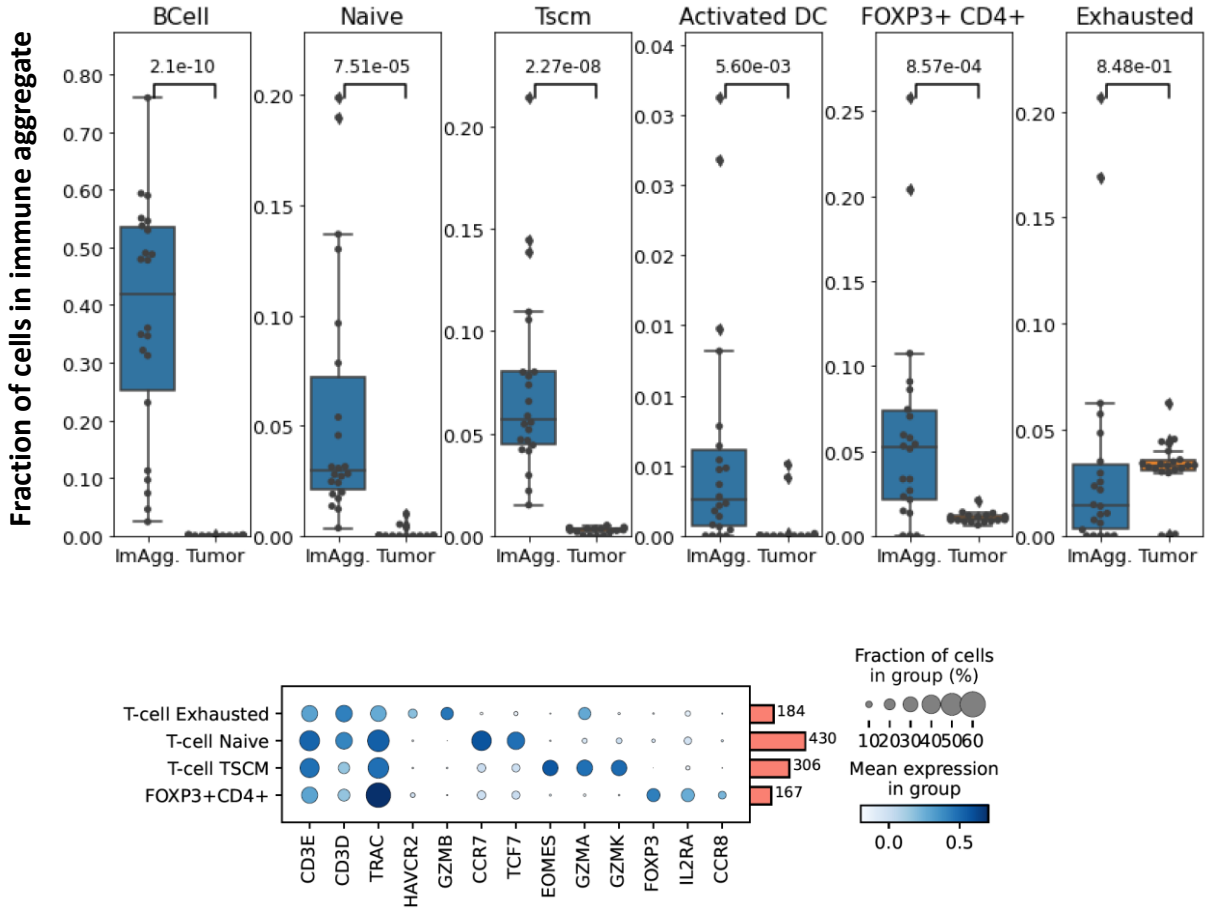
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Spatial transcriptomic analysis of immune aggregate niches shows enrichment of T_{SCM} and DCs, while exhausted cells localize to the tumor

In-situ MERFISH analysis of immune aggregate structure in tumor of CRC patient



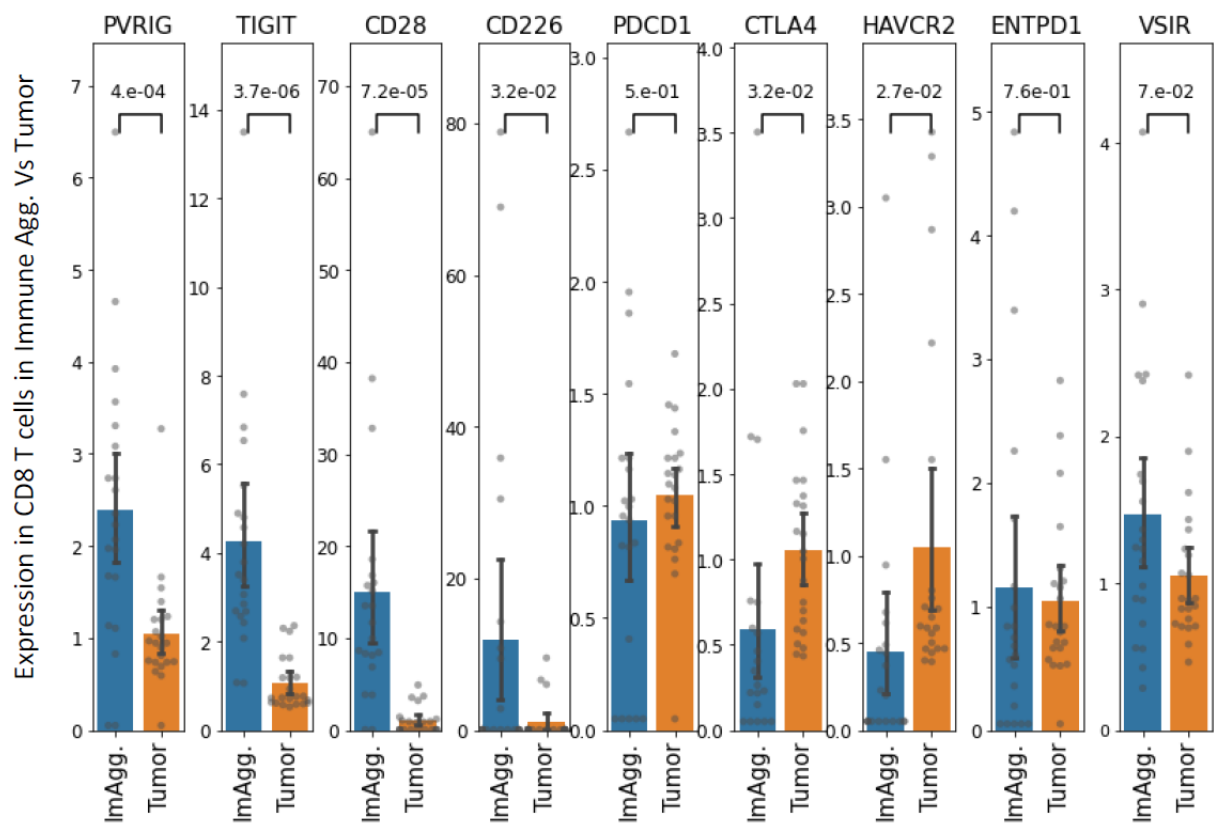
- Immune aggregate regions are the intra-tumoral niches in which local T cell activation occur
- Immune aggregate regions are predictive of response to immunotherapy

