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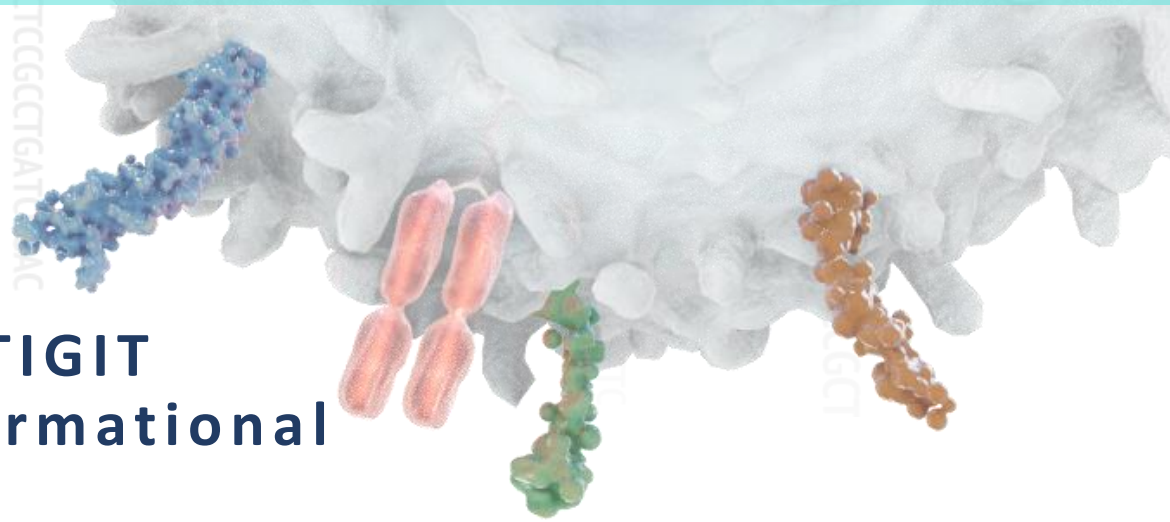

Unlocking the potential of PVRIG & TIGIT pathways to deliver the next transformational cancer immunotherapy drugs

TIGIT Axis Therapies Summit

Eran Ophir, SVP Research & Drug Discovery

December, 2022

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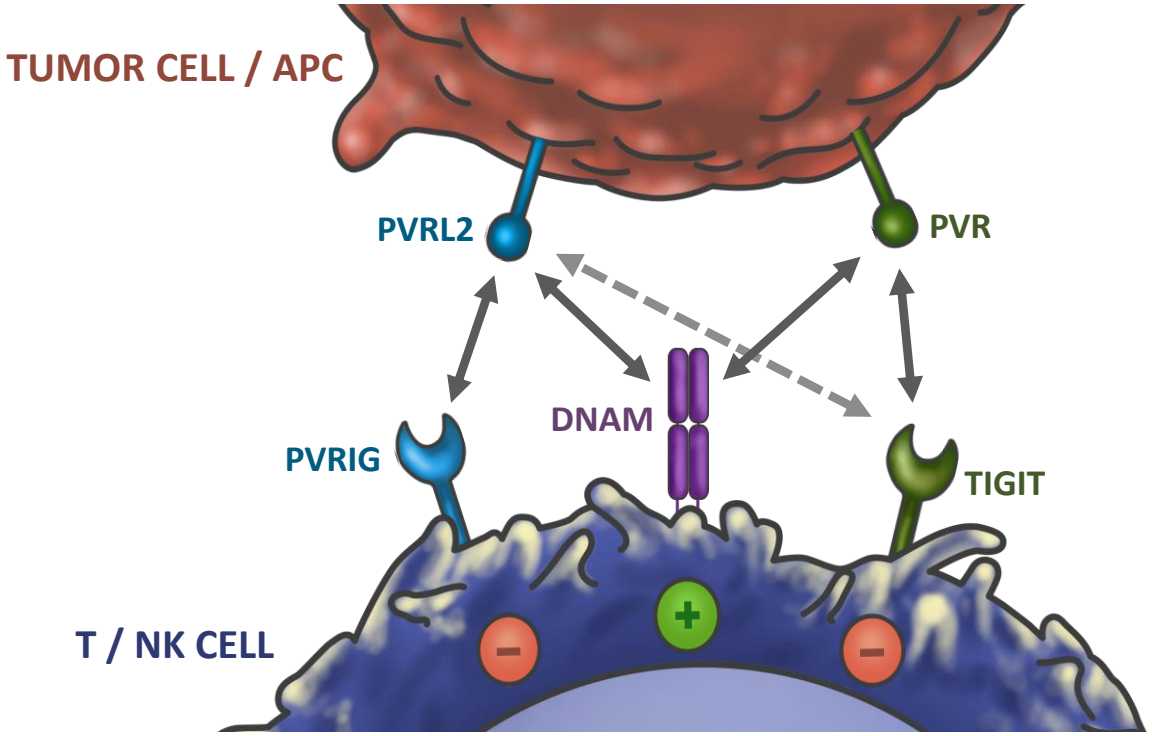
This presentation contains “forward-looking statements” within the meaning of the the Securities Act of 1933 and the Securities Exchange Act of 1934, as amended, and the safe-harbor provisions of the Private Securities Litigation Reform Act of 1995. Forward-looking statements can be identified by the 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.

DNAM-1 axis plays essential role in tumor immunology



- PVRIG binds PVRL2 as a functional ligand and TIGIT binds PVR
- 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)

Modified from Alteber et al. Cancer Discov. 2021

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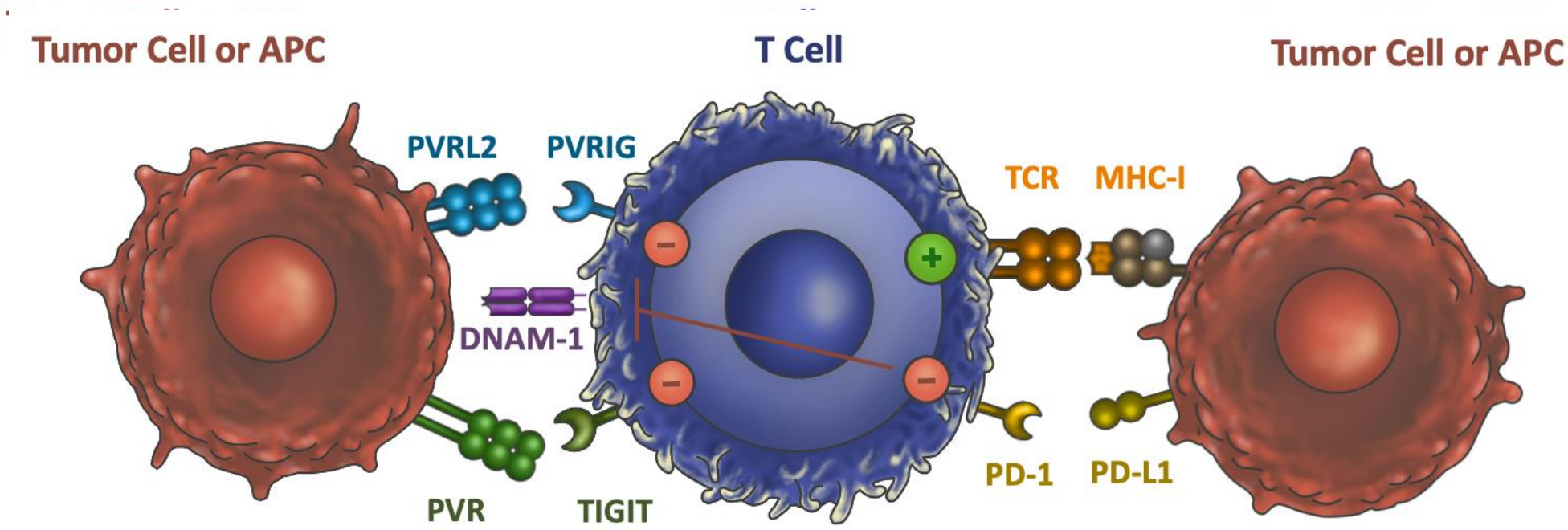
PVRIG, TIGIT and PD-1 are players in the DNAM-1 axis



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

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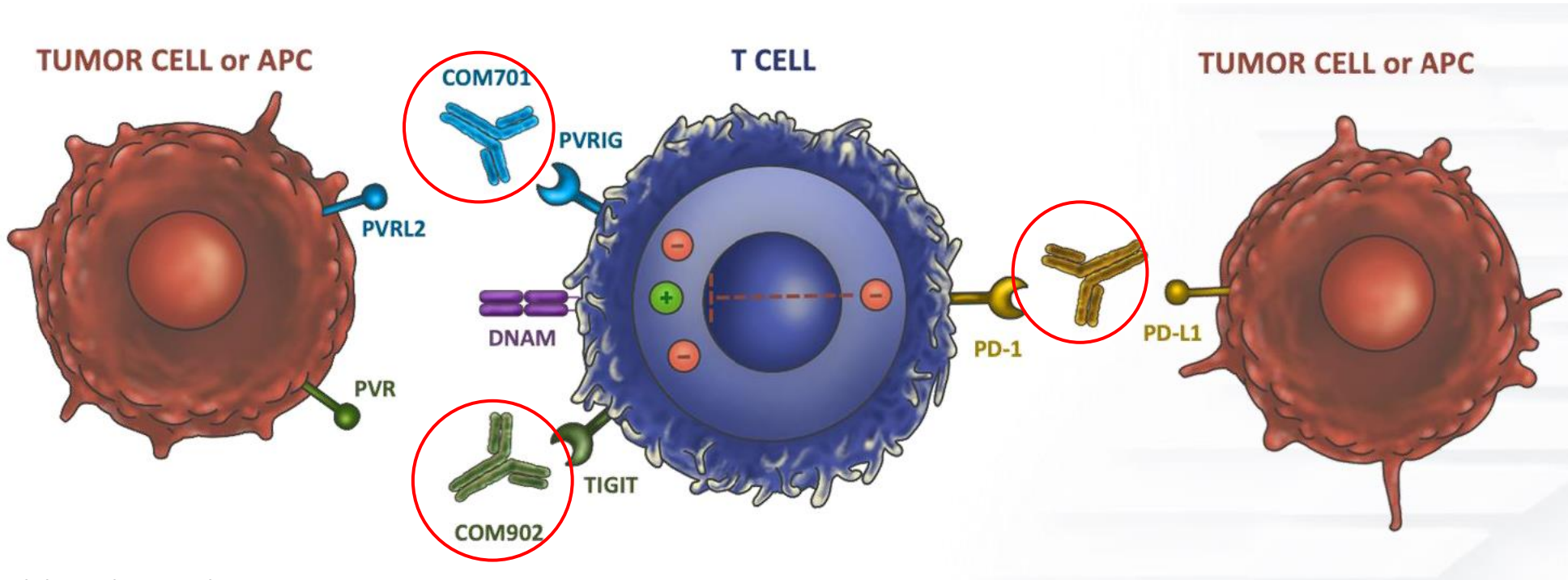
Potential intersection between PVRIG/TIGIT/PD-1 pathways support combination approach to overcome immunotherapy resistance



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

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

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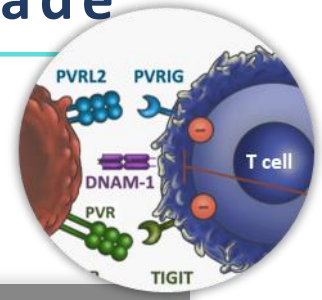
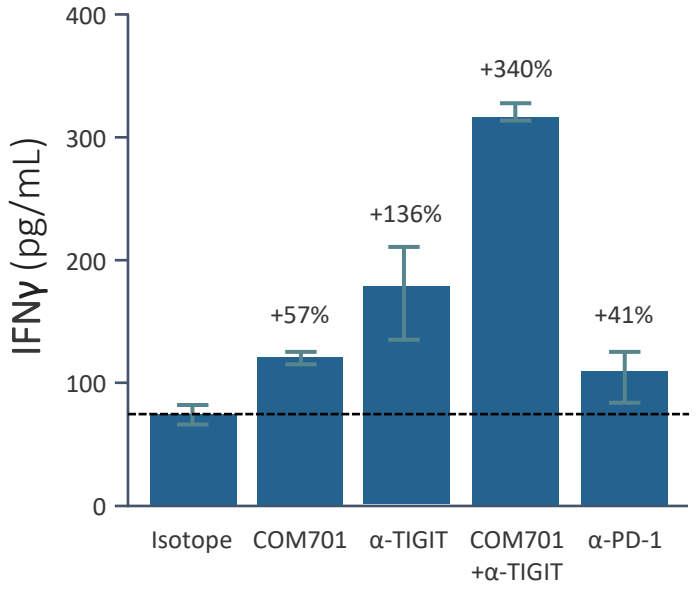
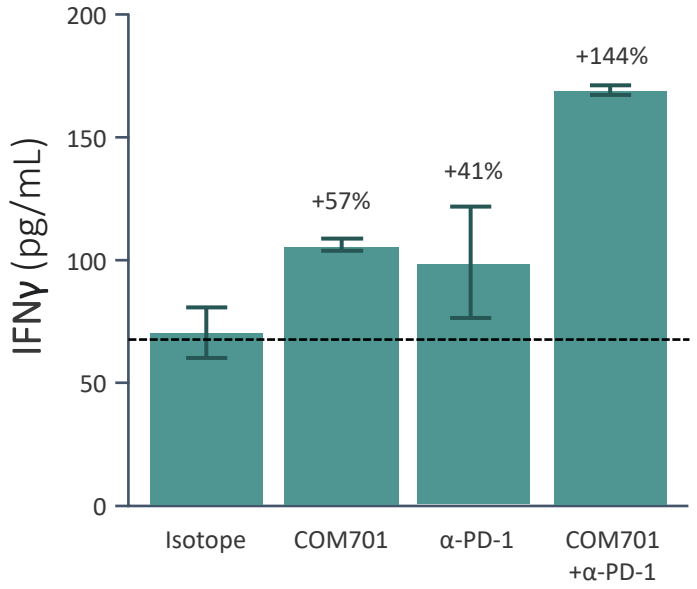
Synergistic T Cell activation with PVRIG, PD-1 and TIGIT blockade



