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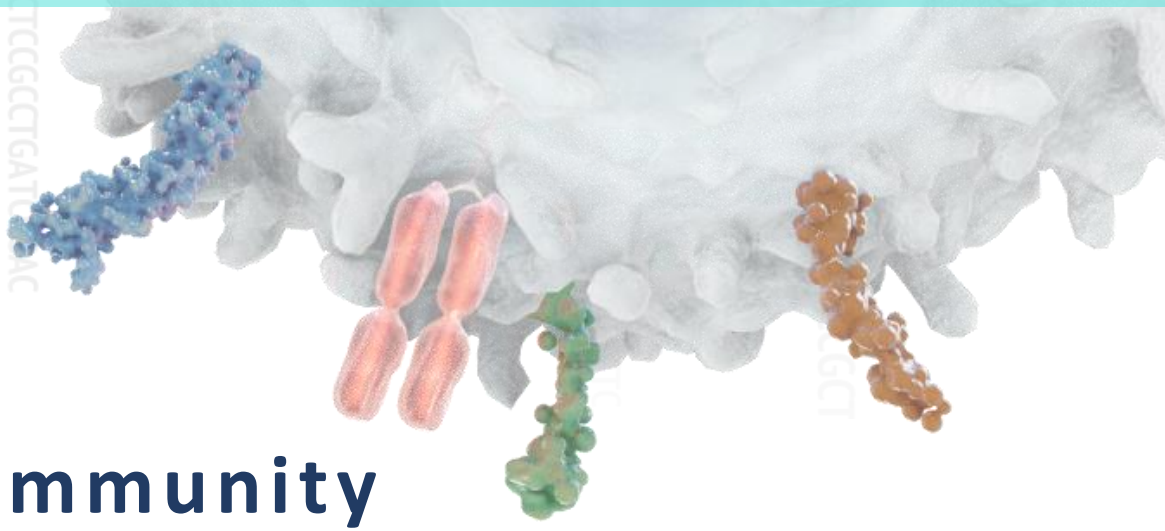

Harnessing PVRIG & TIGIT Combination in Anti-Cancer Immunity

TIGIT Therapies Digital Summit

Eran Ophir, VP Research & Drug Discovery

December 2021

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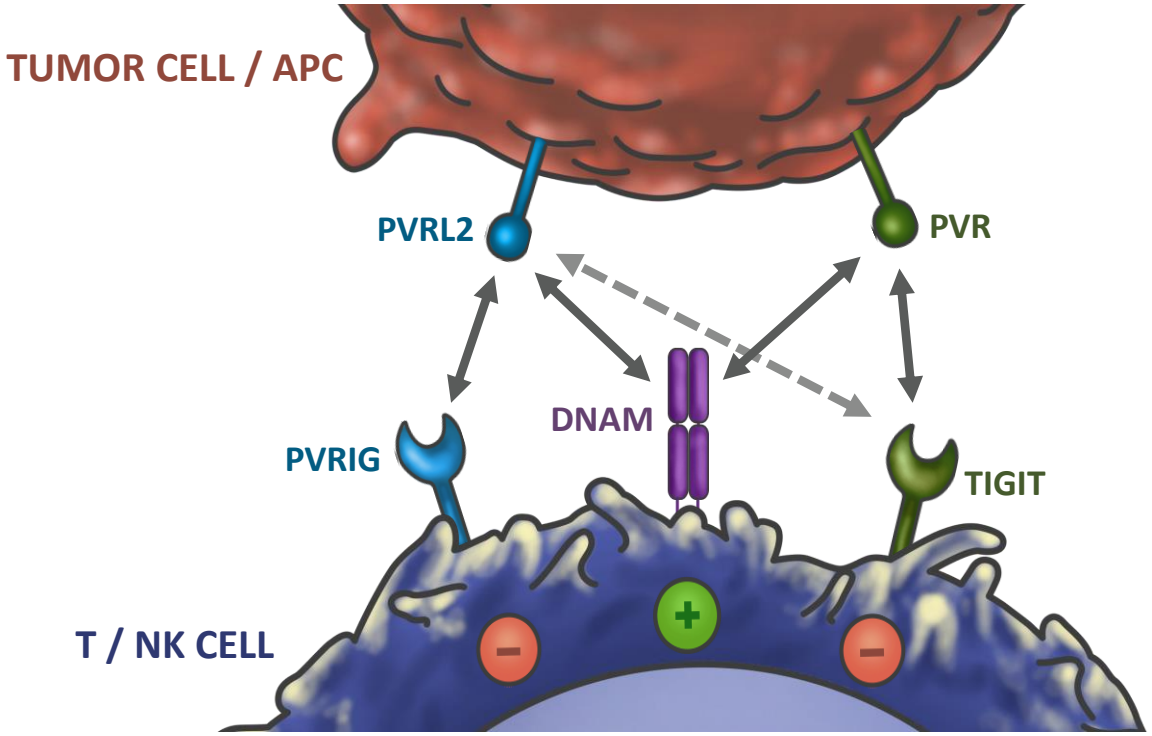
DNAM-1 Axis Plays Essential Role in Tumor Immunology



- PVRIG binds PVRL2 as a functional ligand (TIGIT has a low affinity for PVRL2)
- 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)

Alteber *et al.* Cancer Discov. 2021

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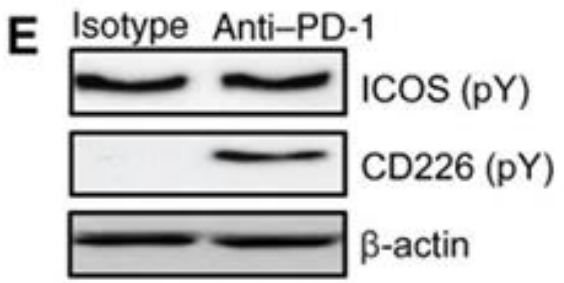
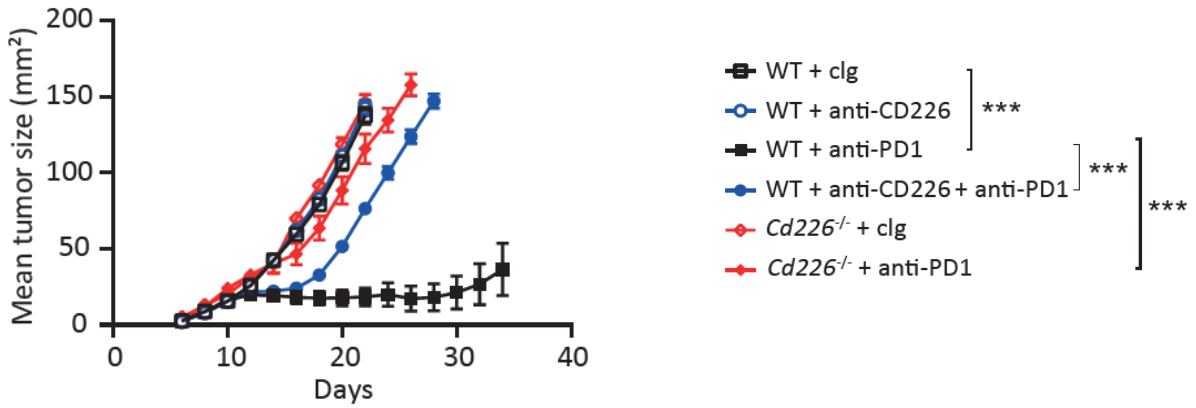
DNAM-1 Intersects with the PD-1 Pathway and is Required for In-vivo Response to PD-1 Blockade