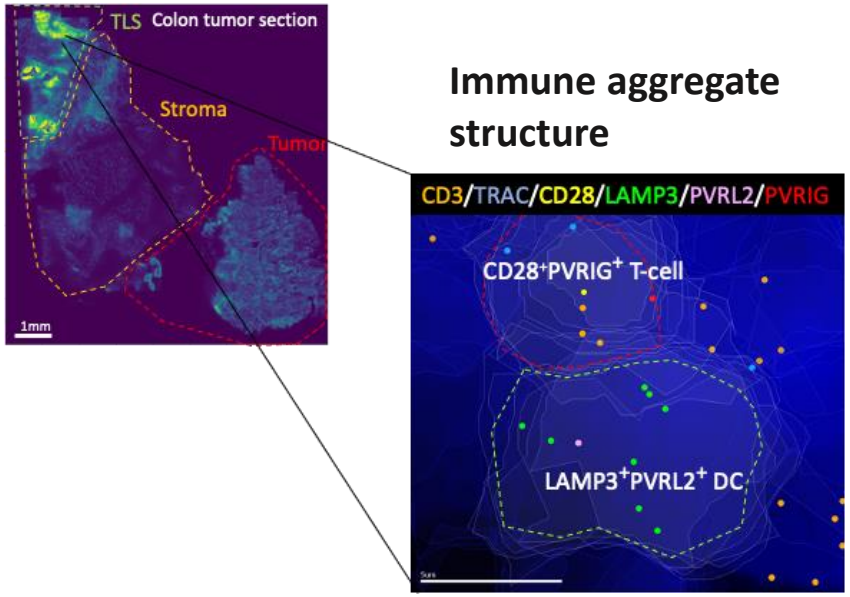


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PVRIG and other genes of the DNAM-1 axis are dominantly expressed in immune aggregate structures

In-situ MERFISH analysis of immune aggregate structure in tumor of CRC patients

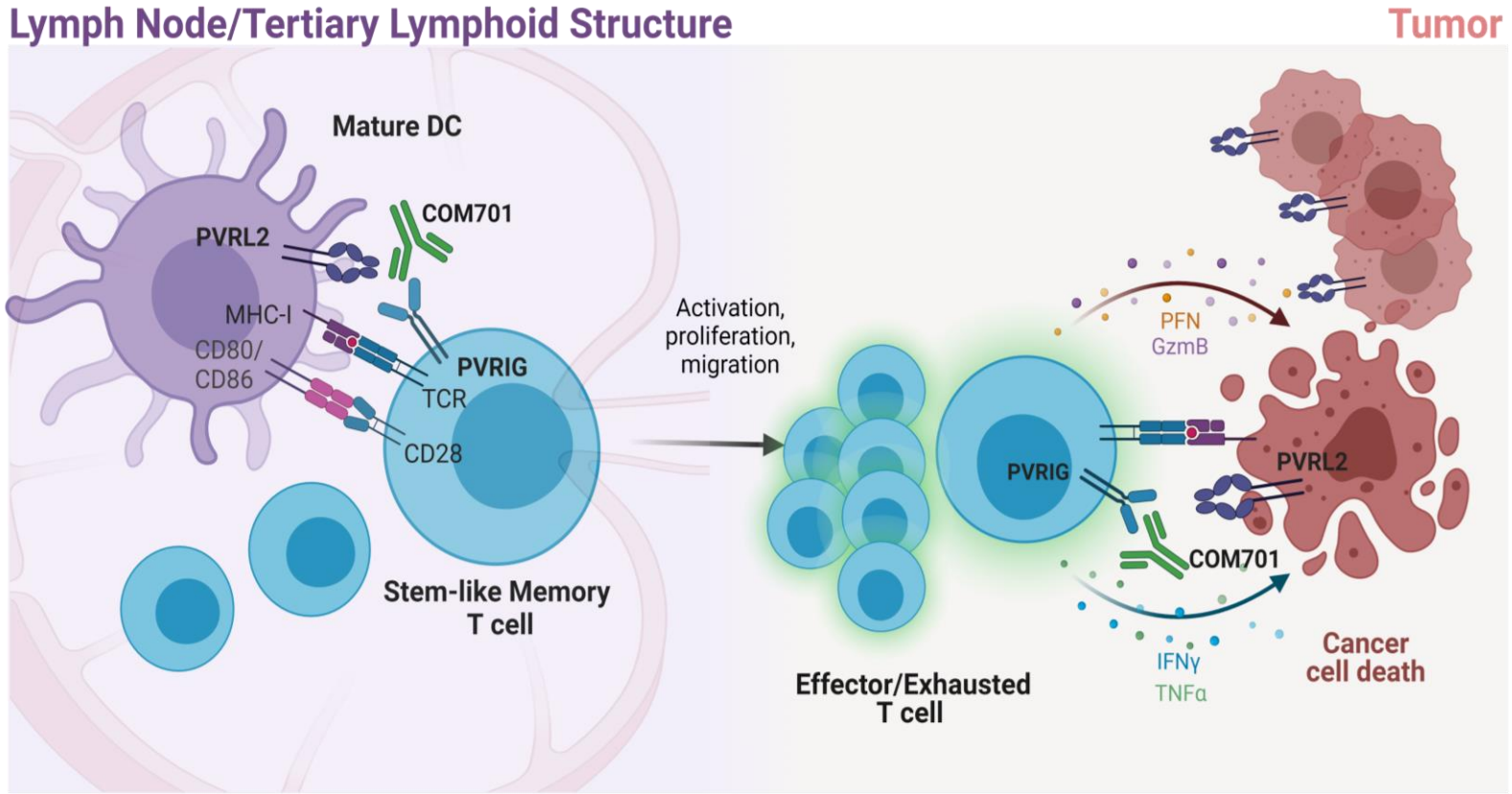




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Strong biological rationale for targeting PVRIG in cold tumors