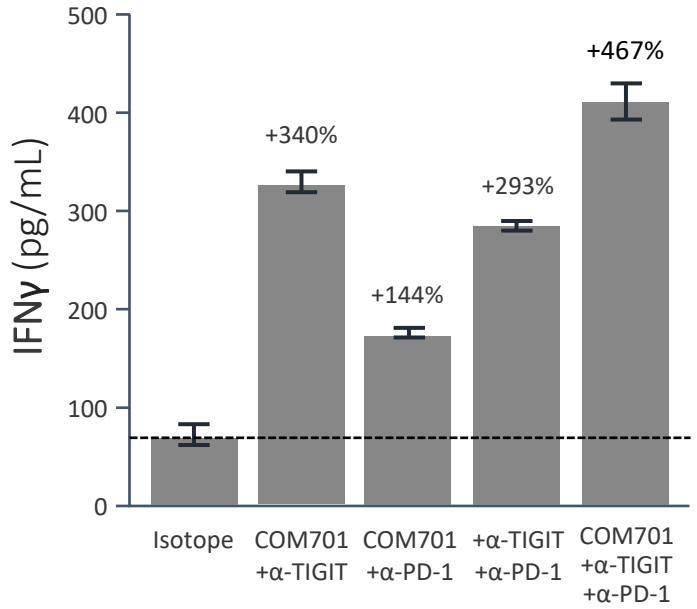
COM701 +/- anti-TIGIT



COM701 +/- anti-PD-1



Triple combination



COM701 – aPVRIG

Whelan, et al., Cancer Immunol Res. 2019

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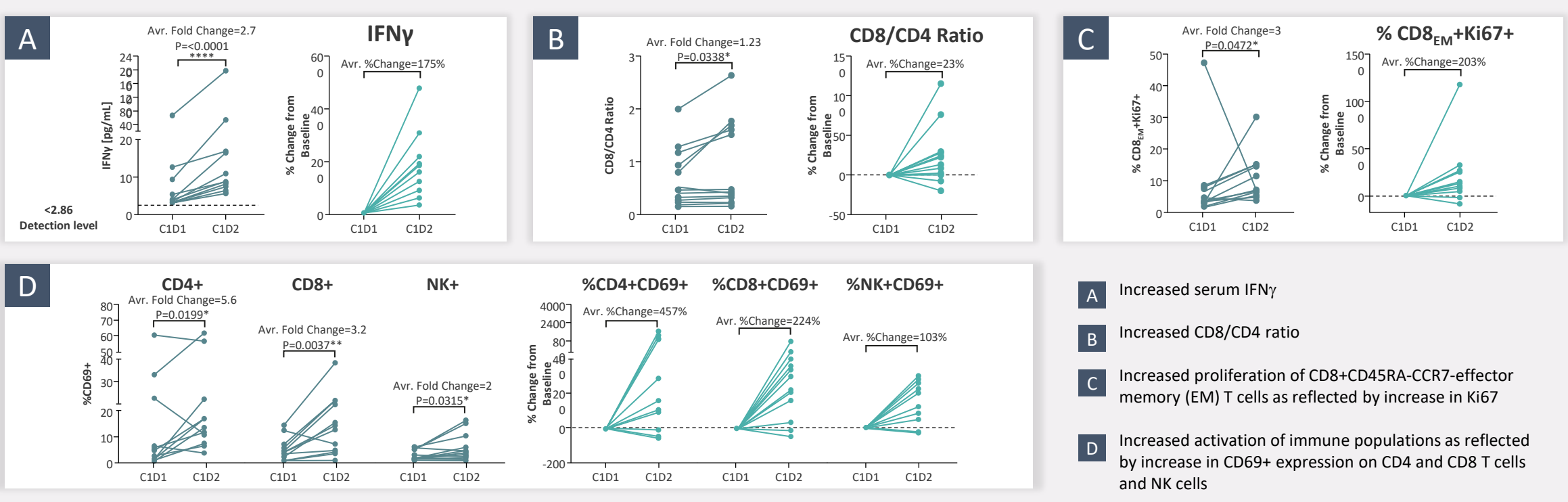
Potent activation of the immune system with COM701, nivolumab and BMS-986207 (anti-TIGIT) triple blockade in patients with advanced cancer

Increased T and NK cell activation, memory T Cell proliferation and IFNγ induction in blood at all COM701 doses



A Increased serum IFNγ

B Increased CD8/CD4 ratio

C Increased proliferation of CD8+CD45RA-CCR7-effector memory (EM) T cells as reflected by increase in Ki67

D Increased activation of immune populations as reflected by increase in CD69+ expression on CD4 and CD8 T cells and NK cells

Dumbrava et al, SITC November 2021 Poster Presentation, modified

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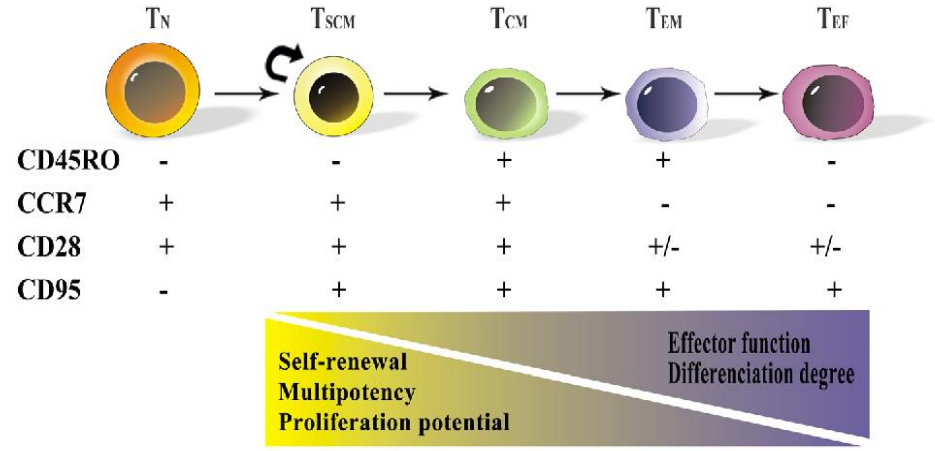
Early differentiated T stem-like cells are potent inducers of anti-tumor activity following adoptive T cell transfer



Xu et al., 2015, J. of Hem and Onc.

Central memory self/tumor-reactive CD8$^+$ T cells confer superior antitumor immunity compared with effector memory T cells

Christopher A. Klebanoff*†‡, Luca Gattinoni†‡, Parizad Torabi-Parizi*§, Keith Kerstann†, Adela R. Cardones¶, Steven E. Finkelstein†, Douglas C. Palmer†, Paul A. Antony†, Sam T. Hwang¶, Steven A. Rosenberg†, Thomas A. Waldmann‖, and Nicholas P. Restifo†**

Klebbanoff et al., 2005, PNAS.

Wnt signaling arrests effector T cell differentiation and generates CD8$^+$ memory stem cells

Luca Gattinoni[1,2], Xiao-Song Zhong[1,2], Douglas C Palmer[1], Yun Ji[1], Christian S Hinrichs[1], Zhiya Yu[1], Claudia Wrzesinski[1], Andrea Boni[1], Lydie Cassard[1], Lindsay M Garvin[1], Chrystal M Paulos[1], Pawel Muranski[1] & Nicholas P Restifo[1]

Gatiinoni et al., 2009, Nat Med

Stem-like CD8 T cells mediate response of adoptive cell immunotherapy against human cancer

Sri Krishna[1]*, Frank J. Lowery[1]*, Amy R. Copeland[1], Erol Bahadiroglu[2], Ratnadeep Mukherjee[2], Li Jia[3], James T. Anibal[2], Abraham Sachs[1], Serifat O. Adebola[2], Devikala Gurusamy[1], Zhiya Yu[1], Victoria Hill[1], Jared J. Gartner[1], Yong F. Li[1], Maria Parkhurst[1], Biman Paria[1], Pia Kvistborg[4], Michael C. Kelly[5], Stephanie L. Goff[1], Grégoire Altan-Bonnet[2], Paul F. Robbins[1]†, Steven A. Rosenberg[1]†

Krishna et al., 2020, Science

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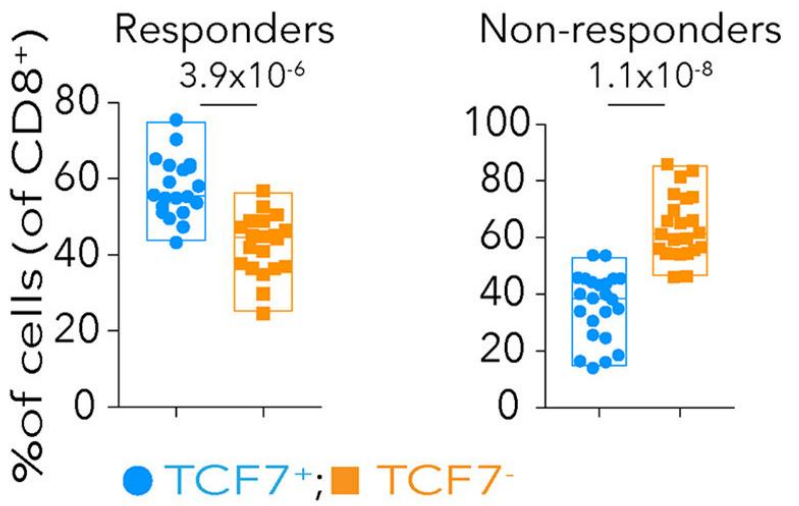
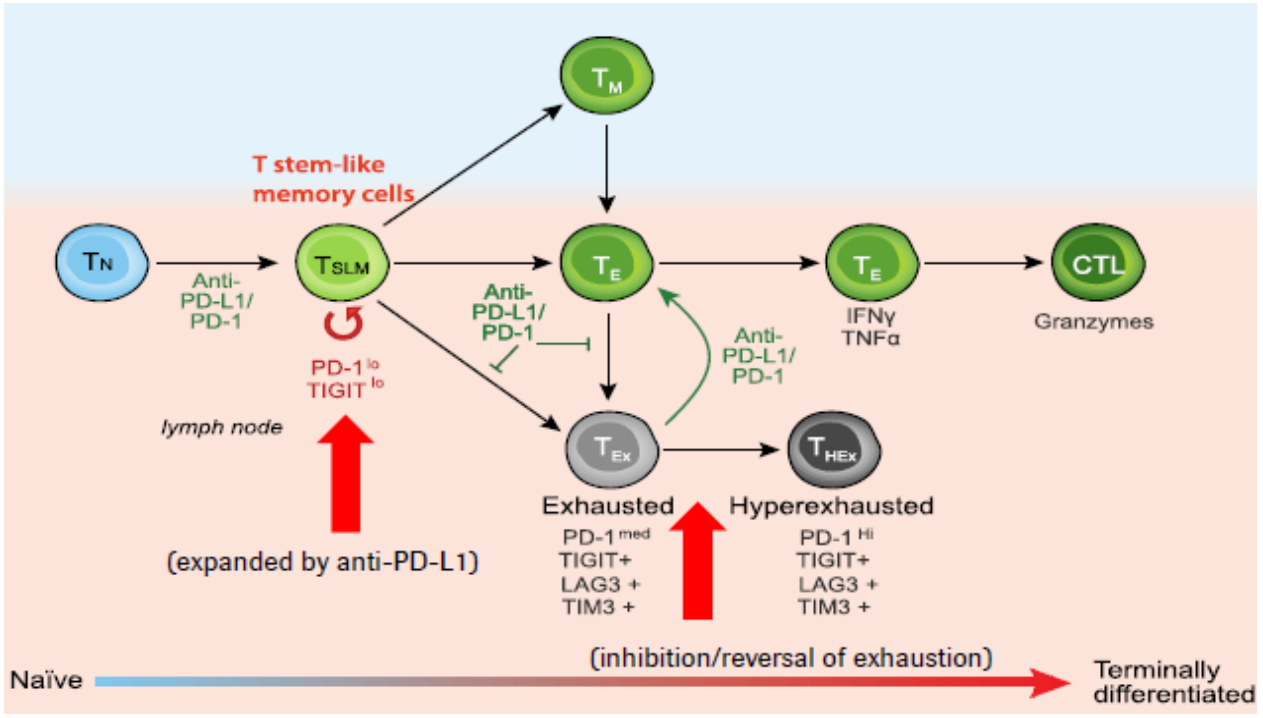
Growing evidence of early differentiated T stem-like memory cells (Tscm) importance in response to checkpoint blockade

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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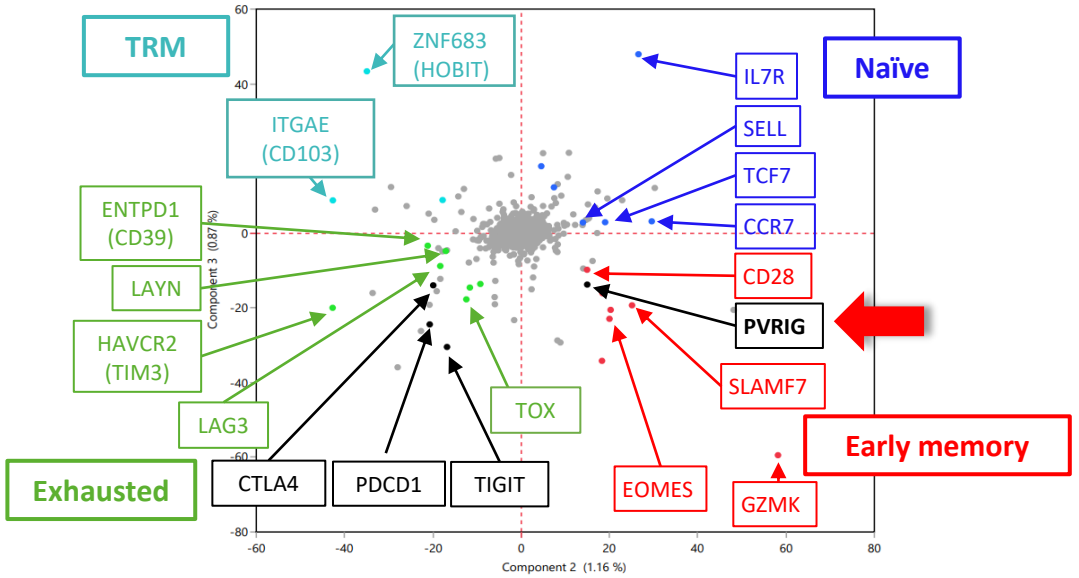
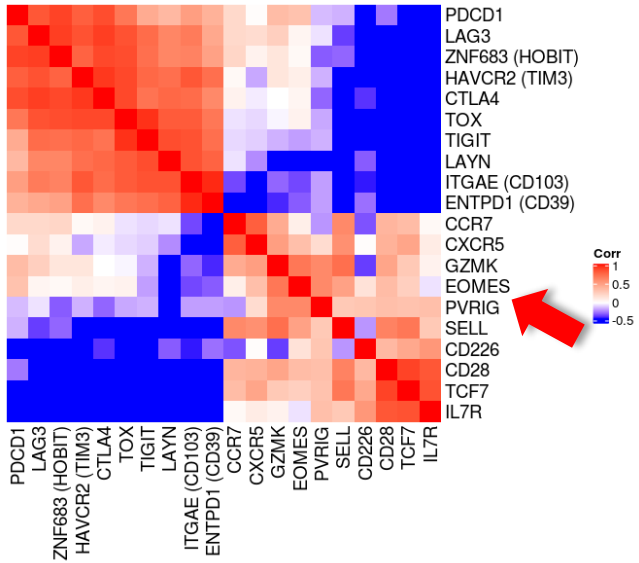
PVRIG uniquely clusters with early differentiated/Tscm genes