PD-1 inhibition blocks DNAM-1 (CD226) dephosphorylation and inactivation



Wang et al., Science Immunology, 2018

DNAM-1 KO or inhibition reverses anti-PD-1 tumor growth inhibition



Weulersee et al. Immunity 2020

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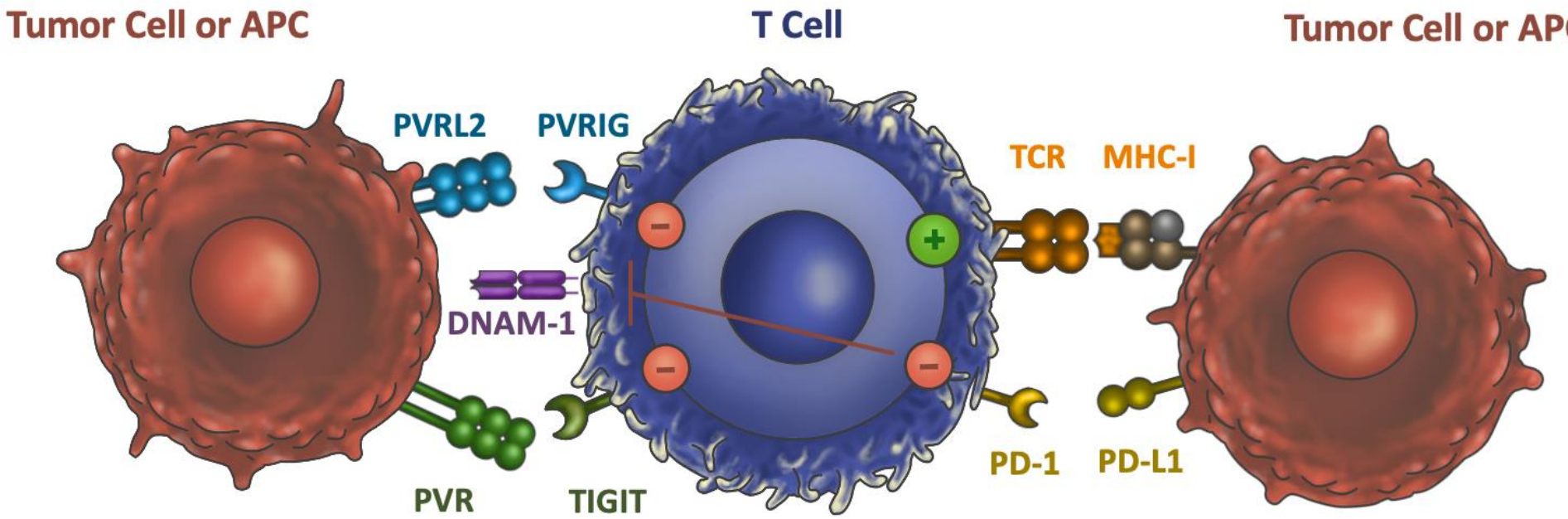
PVRIG, TIGIT and PD-1 are Players in the DNAM-1 Axis



Alteber *et al.* Cancer Discov. 2021

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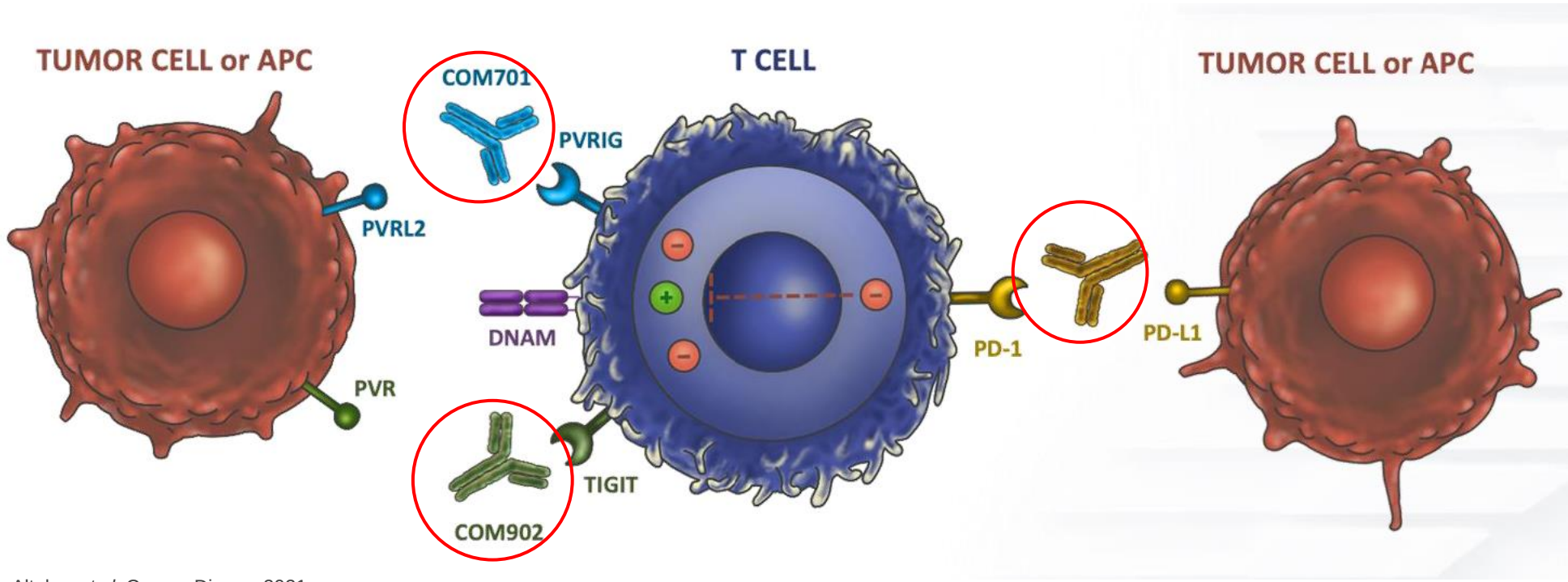
Potential Intersection Between PVRIG/TIGIT and PD-1 Pathways Support Combination Approach to Overcome Immunotherapy Resistance