PVRIG^{+} T_{SCM} interaction with PVRL2^{+} DCs hypothesis

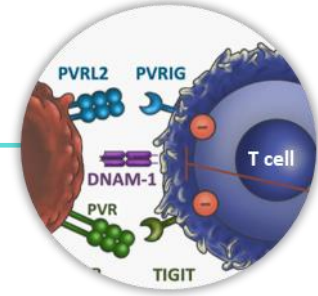


COM701, anti-PVRIG antibody may sensitize cold tumors to PD-1 and TIGIT

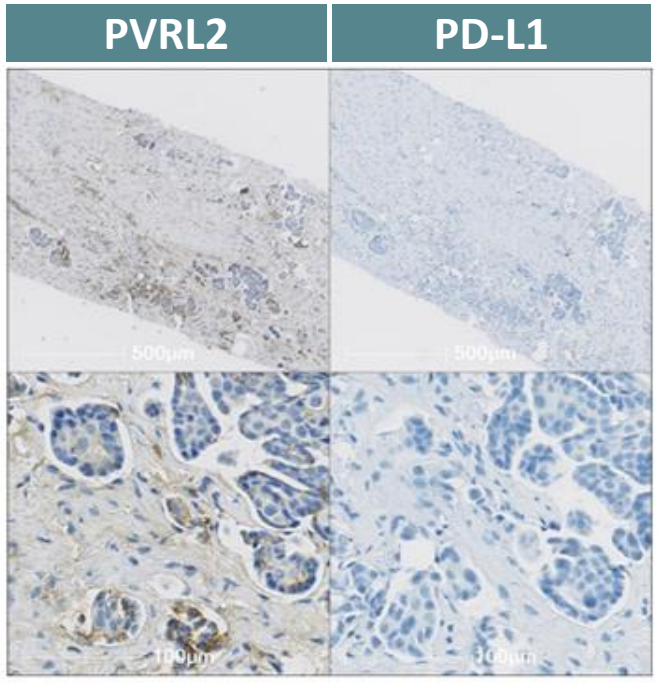
T_{SCM}: Early differentiated stem like memory T cells

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Confirmed PR in patient with primary peritoneal PD-L1^{neg} ovarian cancer treated with COM701 monotherapy

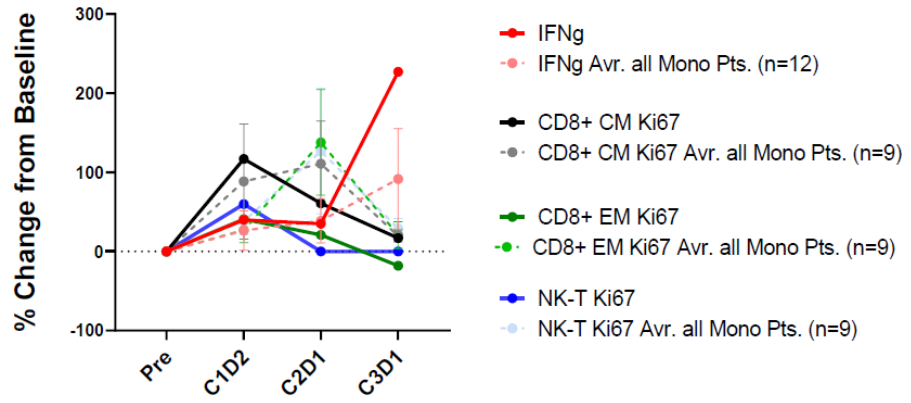


Patient received 3 prior lines of anti cancer therapy



- 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

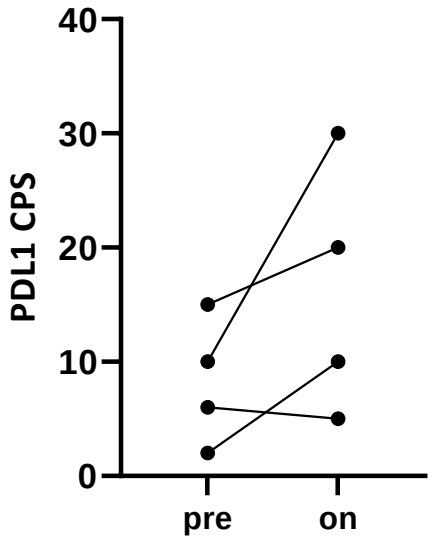
PR in patient with non-inflamed TME demonstrating immune activation in peripheral blood