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



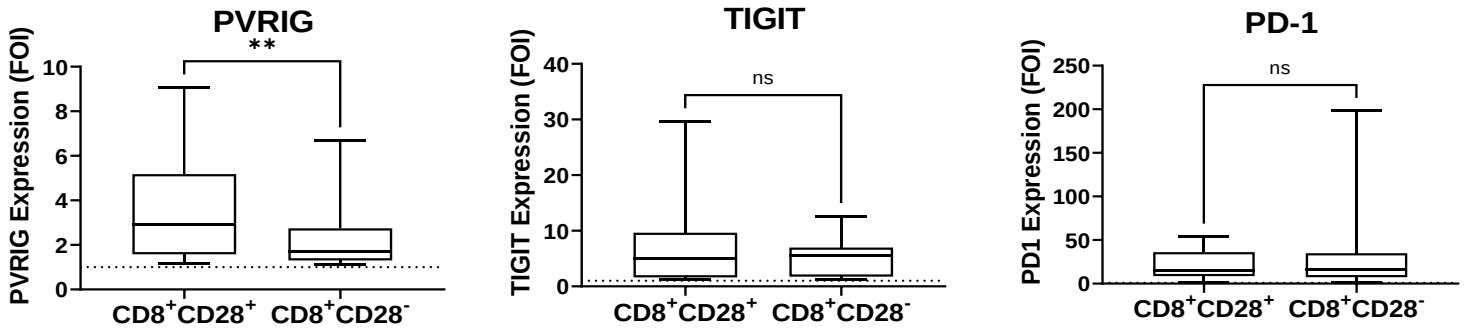
GSE99254_NSCLC Dataset internally analyzed

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)

Alteber et al, Oral presentation SITC 2022

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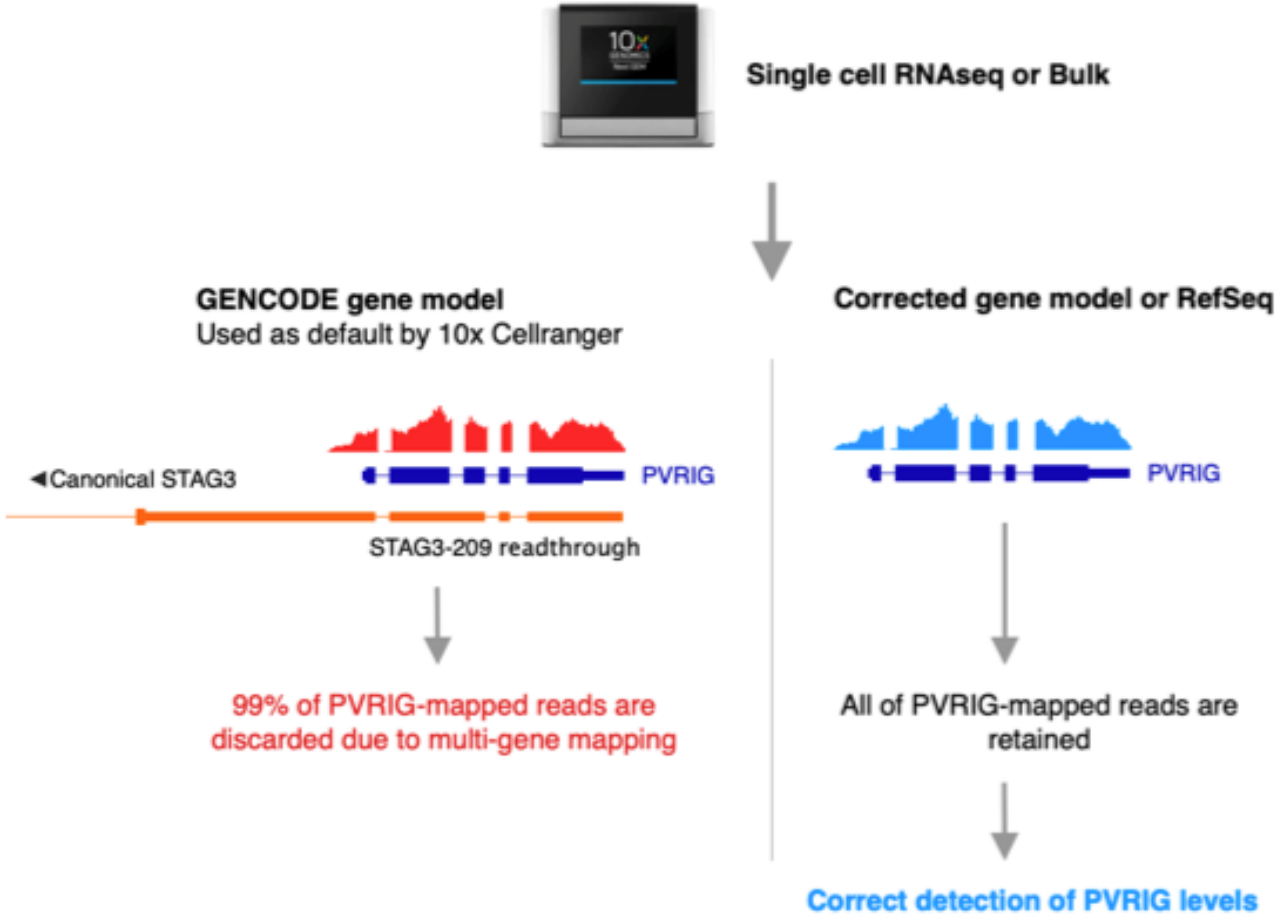
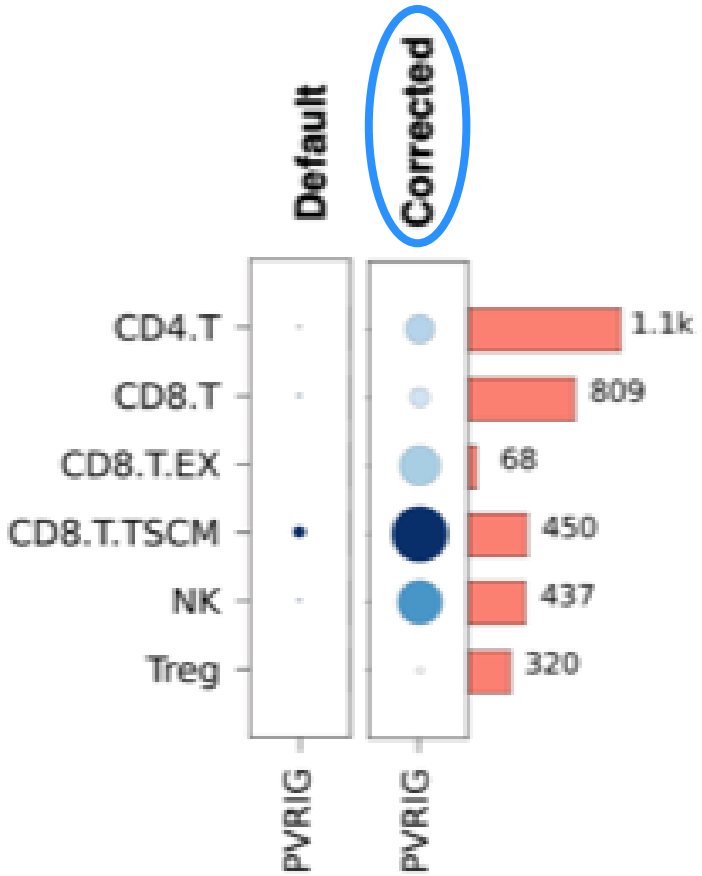
Gene model correction for PVRIG in single cell data enables accurate detection of its functional relevance





https://www.biorxiv.org/content/10.1101/2022.11.02.514879v1

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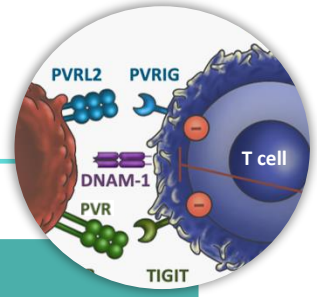
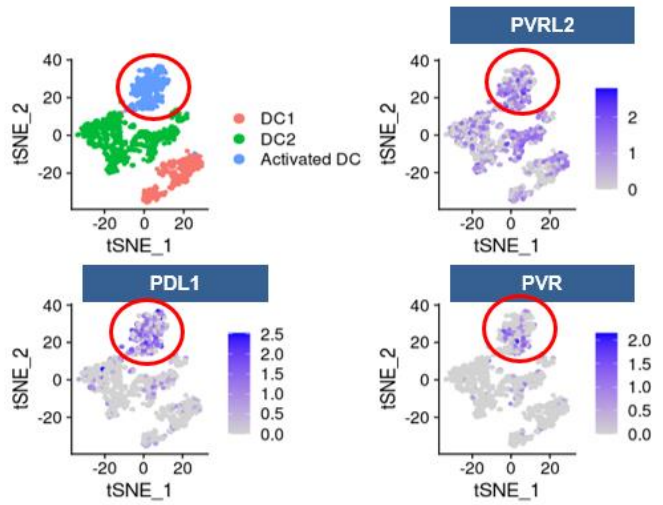
PVRL2 has a dominant expression on dendritic cells