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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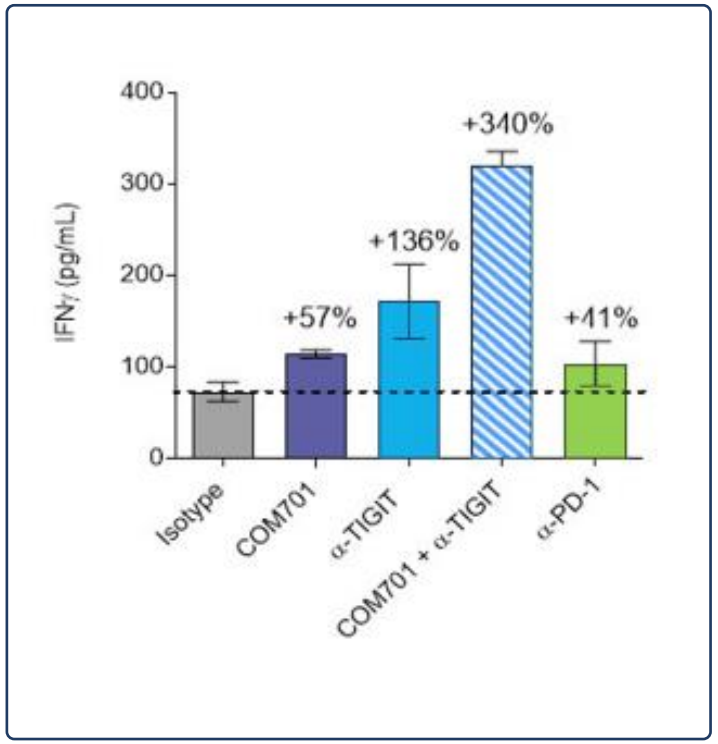
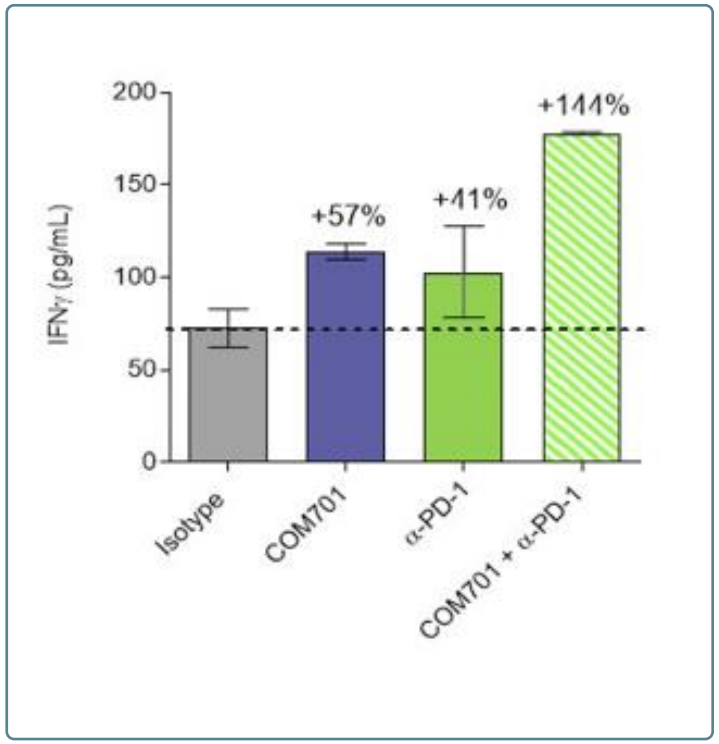
Synergistic T Cell Activation With PVRIG, PD-1 and TIGIT Blockade

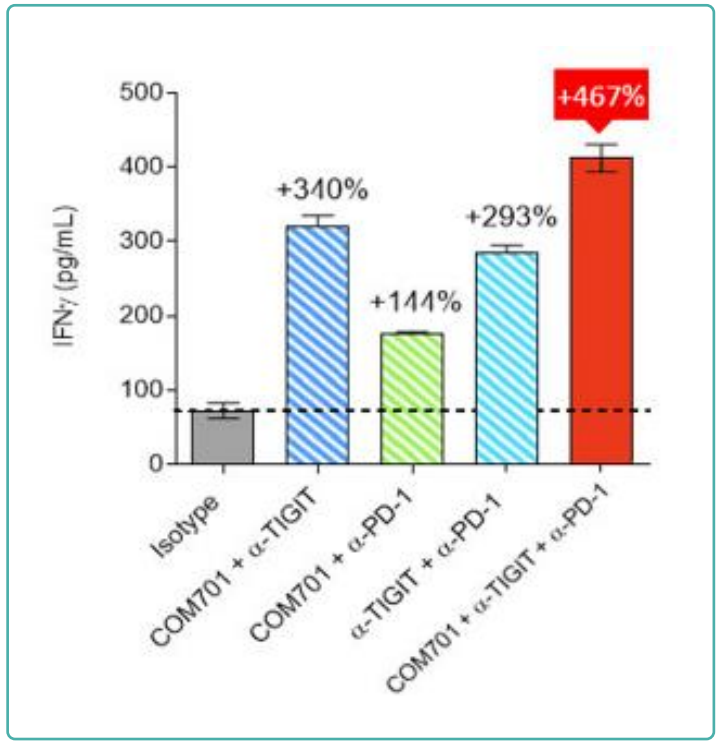
COM701 +/- anti-TIGIT



COM701 +/- anti-PD-1



Triple combination



COM701 - anti-PVRIG antibody

Whelan, et al., Cancer Immunol Res. 2019

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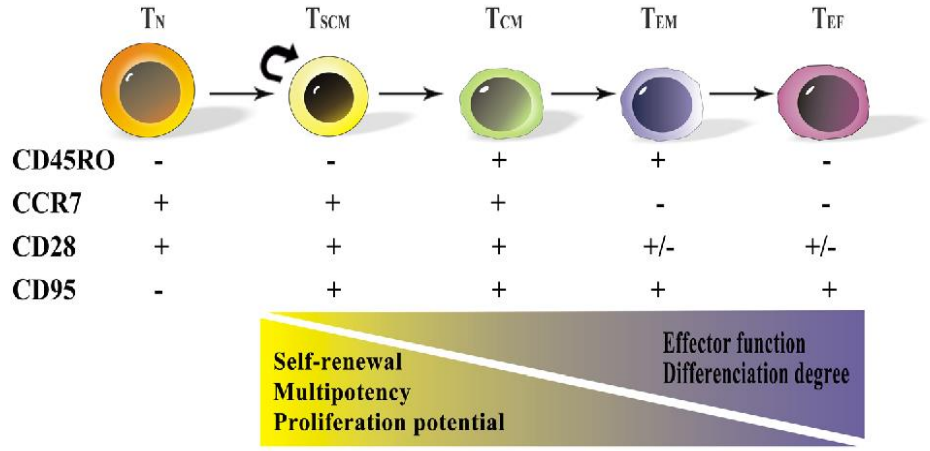
Early Differentiated T stem-like cells are Potent Inducers of Anti Tumor Activity Following Adoptive T cell Transfer



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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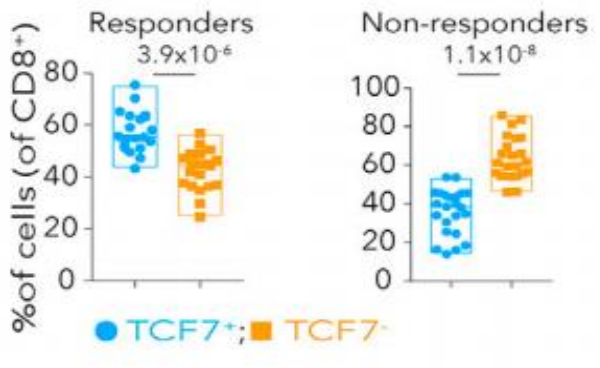
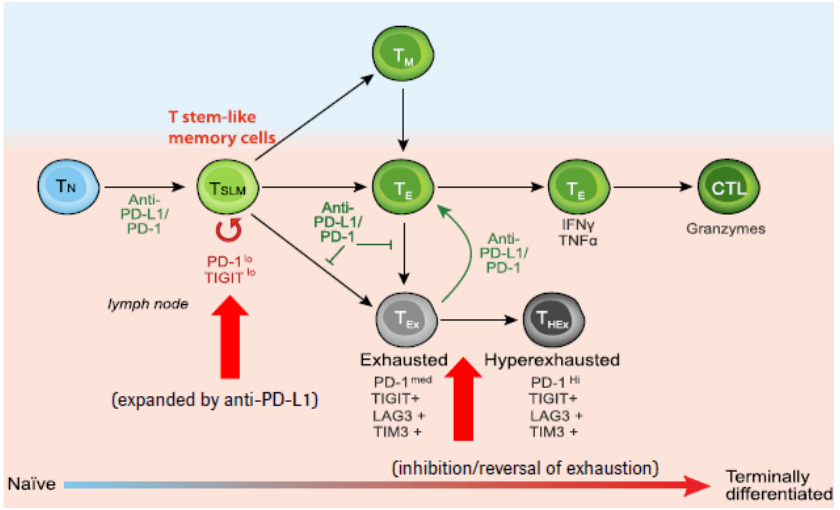
Growing Evidence of Early Differentiated T stem-like memory cells Importance in Response to Checkpoint Blockade