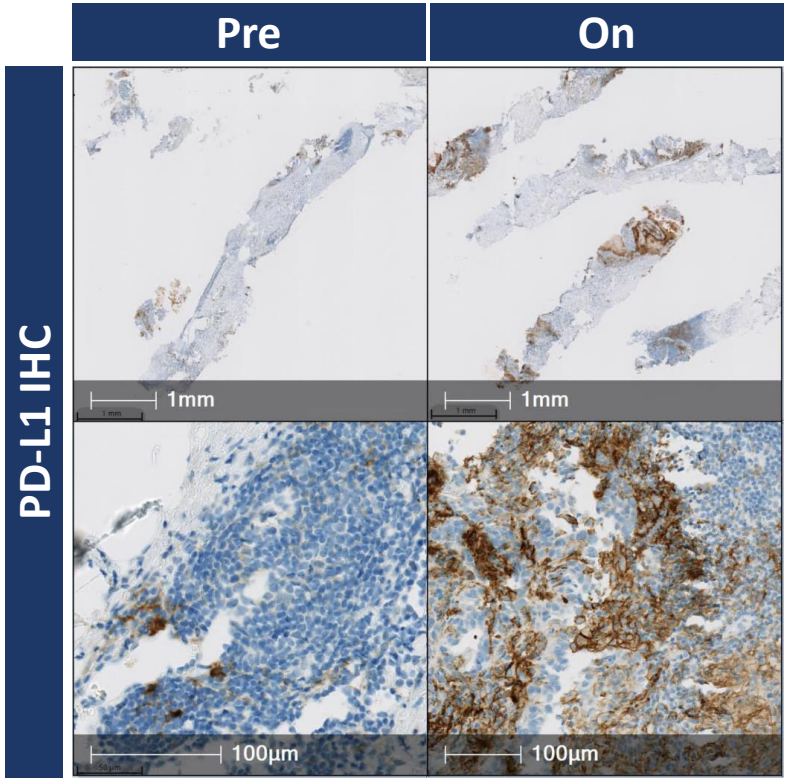
Ophir E et al SITC 2022

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COM701 monotherapy induces TME immune modulation in patients with ovarian cancer

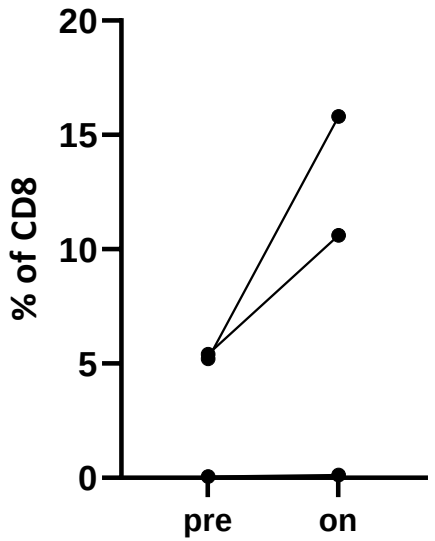
PD-L1 expression





Alteber et al, Oral presentation SITC 2022

CD8 expression (IF)

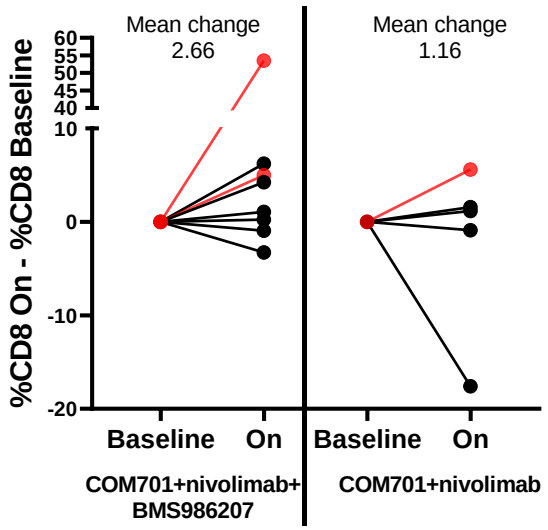


- 3 out of 4 patients showed an increase in CPS PD-L1
- 2 out of 3 patients showed an increase in % CD8
- PD-L1 upregulation and increased CD8 infiltration indicate on immune activation induced by COM701 monotherapy

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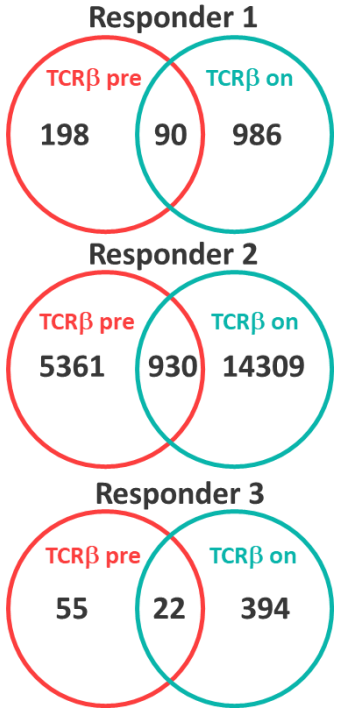
TME modulation is induced by PVRIG blockade by COM701+nivolumab±anti-TIGIT (BMS-986207) in PROC patients

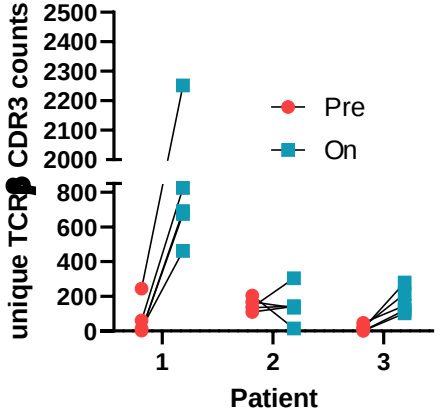
% of CD8 infiltration on treatment



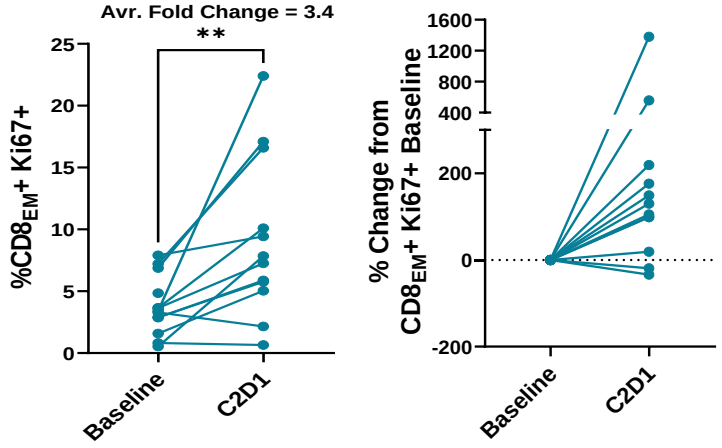
8/13 patients increased CD8 post treatment
Most prominent in patients with clinical benefit

TME T cell clonal expansion in patients with clinical benefit from COM701+ nivolumab± BMS-986207





Increase in peripheral CD8 T_{EM} cells in patients treated with COM701+nivolumab