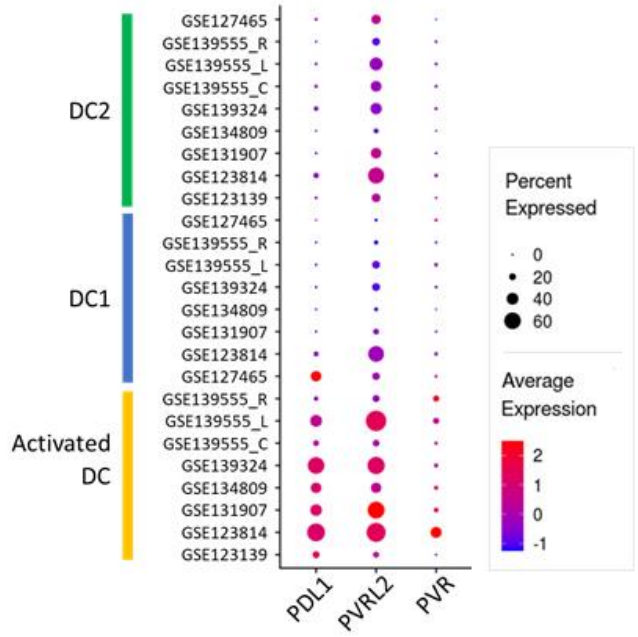


DC Population in SCC/BCC

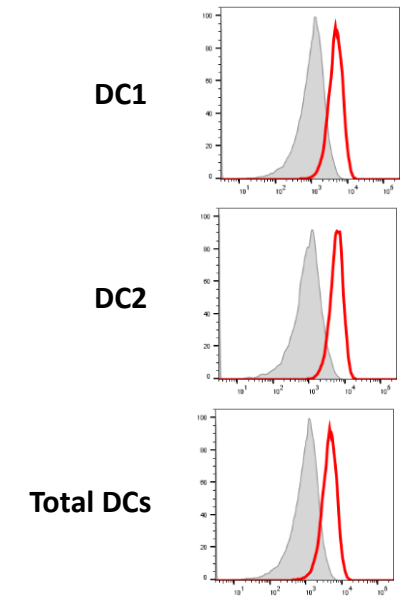


GSE123814 Dataset internally analyzed

Multiple scRNA cancer datasets



Ovarian cancer



Internal FLOW cytometry Data

Alteber et al , Poster presentation SITC 2021

PVRIG blockade may enhance Tscm-DC interaction and induce potent Tscm activation

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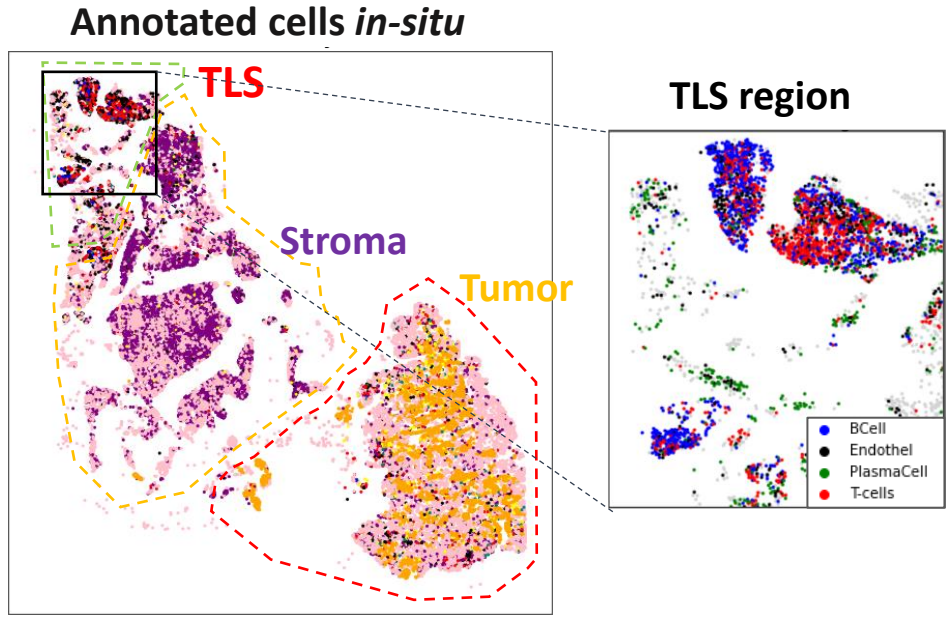
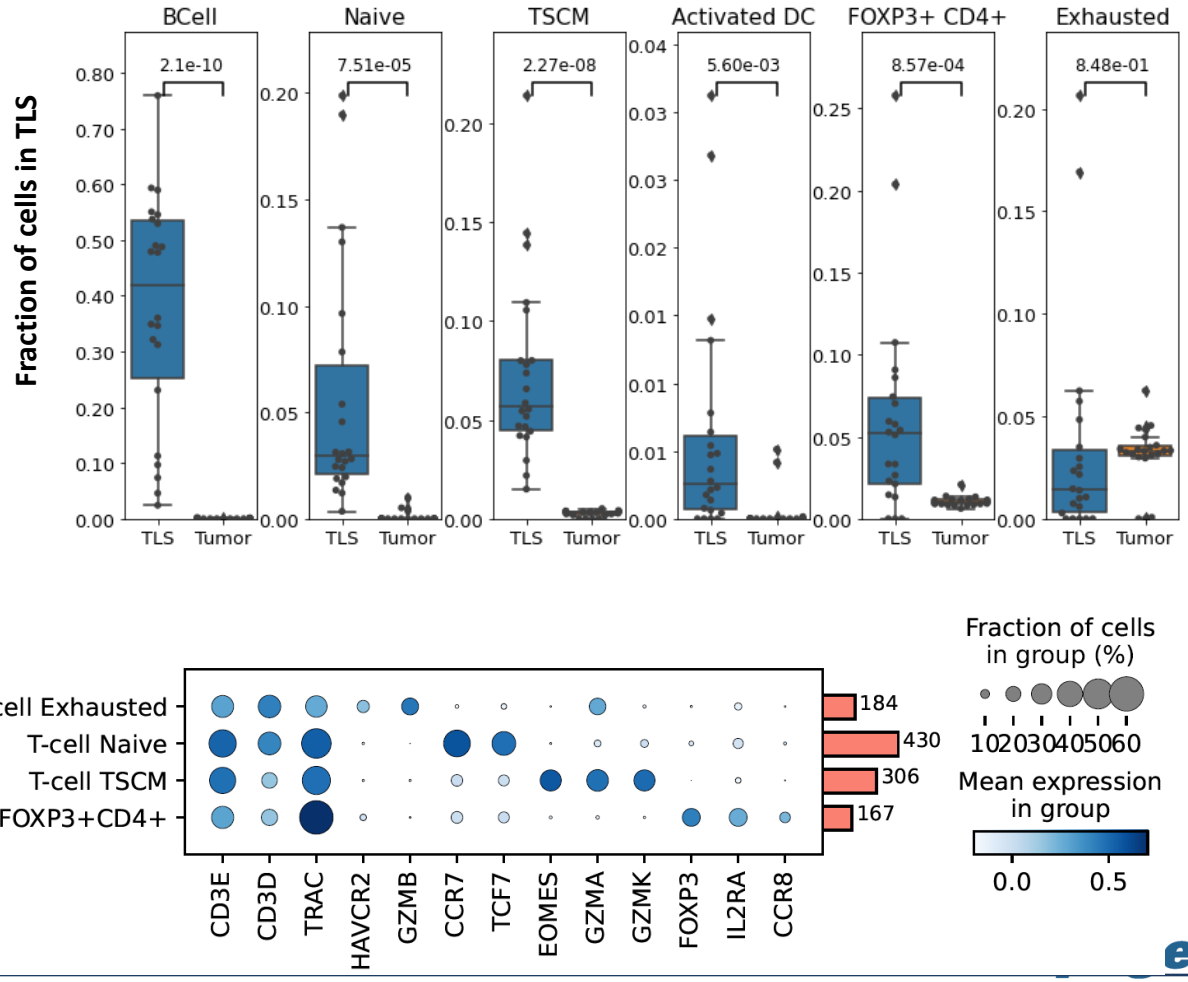
Spatial transcriptomic analysis of TLS regions shows enrichment of Tscm and DCs while exhausted cells localize to the tumor

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

Alteber et al, Oral presentation SITC 2022

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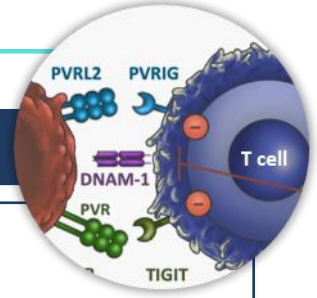
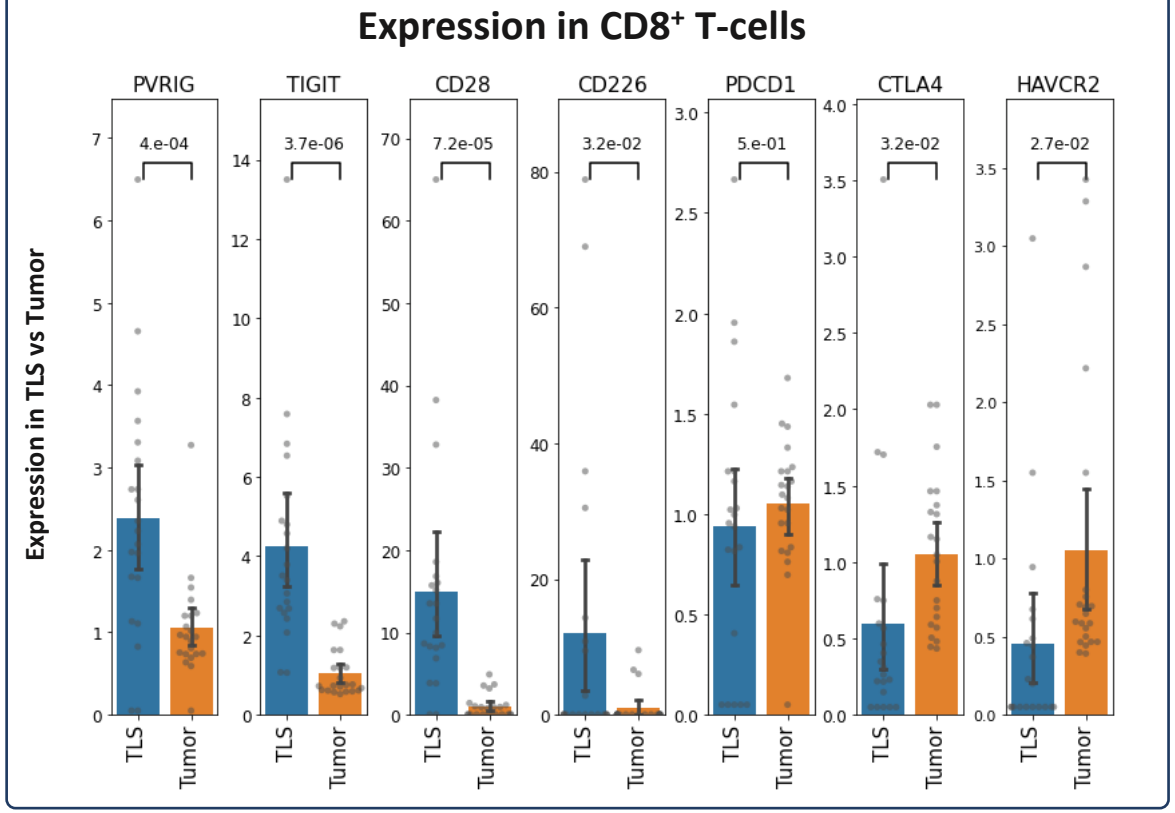
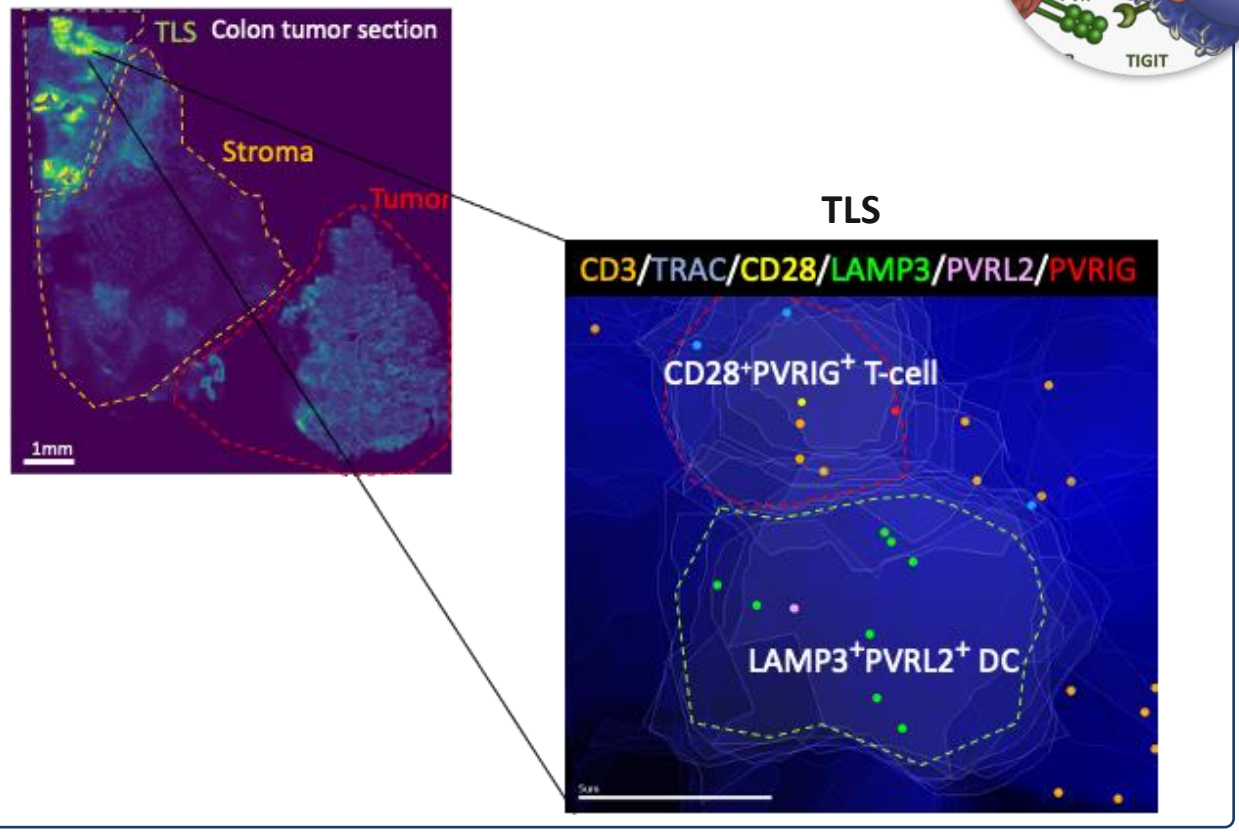
PVRIG and other genes of the DNAM-1 axis are dominantly expressed in TLS region



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





Alteber et al, Oral presentation SITC 2022

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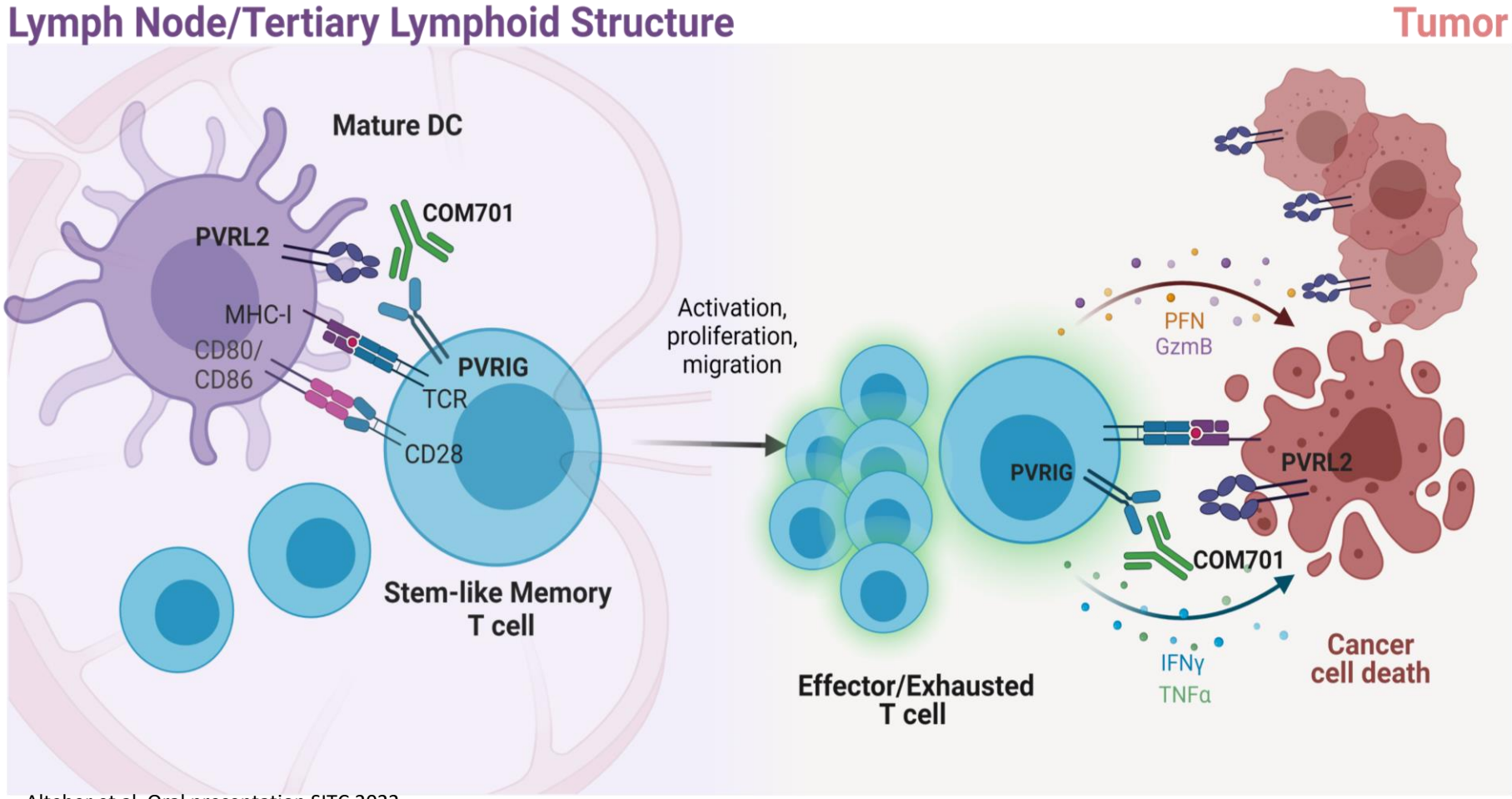
COM701 may turn less inflamed tumors into hot tumors



Alteber et al, Oral presentation SITC 2022

COM701 might play a dominant role controlling T cells expansion

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COM701 shows clinical activity in platinum resistant ovarian cancer

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

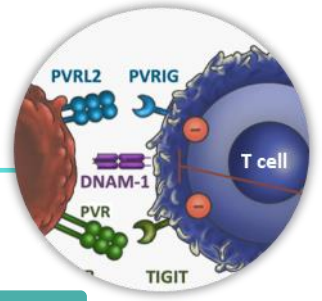
SOC 2L+	ORR %	mPFS (months)	mOS (months)
Single agent chemo	~8-12	~3-4	~13