Fraction of Tscm (TCF7^{+}) cells is a predictive of PD-1 response in melanoma



Sadeh-Feldman et al., 2018, Cell



Modified from Chen and Mellman Nature 2017

- Anti-PD-L1 expands a key population of PD-1-positive Tscm which also express TIGIT
- TIGIT and PD-1 co-blockade might enable optimal Tscm activation and DNAM-1 co-stimulation

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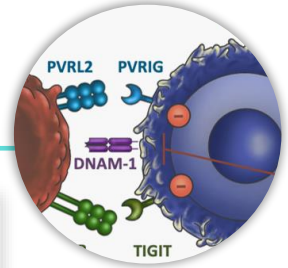
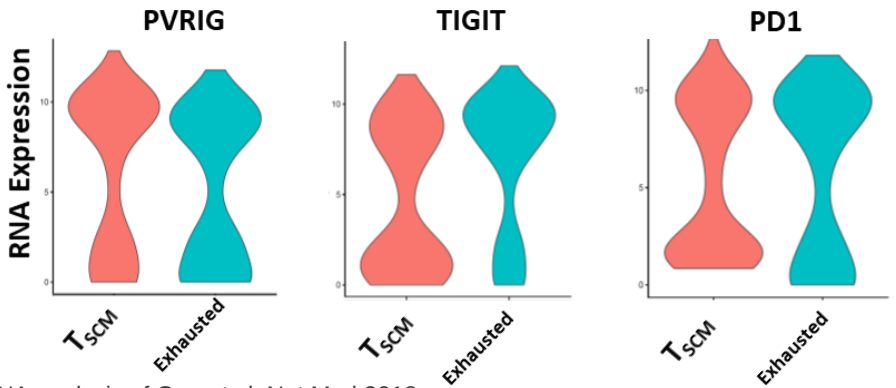
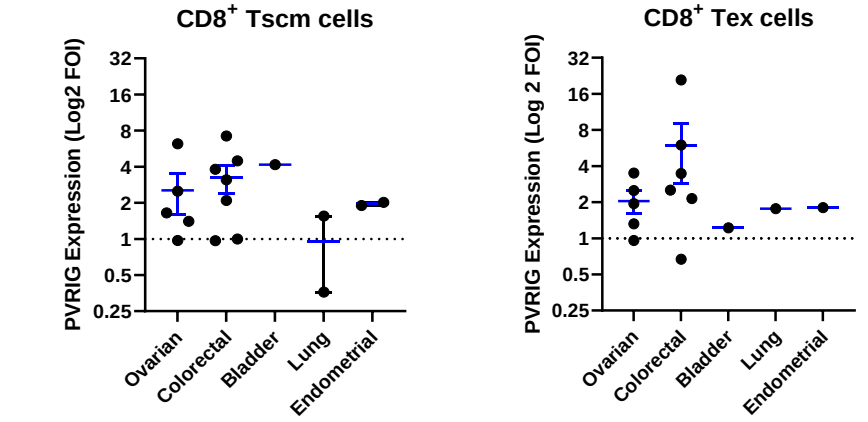
PVRIG is Expressed by Early Differentiated Tscm and has Higher Expression on Early Differentiated CD8+ T Cells

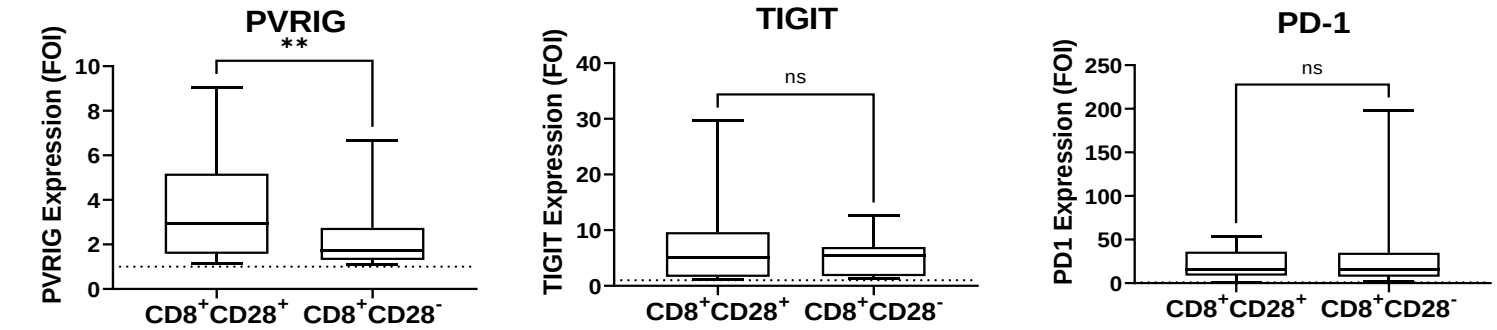




scRNA analysis of Gau et al. Nat Med 2018



Internal FLOW cytometry Data



Internal FLOW cytometry Data

Potential for enhanced Tscm activation, expansion and generation of effector T cells