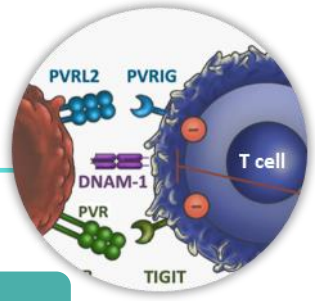


12 patients

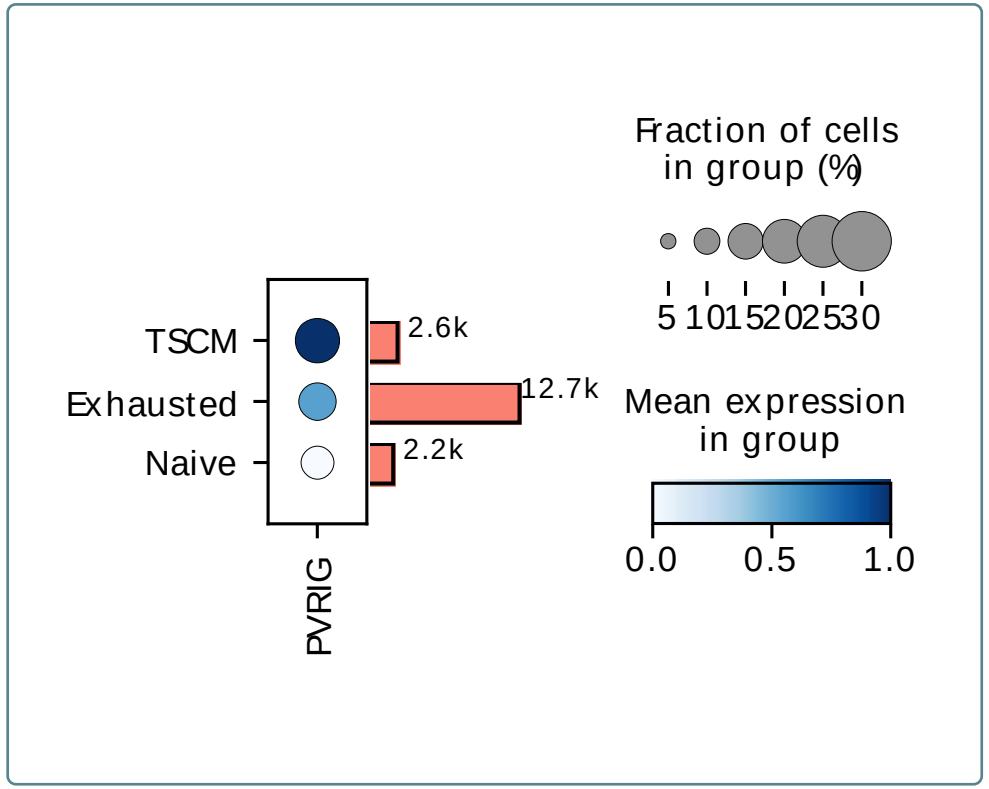
- Definition: Clinical Benefit (CB)= CR+PR+SD>180 days on study; No Clinical Benefit (NCB) = PD +SD<180 days on study

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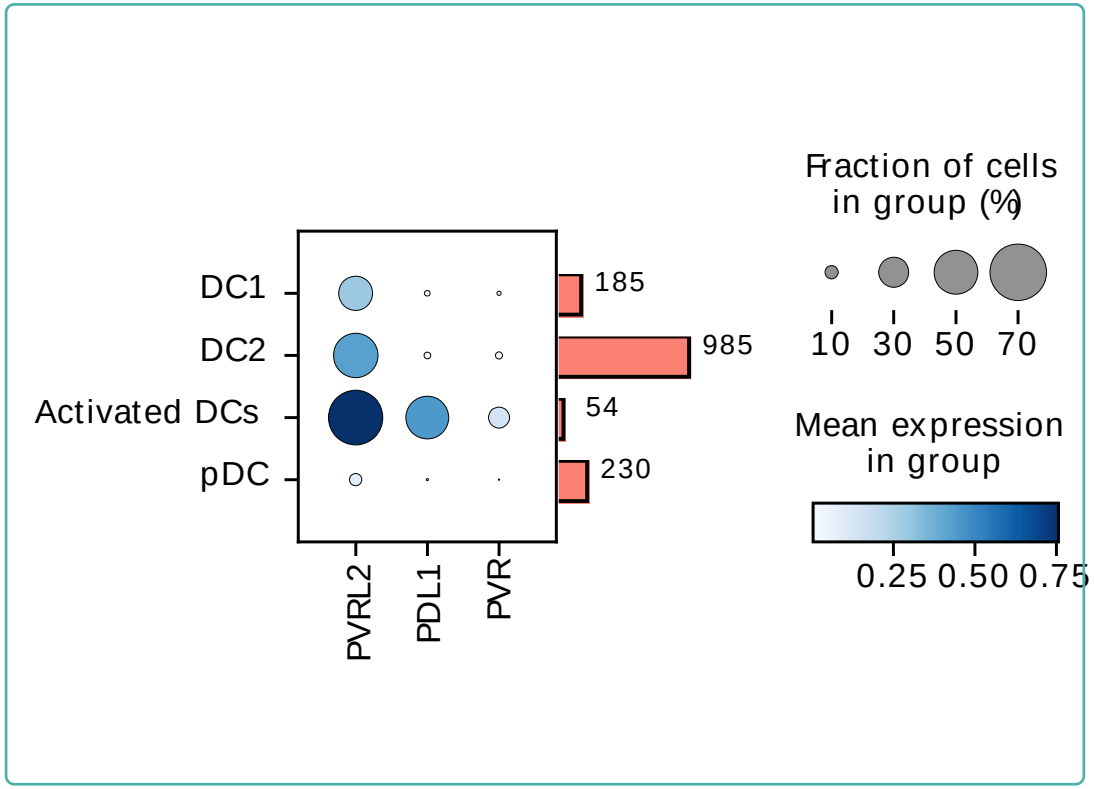
PVRIG is highly expressed on T_{SCM} and PVRL2 on DCs in liver metastases of patients with MSS CRC