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

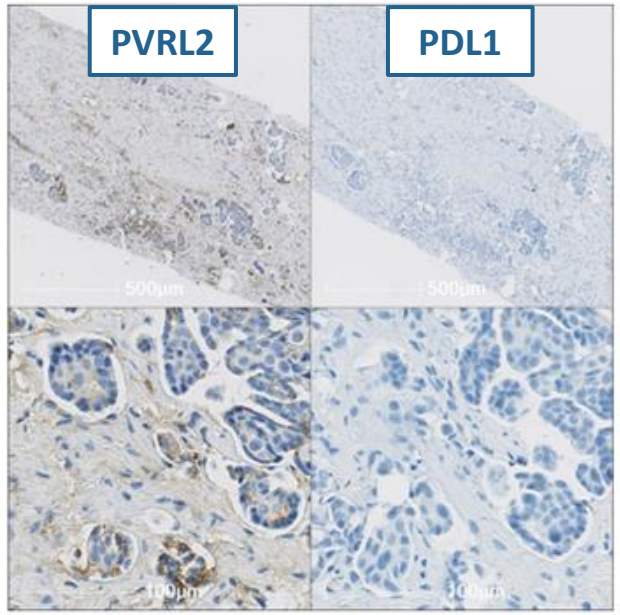
* Keyvibe-001; **0% ORR in PDL1 CPS<1**

	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%)

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



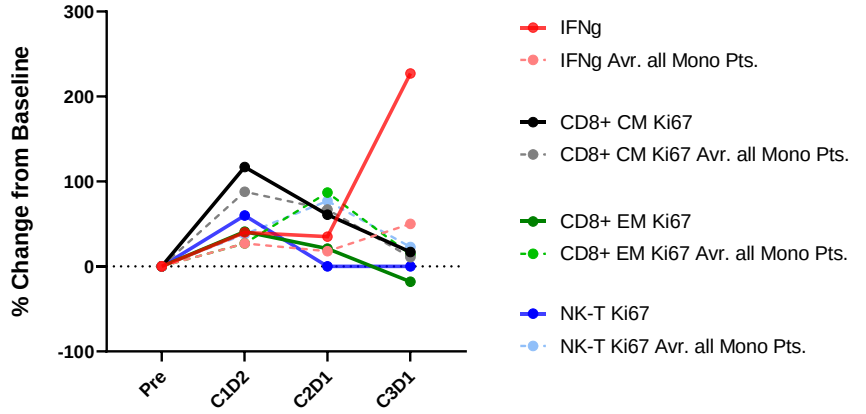
Patient received 3 prior lines of anti-cancer therapy



- 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 biopsy

Alteber et al, Oral presentation SITC 2022

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

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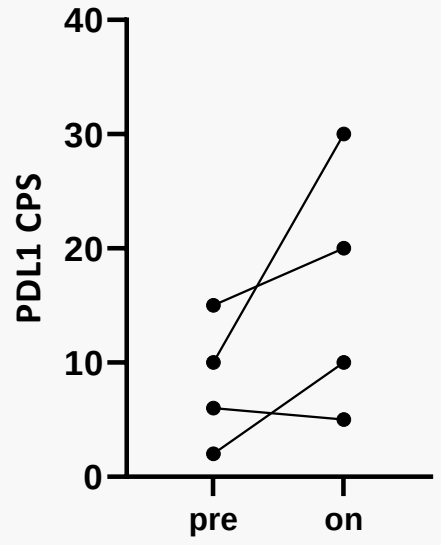
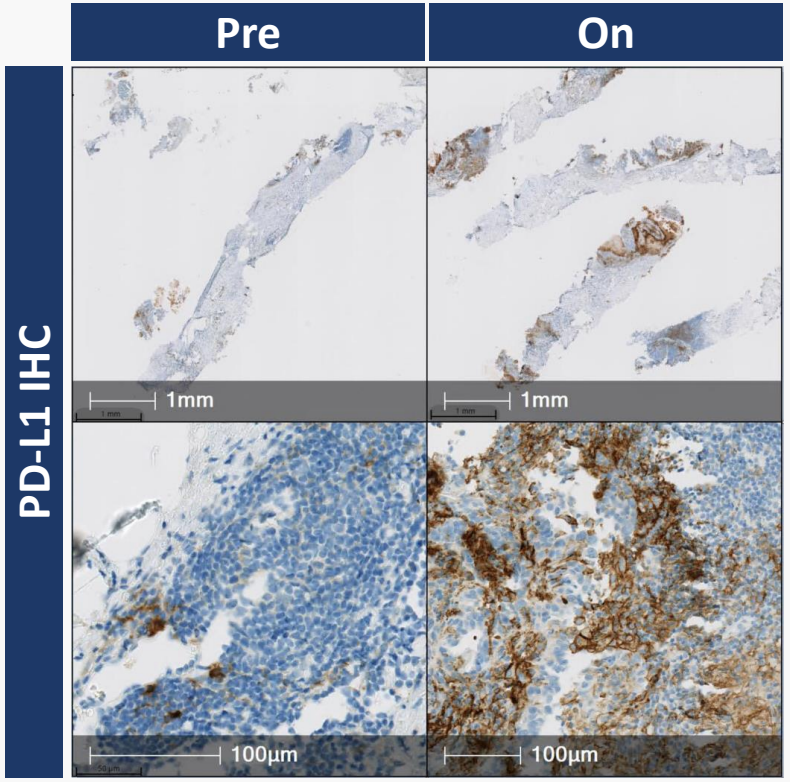
COM701 monotherapy induces TME immune modulation in patients with ovarian cancer

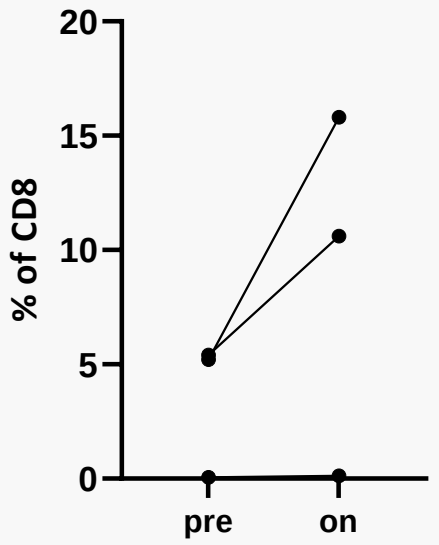
PD-L1 expression





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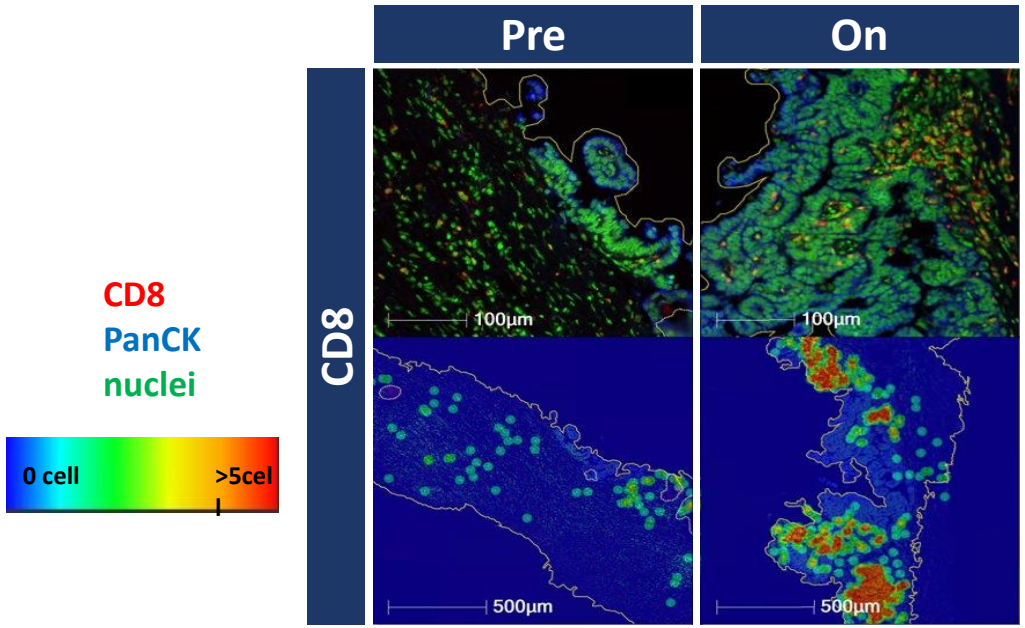
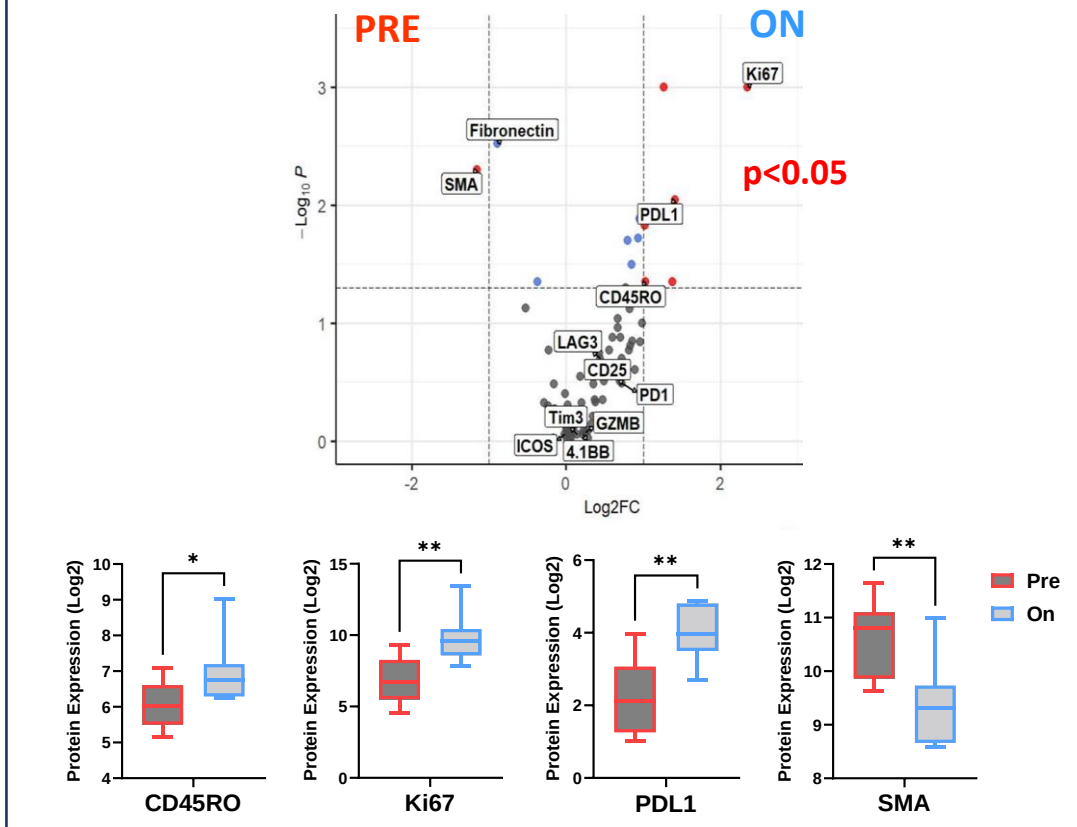
COM701 monotherapy induced immune activation in the TME of patient with ovarian cancer

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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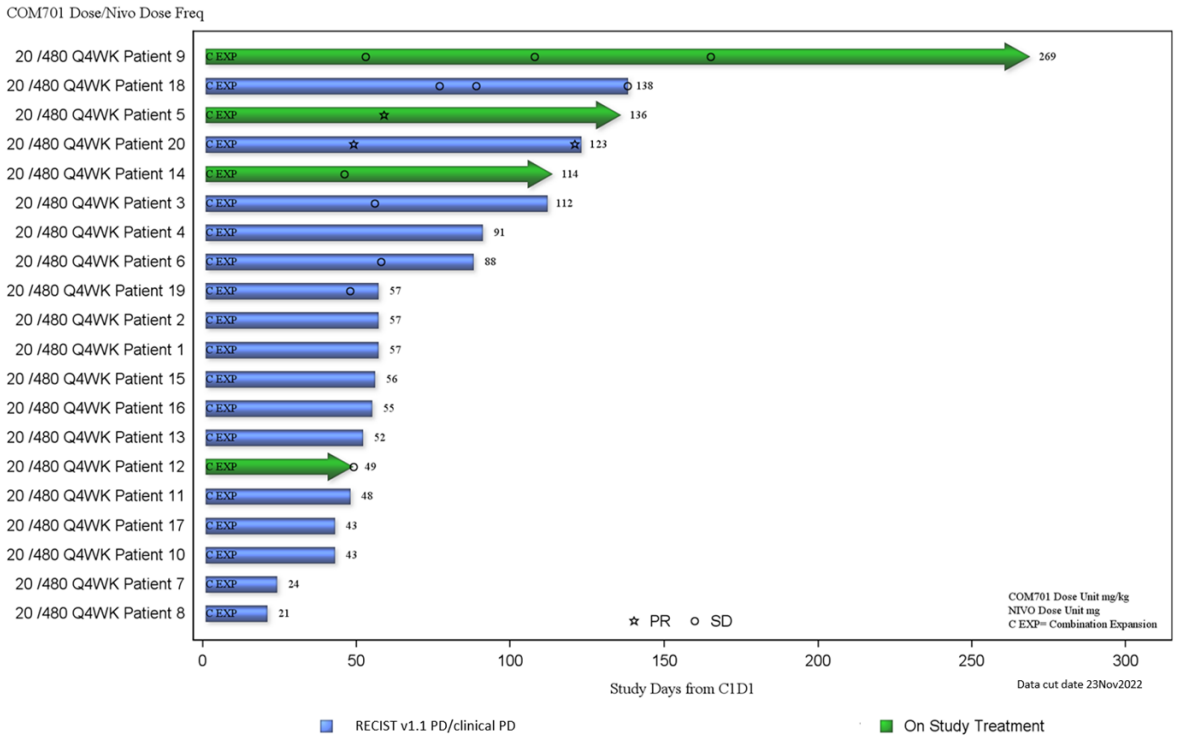
Alteber et al, Oral presentation SITC 2022