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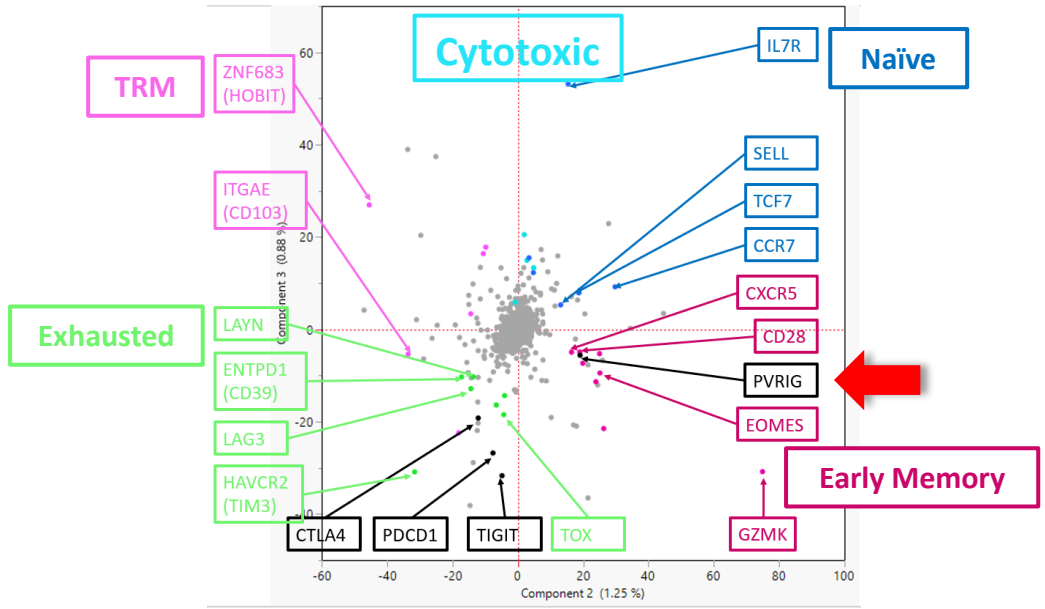
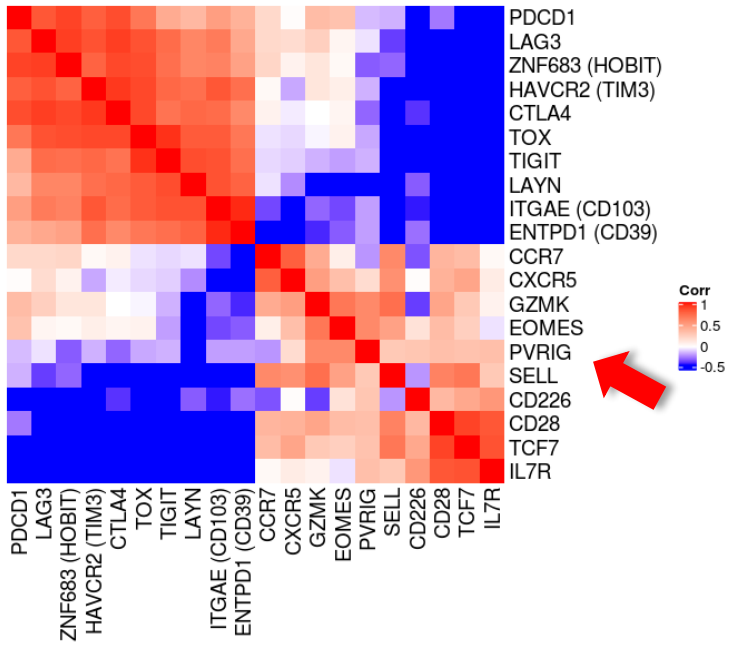
PVRIG Uniquely Clusters with Early Differentiated/Tscm Genes

PCA Analysis of CD8+ T cell genes, NSCLC



GSE99254_NSCLC Dataset internally analyzed

Unsupervised correlation analysis of scRNA, CRC



GSE108989_CRC Dataset internally analyzed

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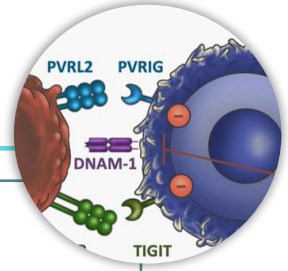
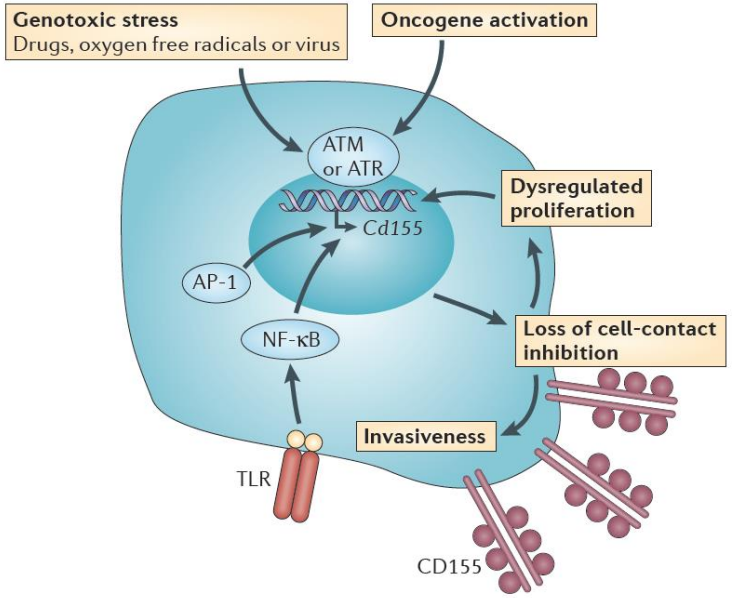
PVRL2 and PVR are Expressed in Inflamed and Non-Inflamed Tumors Types



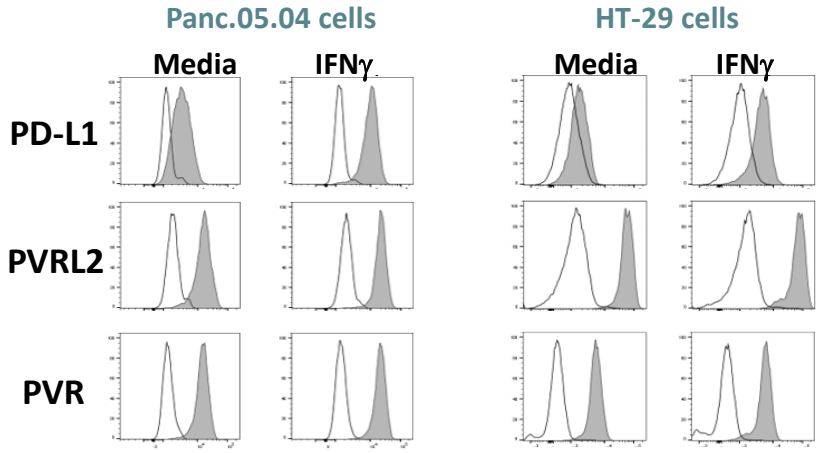
PVR/PVRL2 on tumor cells induced by:

1. Genotoxic stress (DNA damage, oxidative stress)
2. Tumorigenesis (loss of contact inhibition/increased invasiveness)



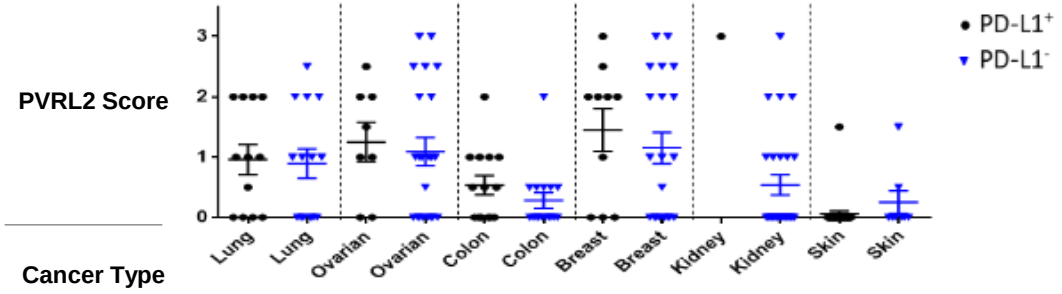
Martinet et al. Nature Rev. Imm. 2015

PVR/PVRL2 on tumor cells are not modulated by IFN-γ



Modified from Whelan, et al., Cancer Immunol Res. 2019

PVRL2 commonly expressed in PD-L1 negative tumors



SITC, November 2017, Whelan, et al., poster presentation

PVRIG+TIGIT co-blockade may address PD-L1^{low} non-inflamed tumor types

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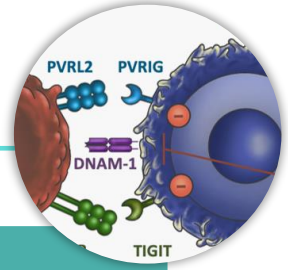
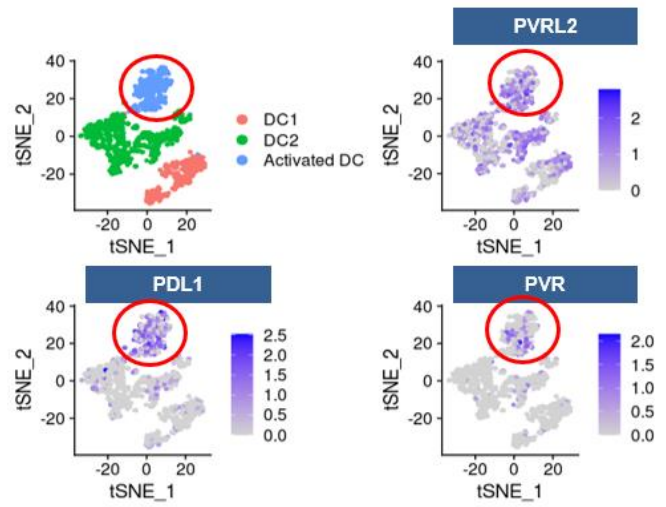
PVRL2 Has a Dominant Expression on Dendritic Cells

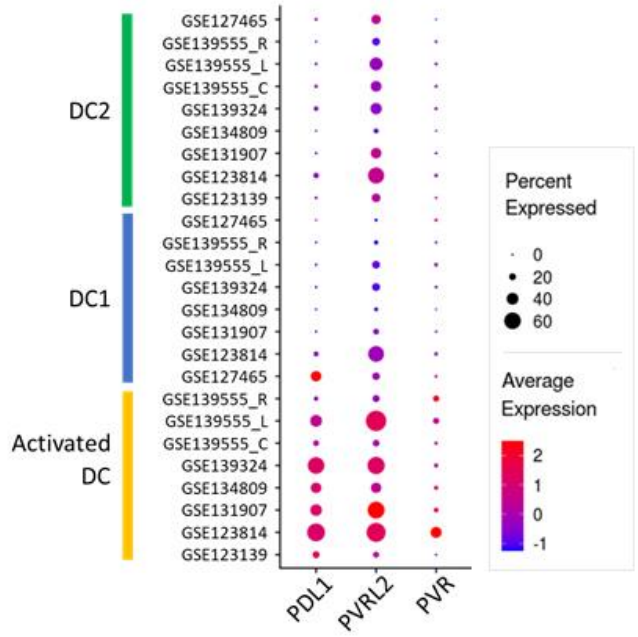


DC Population in SCC/BCC

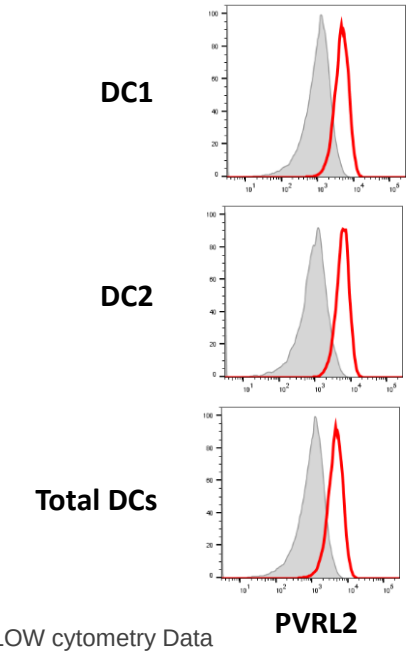


GSE123814 Dataset internally analyzed

Multiple scRNA cancer datasets



Ovarian cancer



Internal FLOW cytometry Data

PVRIG blockade may enhance interaction and activation of Tscm by DCs in PD-L1^{low} non-inflamed tumor types

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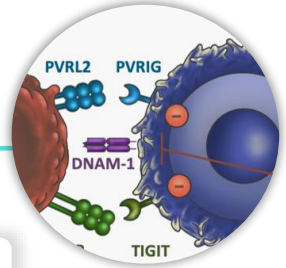
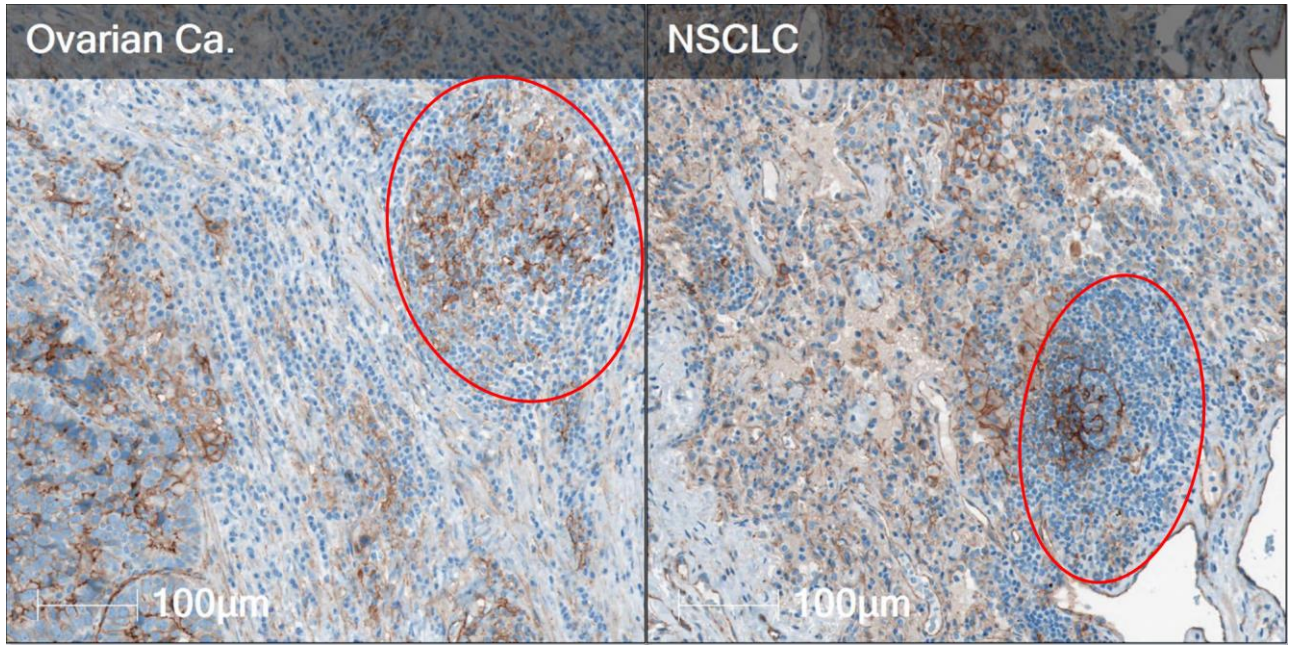
PVRL2 is Expressed in Tertiary Lymphoid Structures



PVRL2



Tertiary lymphoid structures are Lymphoid Structures in the tumor bed in which local T cell activation occur