High PVRIG on $CD8^+$ T_{SCM} cells



Dominant PVRL2 on DCs

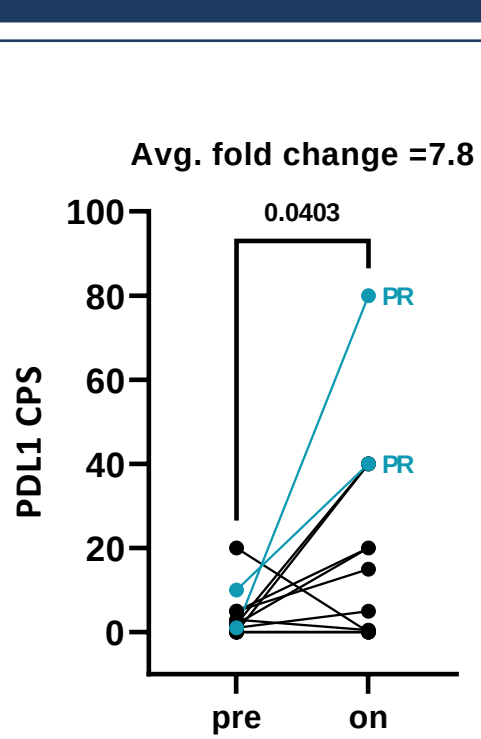


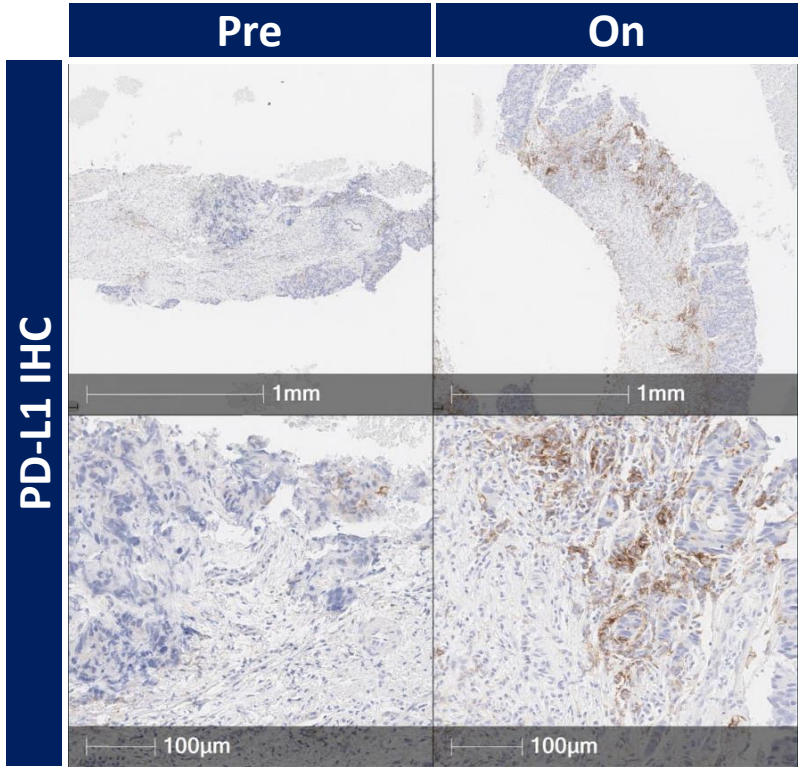
GSE173351, 6 MSS CRC patients (samples taken from liver metastases)

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COM701 + nivolumab combination induces TME immune modulation MSS CRC patients