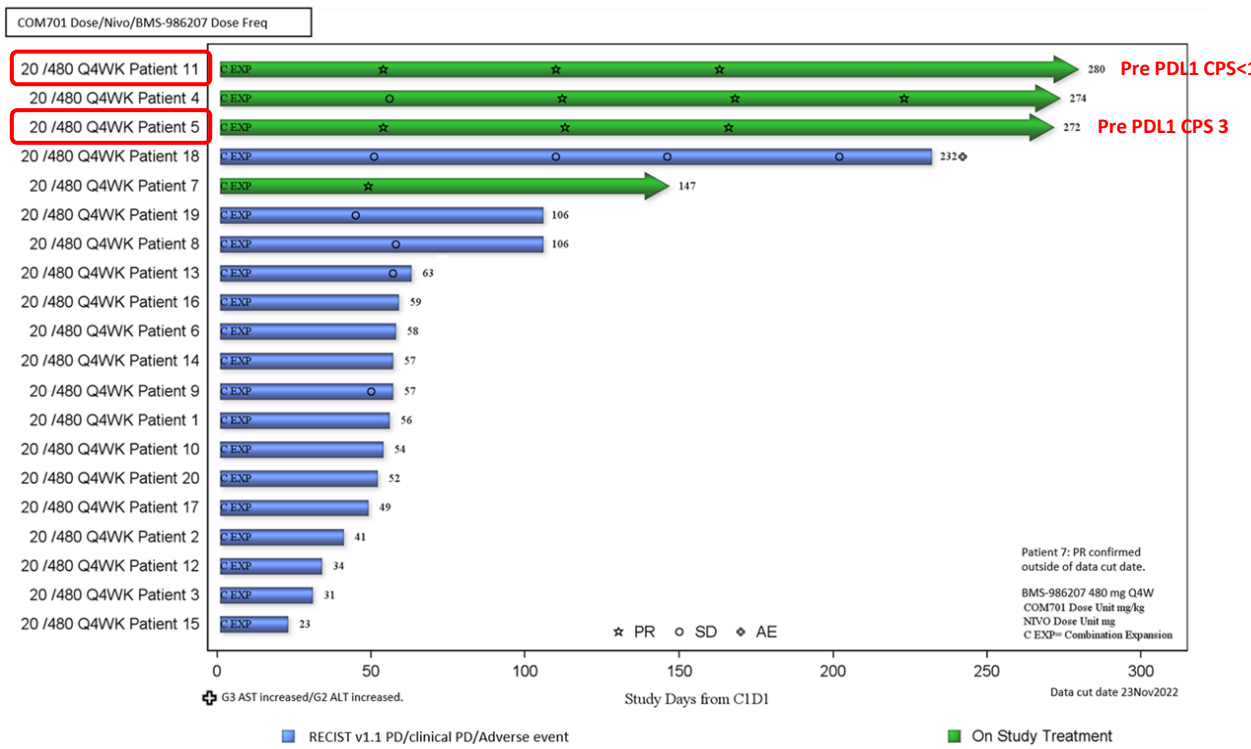
Platinum resistant ovarian cancer
COM701 Combinations–swimmer plot

COM701+Nivolumab



Yeku et al, Poster presentation ESMO-IO 2022

COM701+ BMS-986207 (a-TIGIT)+ nivolumab



Moroney et al, Poster presentation ESMO-IO 2022

All 4 responders on triplet are ongoing with 3 responders with >9 months duration of response

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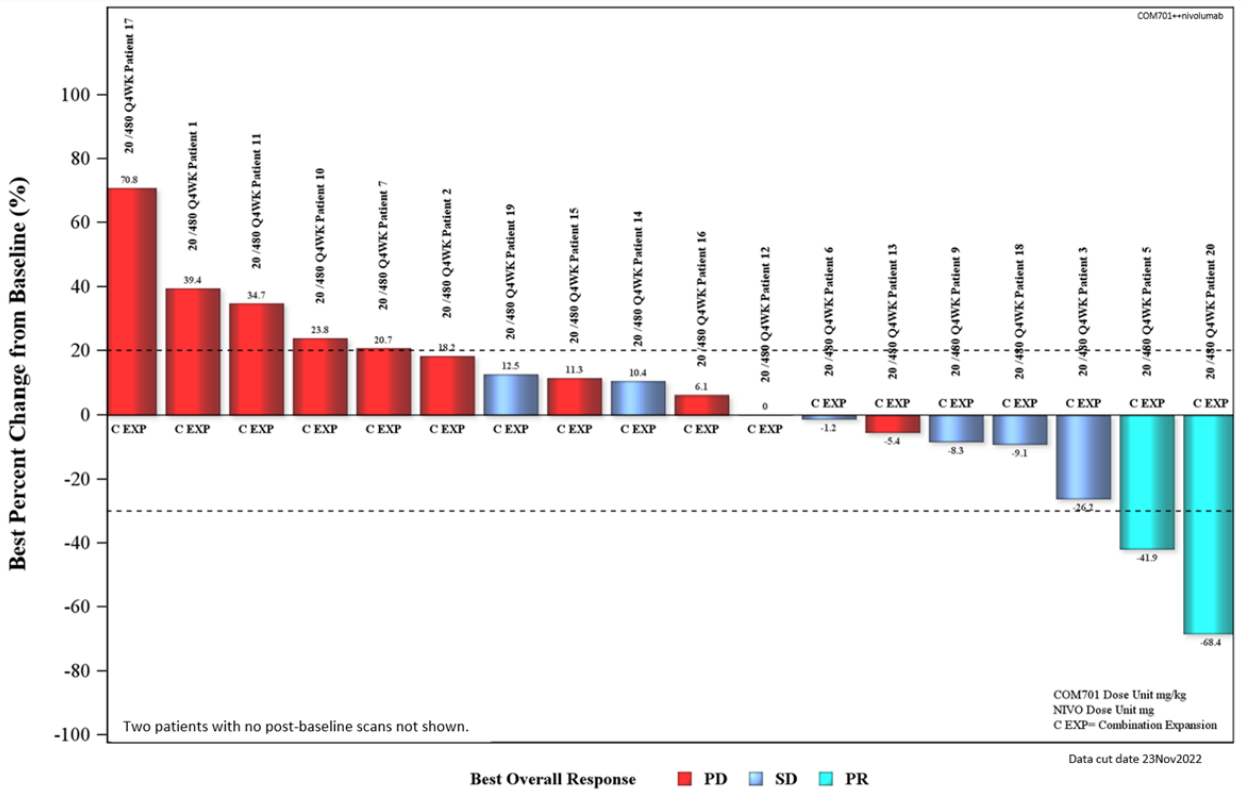
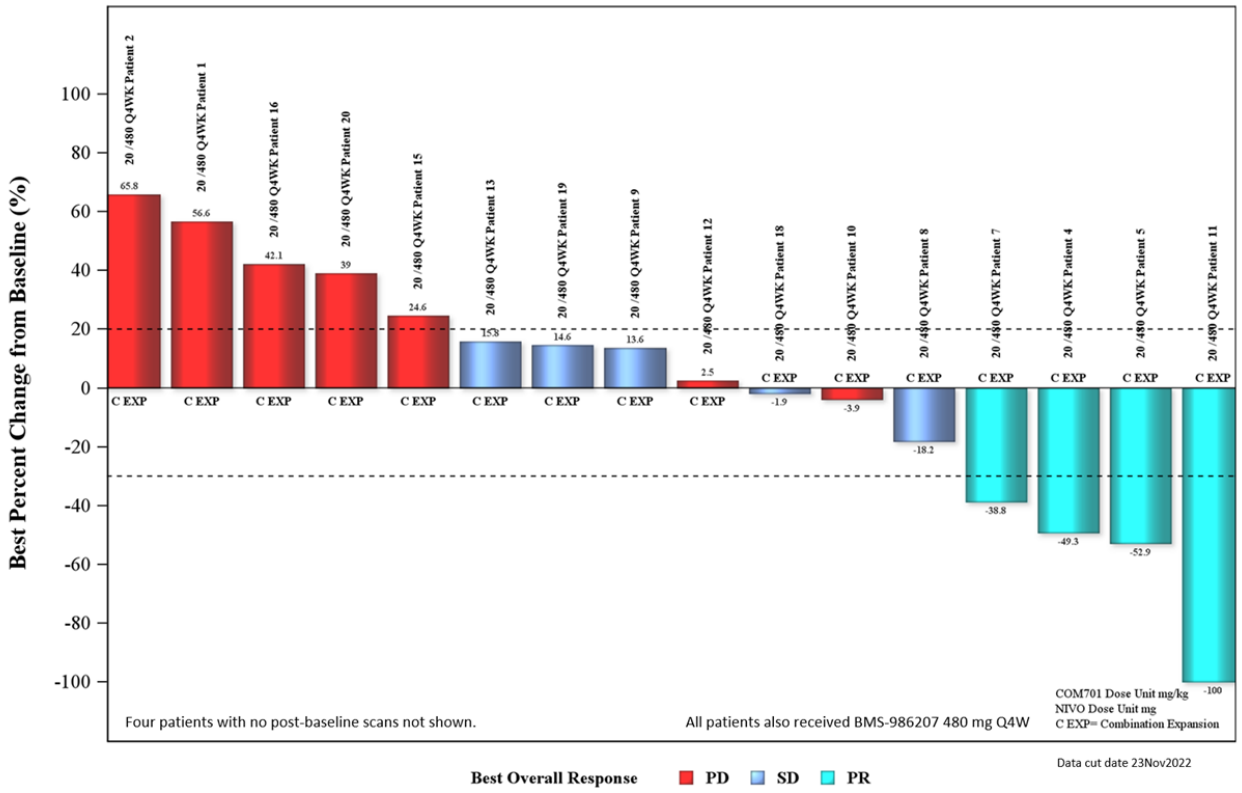
Platinum resistant ovarian cancer
COM701 Combinations–waterfall plots

COM701 + nivolumab



Yeku et al, Poster presentation ESMO-IO 2022

COM701 + BMS-986207 (anti-TIGIT) + nivolumab



Moroney et al, Poster presentation ESMO-IO 2022

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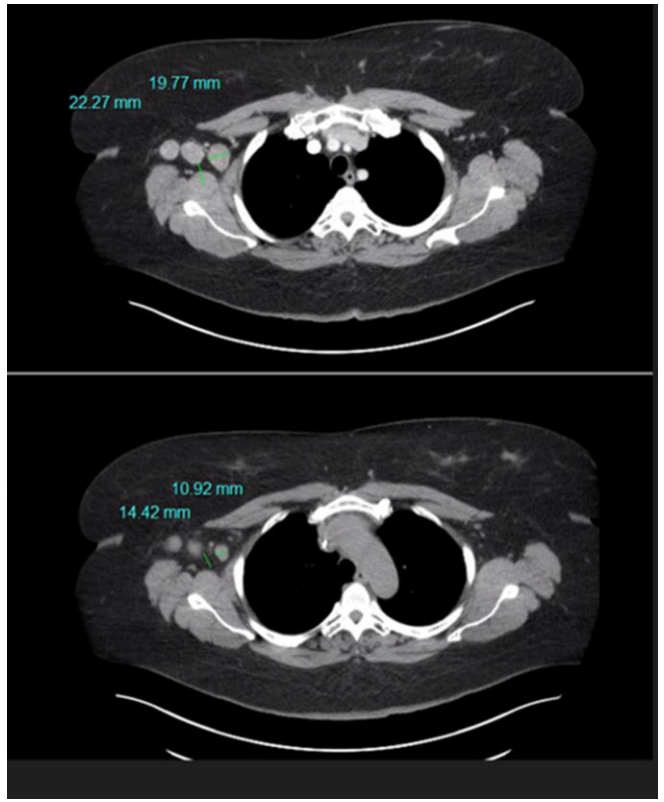
CLINICAL VIGNETTE - COM701 + nivolumab

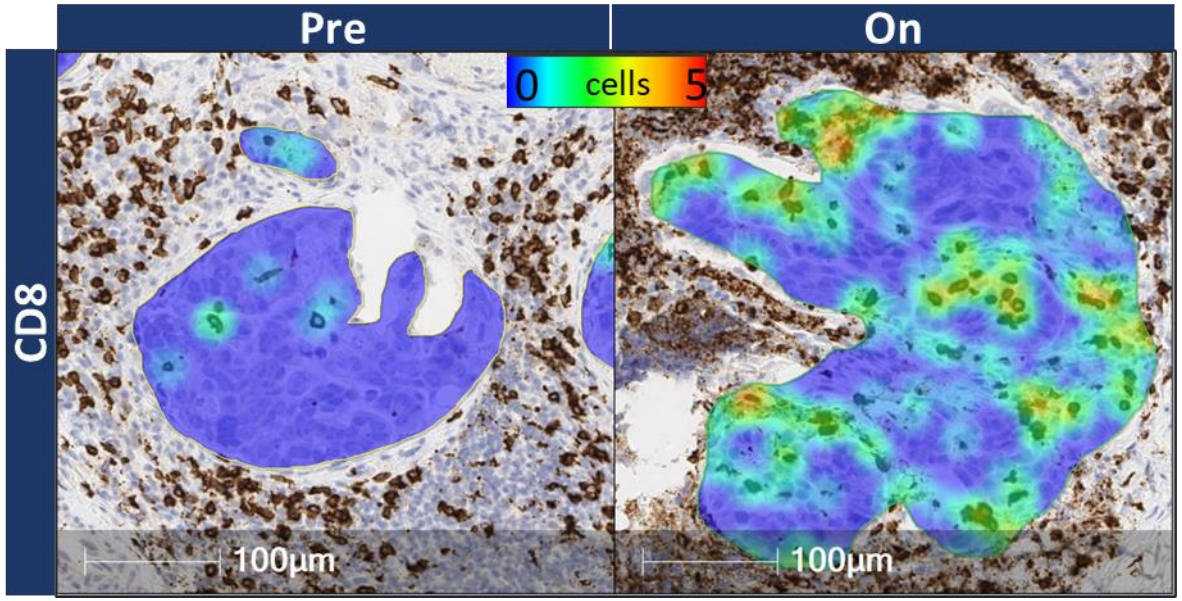
53yr old female, histology - high grade serous adenocarcinoma .
Received 7 prior lines including 4th line: **nivolumab**/+lucitanib (TKI) [**best response PD**]

Reduction in target lesion



PR – 35% reduction in target lesion at 1st post imaging assessment

Increased CD8+ T cell infiltration post-treatment



	Pre	On
% CD8 Positive in tumor area	15.7%	25.7%
Average CD8 Density (CD8/µm²)	8.5×10^{-4}	16×10^{-4}