- **Predictive of PD-1 response**

Helmink et al Nature 2020

Potential of PVRIG blockade to enhance T cell proliferation at the tumor bed

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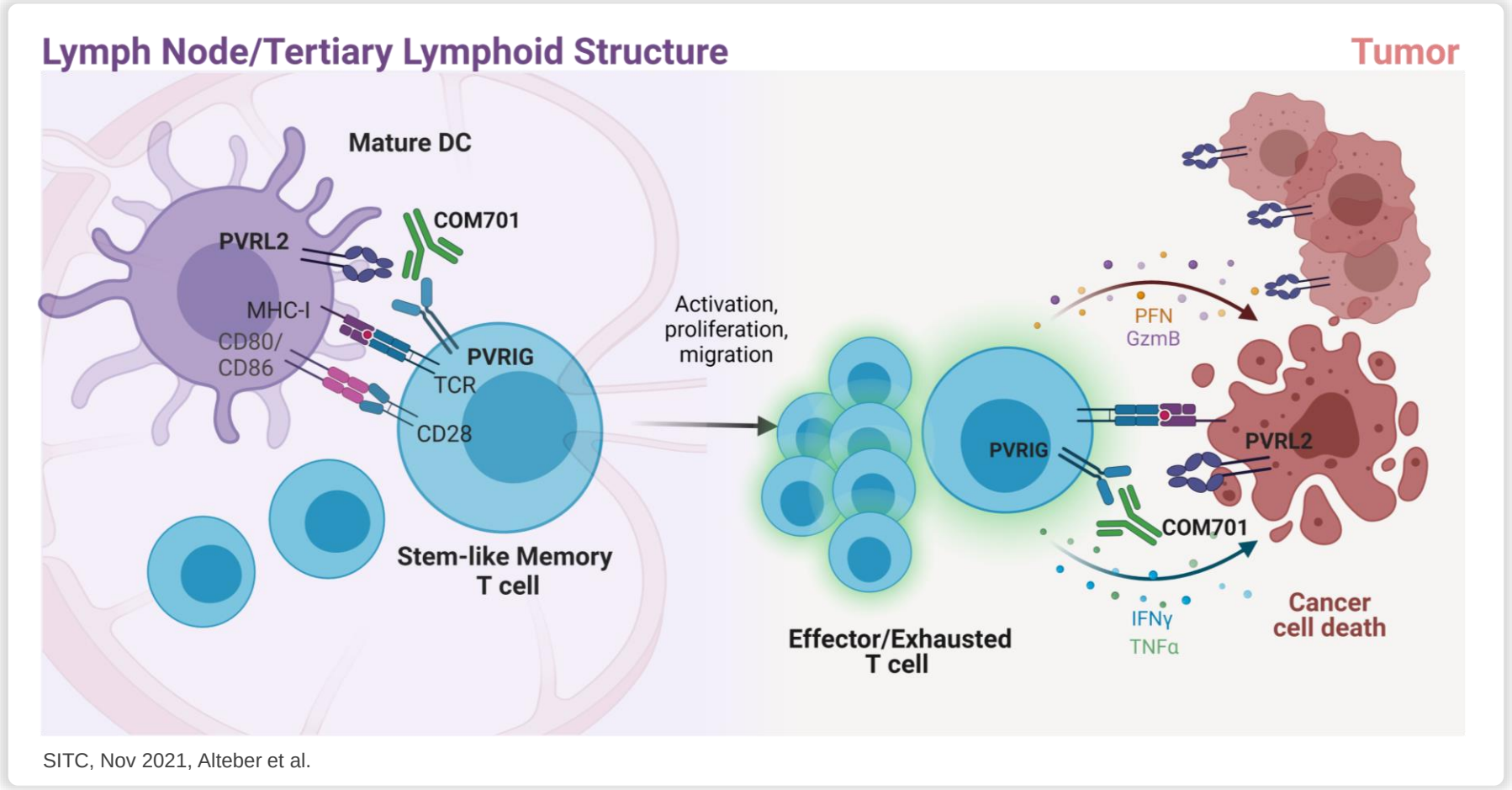
PVRIG+ Stem-like Memory T cells Interaction with PVRL2+ DCs Hypothesis



SITC, Nov 2021, Alteber et al.

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COM701 Clinical Programs

Phase 1 Arm A – Monotherapy	Identifier: NCT03667716	Phase 1 Arm B – Dual Combination with nivolumab	Identifier: NCT03667716
Monotherapy Dose Escalation	Monotherapy Cohort Expansion (20 patients; progressed on SOC)	Dual Combination: Escalating doses of COM701 with fixed dose of nivolumab	Dual Combination Cohort Expansion (progressed on SOC)
All-comers (progressed on SOC)	Ovarian, Breast, Endometrial and CRC (MSS), NSCLC	All-comers (progressed on SOC)	Ovarian, Breast, Endometrial and CRC (MSS)
Enrollment completed; data presented at AACR '20 and ASCO June '21	Enrollment completed; data presented at ASCO June '21	Initial data presented at AACR '20; updated data presented at ASCO June '21	First patient dosed Q2 '21 N=20 per arm

Phase 1/2– Triple Combination	Identifier: NCT04570839	Phase 1 – Combination with COM902	Identifier: NCT04354246
Triple Combination Dose Escalation Escalating doses of COM701 with fixed doses of nivolumab + BMS-986207	Triple Combination Cohort expansion	Dual Combination Evaluation for Safety/Tolerability COM902 + COM701 (both at RDFE)	Dual Combination Cohort Expansion COM902 + COM701
All-comers (progressed on SOC) Data presented at SITC Nov 2021	Ovarian, Endometrial, HNSCC, additional tumor types with high PVRL2 expression First patient dosed Q3 '21 N=20 per arm	All-comers (progressed on SOC) First patient dosed Q3 '21	HNSCC, NSCLC, CRC (MSS) First patient dosed Q4 '21 N=20 per arm

Study Objectives	Safety & Tolerability, PK/PD, Preliminary anti-tumor activity

RDFE: Recommended dose for expansion
HNSCC: Head and neck squamous cell cancer; 2 cohorts: IO-naïve cohort and cohort with prior IO therapy