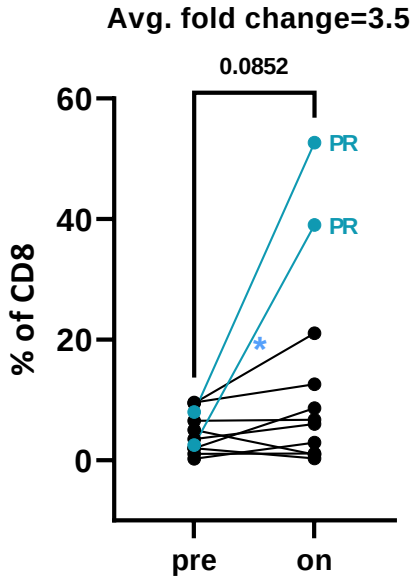
PD-L1 expression





PR = patient with partial response per RECIST

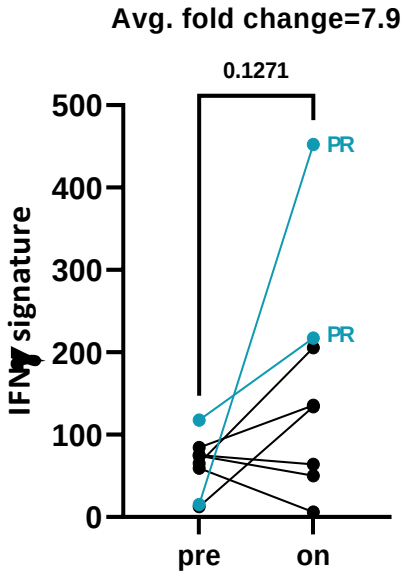
CD8 IHC



* % CD8 by IF

PR = patient with partial response per RECIST

IFNγ signature



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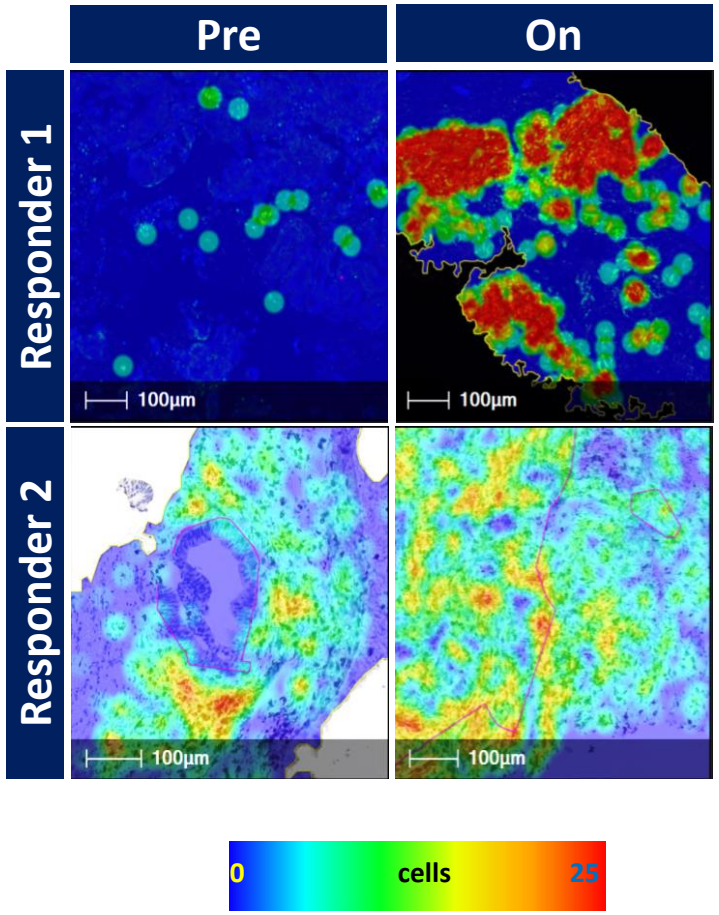
- 9/13 patients showed an increase in CPS PD-L1
- 7/11 patients showed an increase in % CD8
- 5/8 patients showed an increase in IFNγ signature

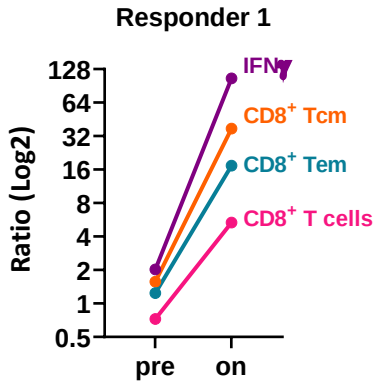
Alteber et al, Oral presentation SITC 2022

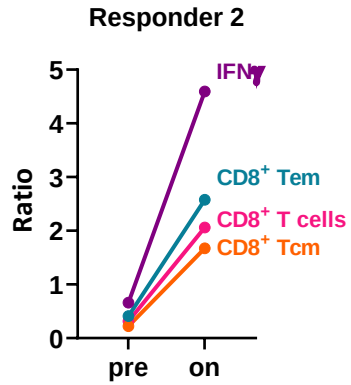
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Extensive TME modulation in MSS CRC patients partially responding to COM701 + nivolumab

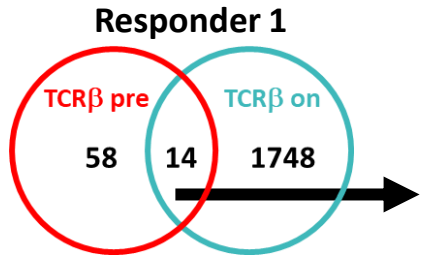
Increased CD8 infiltration and immune modulation

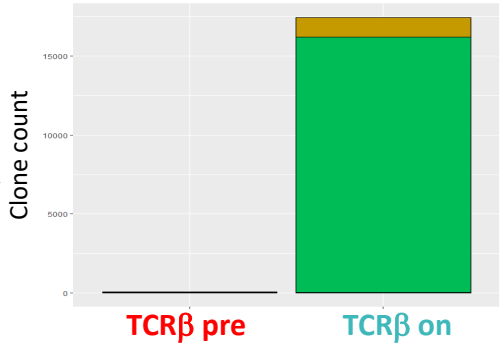




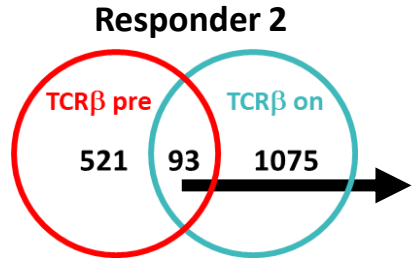


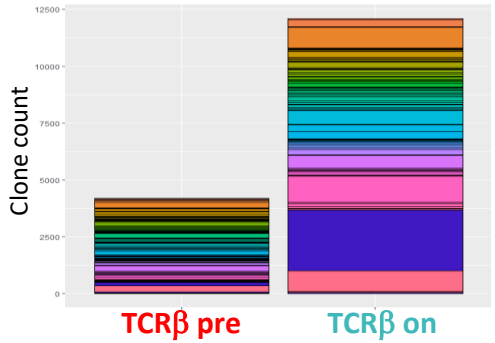
Increased TCR clonality and clonal expansion



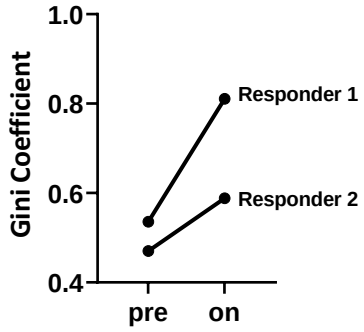


Most dominant clone on treatment pre-existed in the TME pre-treatment





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

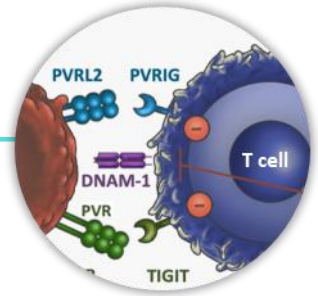


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COM701 + nivolumab induces infiltration of new clones as well as expansion of pre-existing clones in MSS CRC responding patients

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Summary



- PVRIG has a unique dominant expression on T_{SCM}, its ligand, PVRL2, is expressed also on DCs
- Spatial transcriptomic analysis showed that T_{SCM} and DCs preferentially localize to immune aggregates while exhausted T cells localize to the tumor
    - PVRIG is dominantly expressed on $CD8^+$ T cells in immune aggregate niches
- PVRIG blockade may enhance T_{SCM} activation by DCs in lymph-nodes and immune aggregate niches, a potential mechanism which could lead to increased T cell expansion and infiltration also into less 'inflamed' 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 (PROC and MSS CRC) treated with COM701 as mono or in combination with anti- PD-1 and TIGIT, showed increased immune modulation associated with clinical benefit
- PVRIG blockade has the potential to show efficacy in patients with low-infiltrated tumors

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Thank you!