Yeku et al, Poster presentation ESMO-IO 2022

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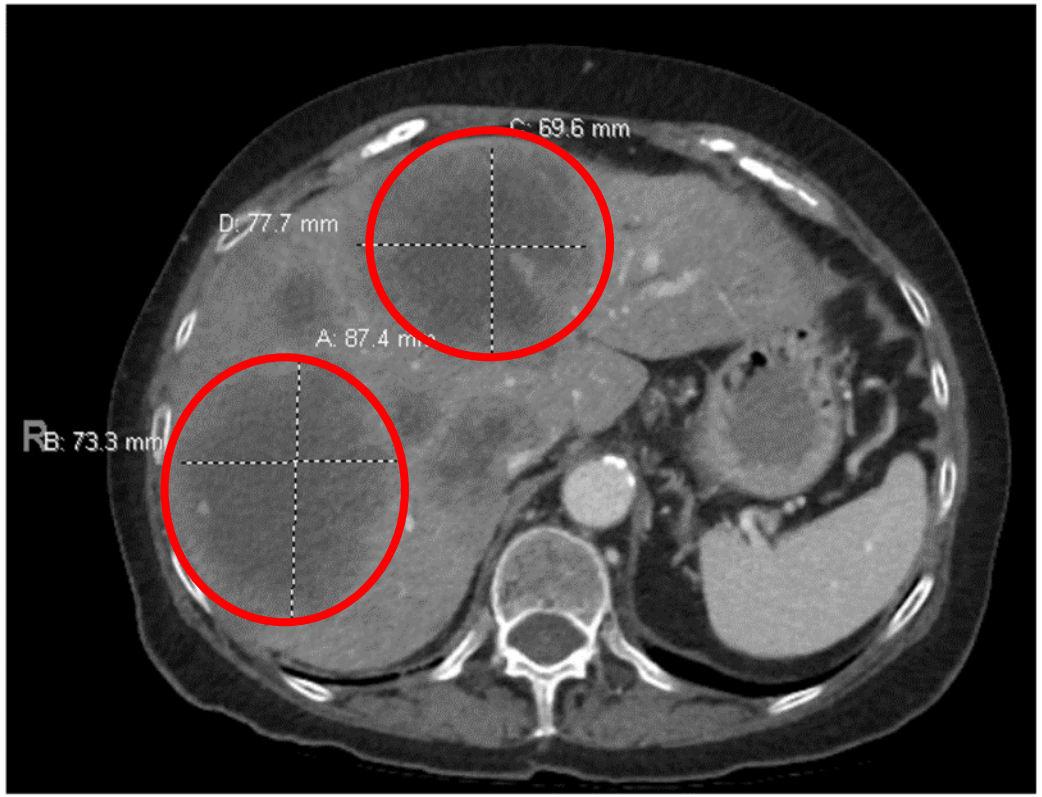
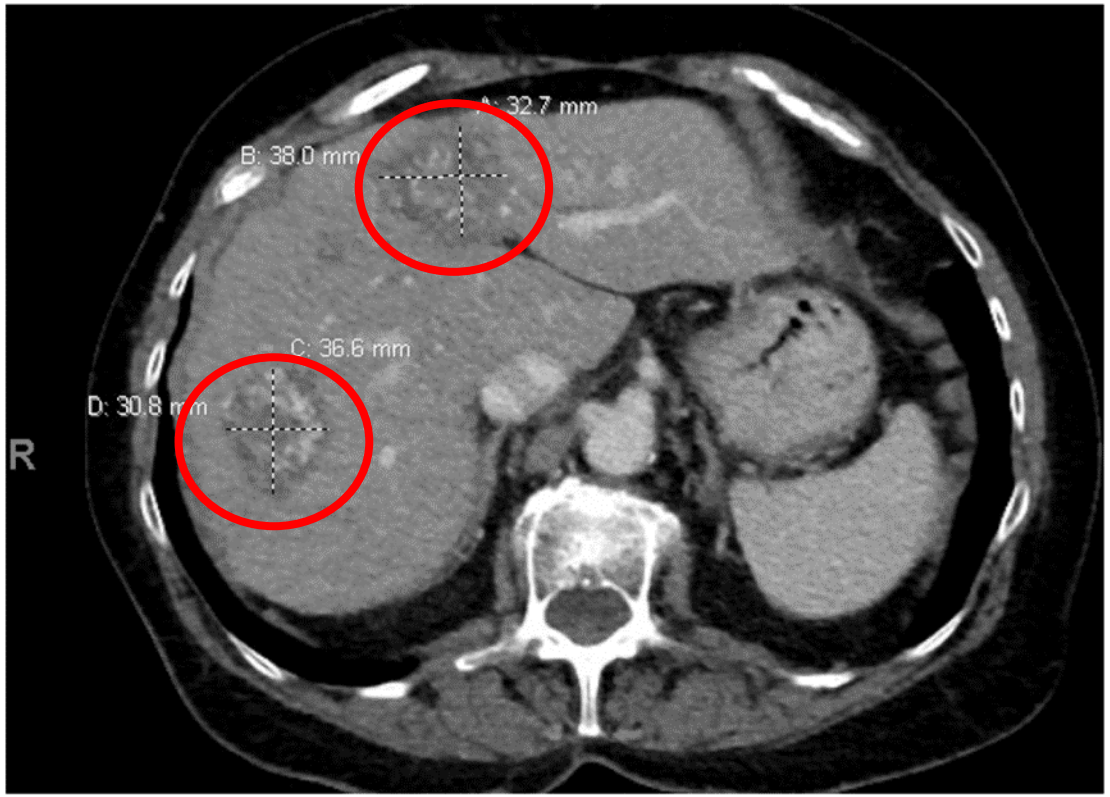
CLINICAL VIGNETTE - COM701+ BMS-986207 (anti-TIGIT)+ nivolumab

68yr old female, histology: high grade serous ovarian carcinoma with a history of 3 prior lines of non-maintenance therapy: carboplatin/paclitaxel, Y90 hepatic radioembolization, carboplatin/pegylated liposomal doxorubicin/bevacizumab [best response for all: PD at 1st re-staging]

On study treatment with confirmed partial response.



Patient 4. Screening – Target lesions.



Patient 4. Cycle 8 – Target lesions. Confirmed PR with 49% reduction in target lesions.

Moroney et al, Poster presentation ESMO-IO 2022

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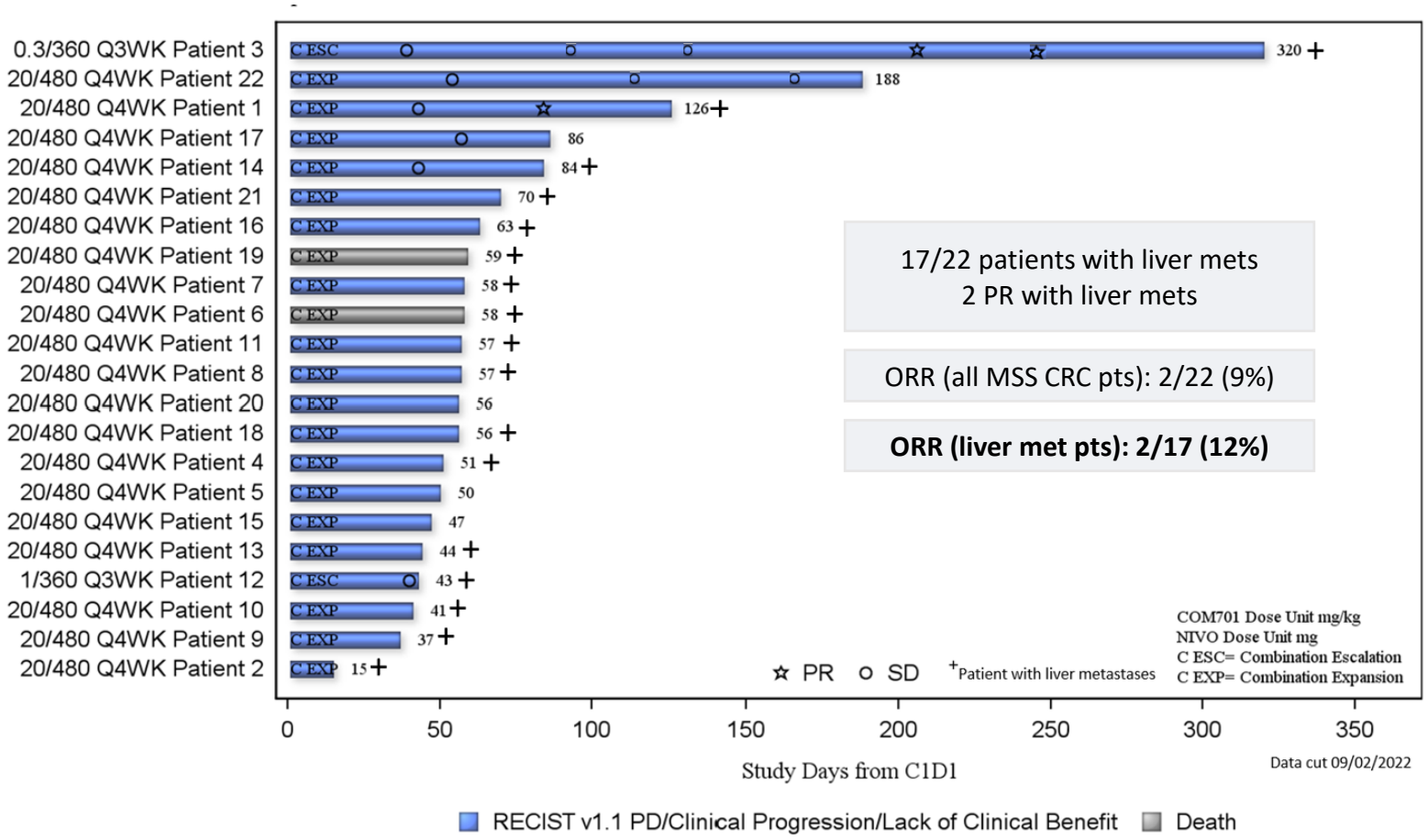
COM701 with nivolumab induce clinical response in patients with MSS CRC and liver metastasis

MSS CRC Benchmark

Last Line SoC	ORR	PFS	OS
Regorafenib	1%	2m	6.4m

Difficult to treat MSS-CRC + liver mets

	ORR	
Regorafenib + Nivo [1]	0/47	MSS CRC with liver mets
Nivo/ atezo/ pembro/ durvalumab [3]	0/54	MSS CRC with liver mets
Baltsilimab+botensilimab [2]	0/17	MSS CRC with liver mets



Adapted from Overman et al, Oral presentation SITC 2022

- * Investigator assessed responses

1. Fakih M et al Journal of Clinical Oncology 2021
2. Bullock AJ et al, 2022 ESMO GI
3. Wang et al, JAMA 2021
4. Mayer et al. N Eng J Med. 2015;372:1909-1919
5. Van Cutsem,, 2012, ASCO

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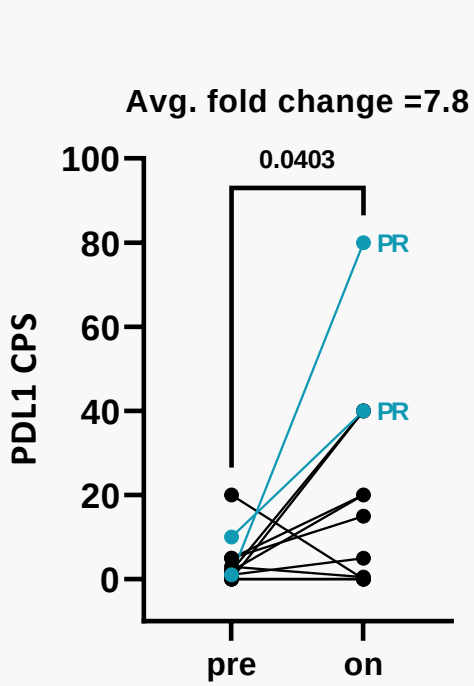
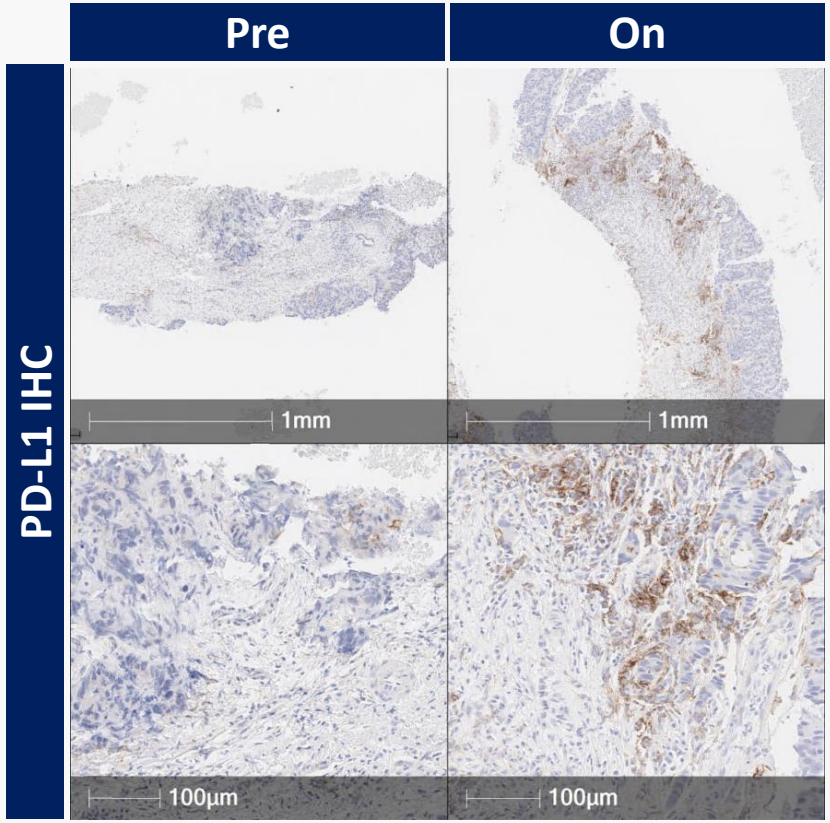
COM701+ nivolumab combination induces TME immune modulation in patients with MSS-CRC