Investigators, clinical trial sites
and
Patients and their families

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Acknowledgments:

Compugen:

Gady Cojocaru, Roy Z. Granit, Inbal Barbiro, Assaf Wool, Masha Frenkel, Amit Novik, Adi Shuchami, Yu Liang, Vered Daniel Carmi, Rob Foreman, Natalia Petrenko, Jiang He, Henry Adewoye, Pierre Ferre, Zurit Levine, Eran Ophir

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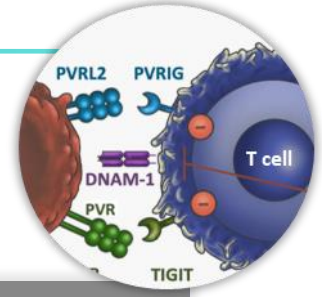
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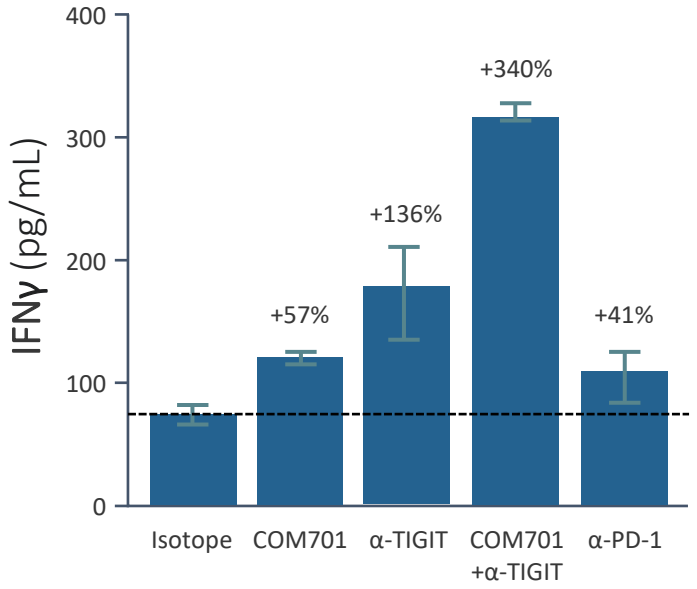
Gynecologic Oncology Division, Helen Schneider Hospital for Women, Rabin Medical Center:
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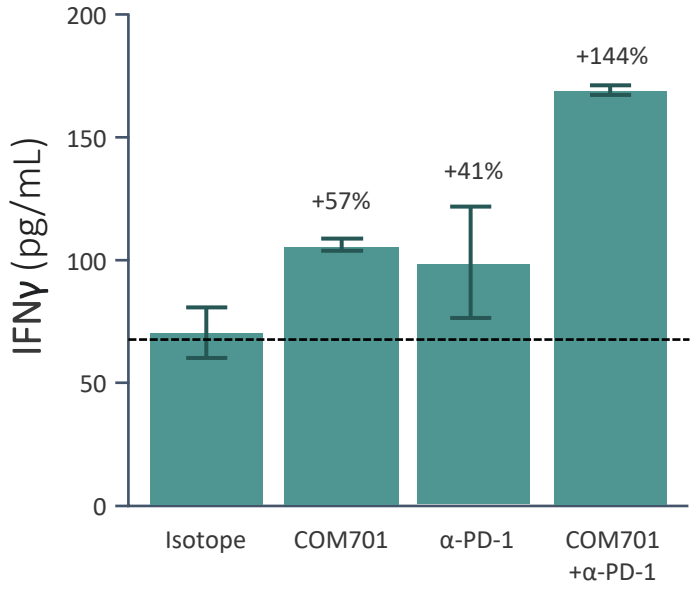
Synergistic T Cell activation with PVRIG, PD-1 and TIGIT blockade



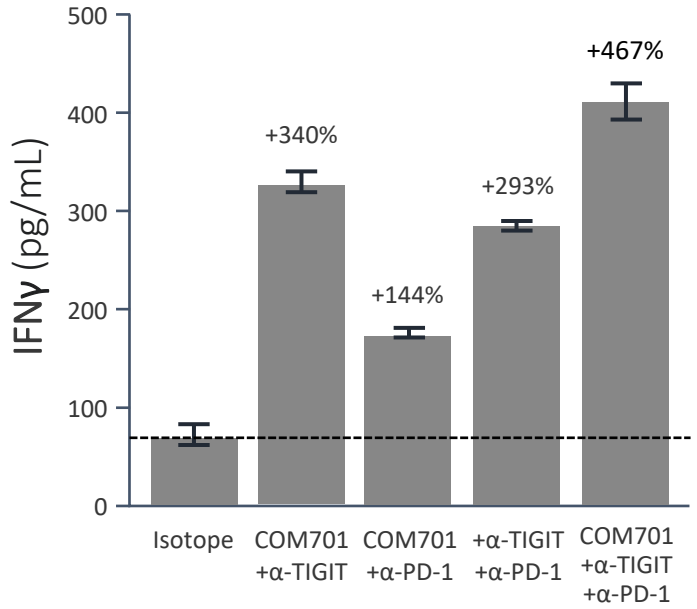
COM701 +/- anti-TIGIT



COM701 +/- anti-PD-1



Triple combination



COM701 – aPVRIG

Whelan, et al., Cancer Immunol Res. 2019

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COM701 shows clinical activity in PROC cancer

Strong preliminary (and ongoing) signal in an indication with high unmet need and typically immunologically unresponsive

SOC 2L+	ORR %	mPFS (months)	mOS (months)
Single agent chemo	~8-12	~3-4	~13

Historical	ORR	PFS
PD(L)1 blockers/ Pembro + Vibostolimab (aTIGIT)*	<10%	2.1m

* Keyvibe-001; **0% ORR in PDL1 CPS<1**

	COM701 Mono'*	COM701 + nivolumab	COM701 + BMS986207 + nivolumab
ORR	1 (16.6%)	2 (10%)	4 (20%)
PR	2 (34%)	2** (10%)	4 (20%)
SD	3 (50%)	7 (35 %)	5 (25%)
DCR	4 (66%)	9 (45 %)	9 (45%)

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