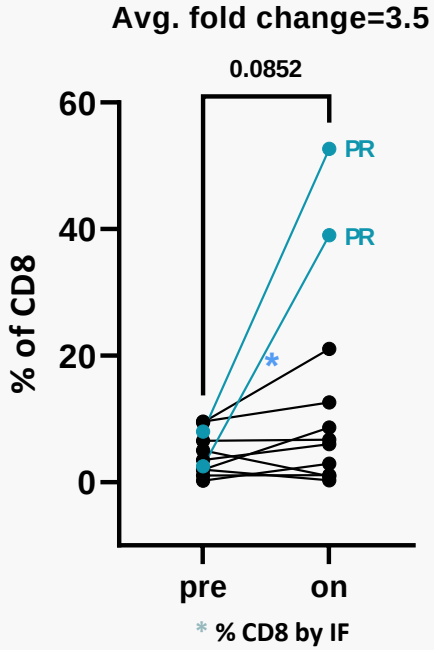
PD-L1 expression



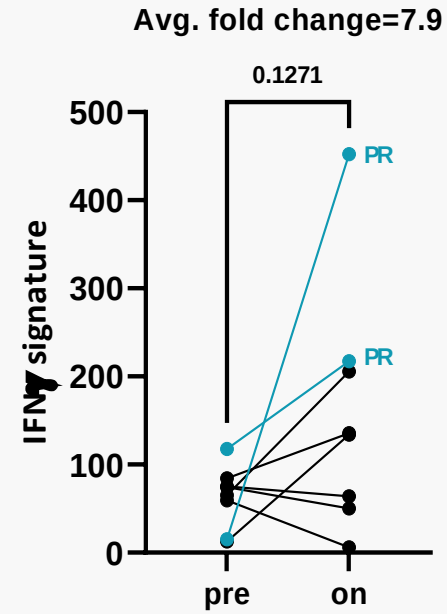


PR = patient with partial response per RECIST

CD8 IHC



IFNγ signature



PR = patient with partial response per RECIST

Personalis - ImmunoID NeXT™

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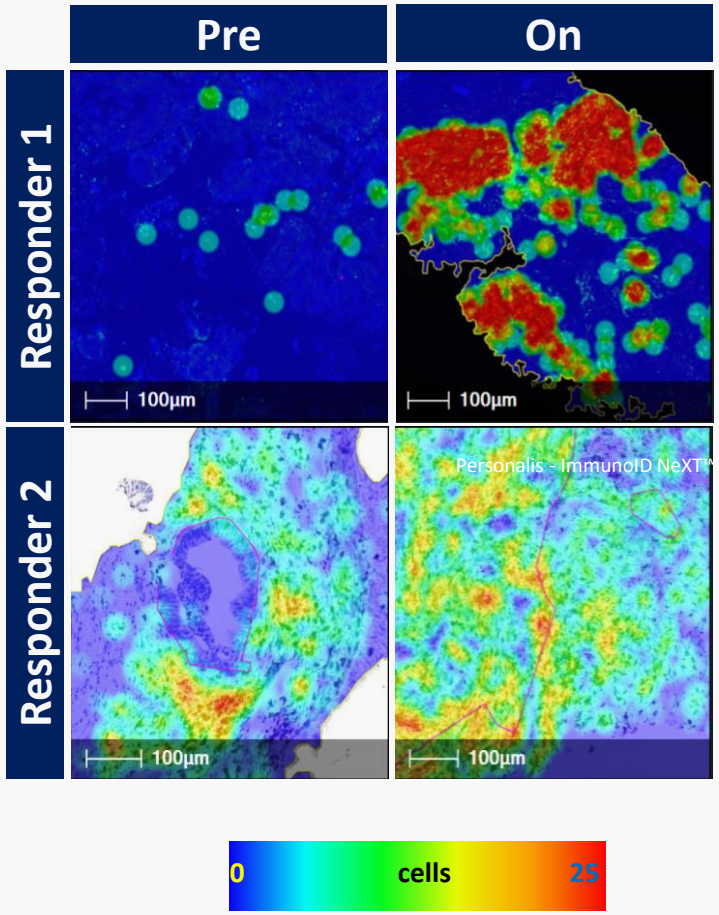
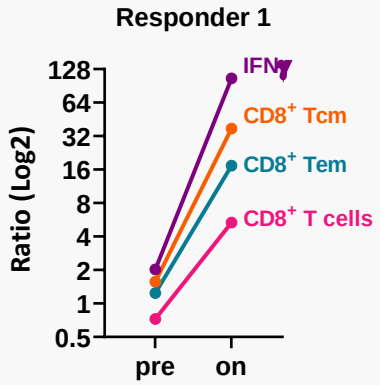
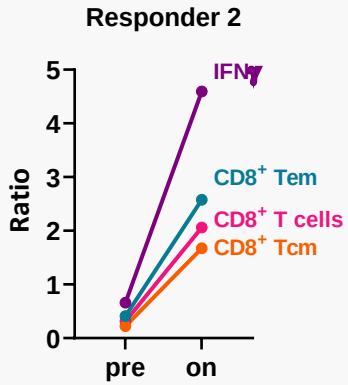
Extensive TME modulation in MSS-CRC patients partially responding to COM701+ nivolumab

Increased CD8 infiltration and immune modulation

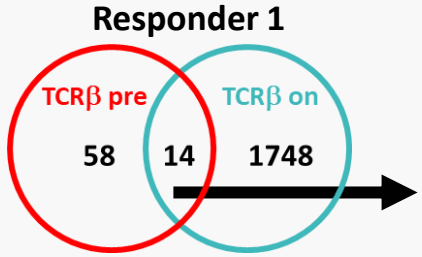


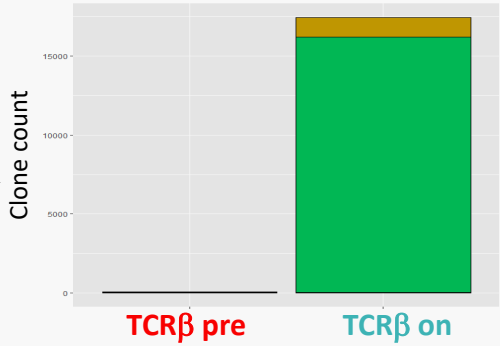




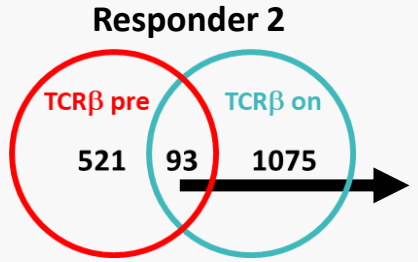
Alteber et al, Oral presentation SITC 2022

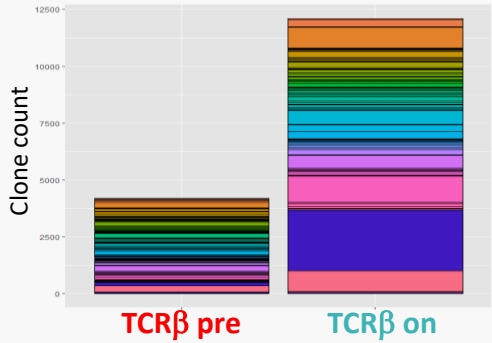
Increased TCR clonality and clonal expansion



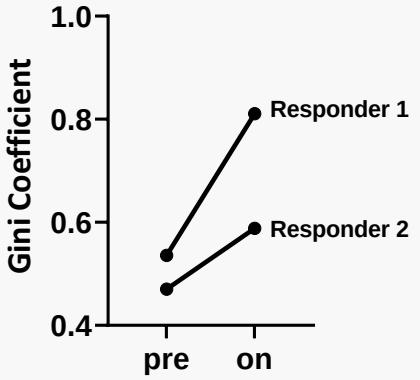


Most dominant clone on treatment pre-existed in the TME pre-treatment





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 both MSS-CRC responding patients

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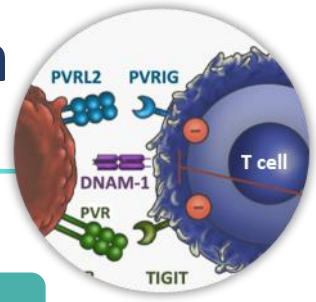
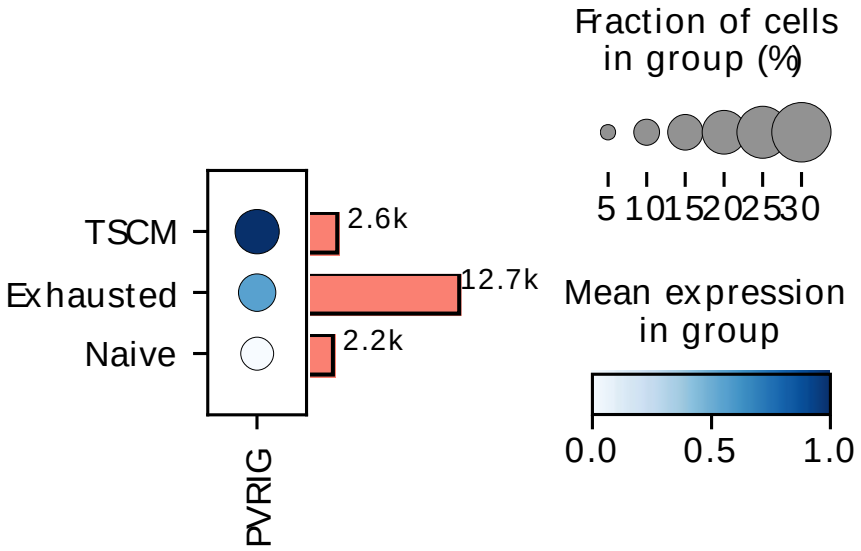
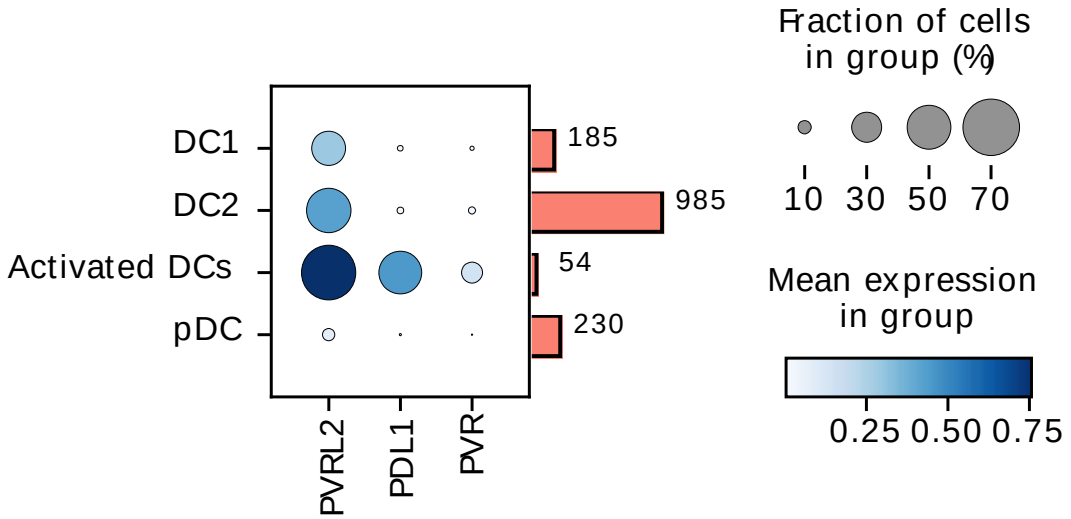
PVRIG is highly expressed on Tscm and PVRL2 on DCs in liver metastases of patients with MSS CRC



High PVRIG on Tscm CD8+ T-cells



Dominant PVRL2 on Dendritic cells



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

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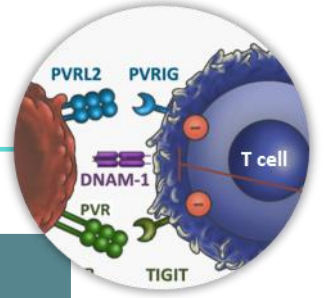
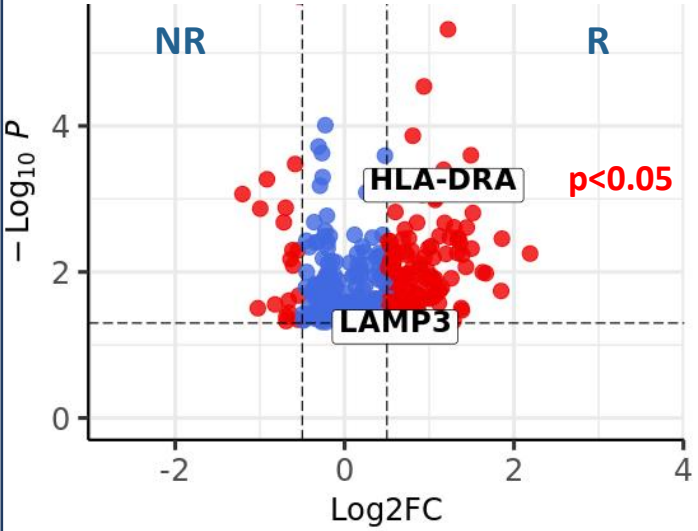
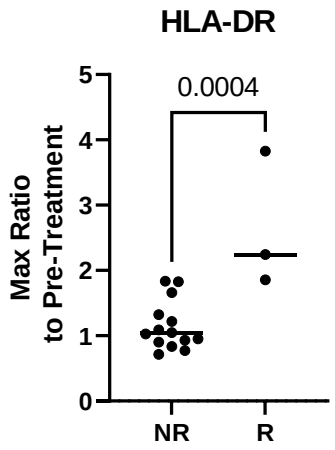
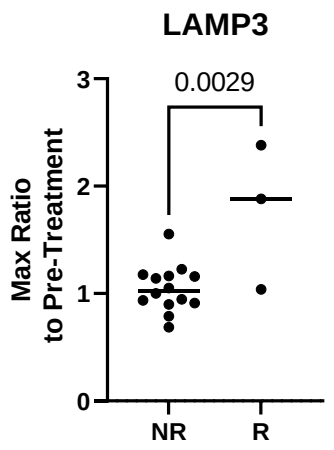
Combination of COM701+nivolumab induced markers of activated DCs in serum of 3 responding patients

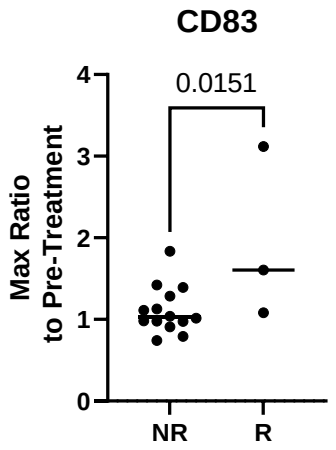


Responders (R) vs non-responders (NR) differential gene expression









Olink® Explore 1536

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

Alteber et al, Oral presentation SITC 2022

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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 anti tumor activity and TME immune-modulation in patients with MSS-CRC and ovarian cancer, typically not responsive to approved CPI
- Favorable safety profile across combinations
- 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

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Acknowledgments:

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Pierre Ferre, Yaron Turpaz, Zurit Levine,

Henry Adewoye

Thank you!

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Investigators, clinical trial sites
and
Patients and their families

Our Vision

Transforming patient lives by developing first-in-class therapeutics based on Compugen's computational target discovery platform

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