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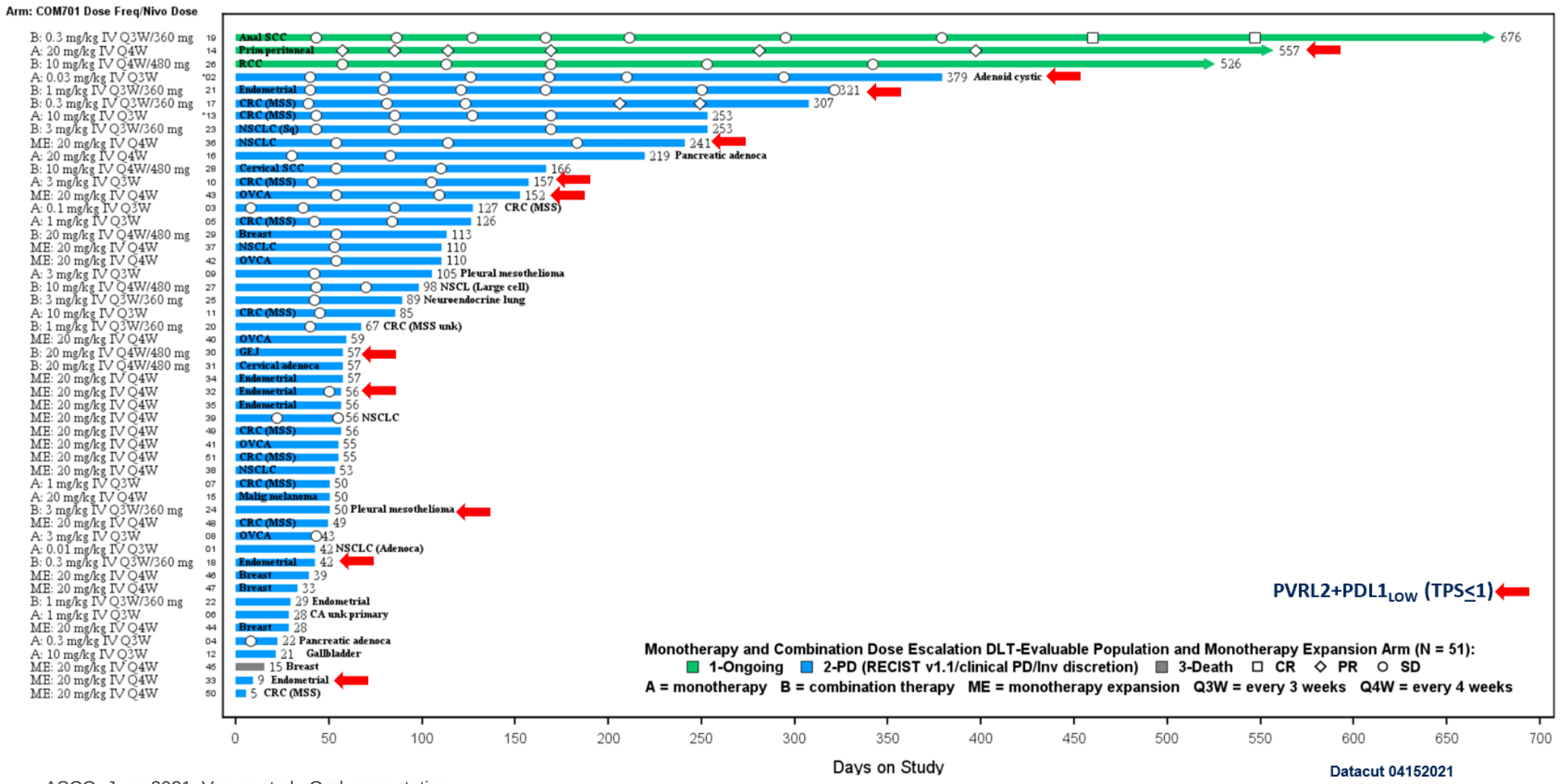
COM701 Monotherapy and Nivolumab Combination Therapy: Swimmer Plot



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

Preliminary anti-tumor activity also in patients with PVRL2^{+}PDL1^{low} tumors

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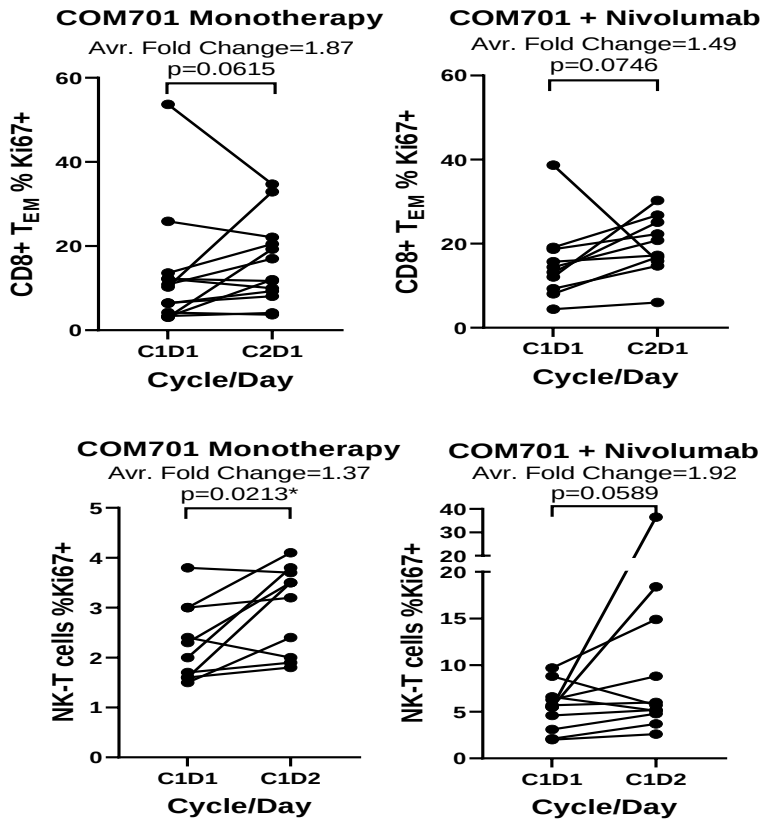
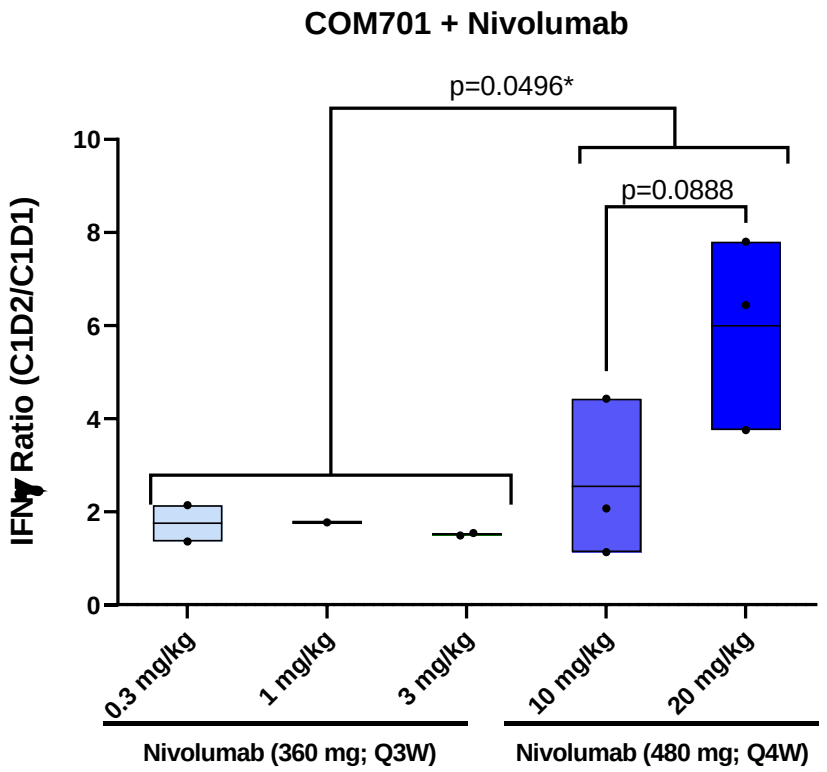
Increased Immune activation in Peripheral Blood of Patients Treated with COM701 Monotherapy and Nivolumab Combination Therapy

A trend of increasing proliferation of CD8+ T_{EM} (effector memory T cells) and NK-T cells in peripheral blood



Increase in serum IFNγ upon COM701+nivolumab treatment with a trend for COM701 dose dependency



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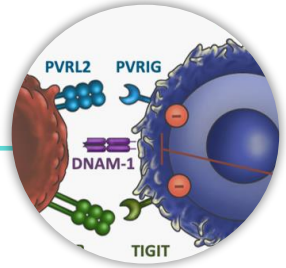
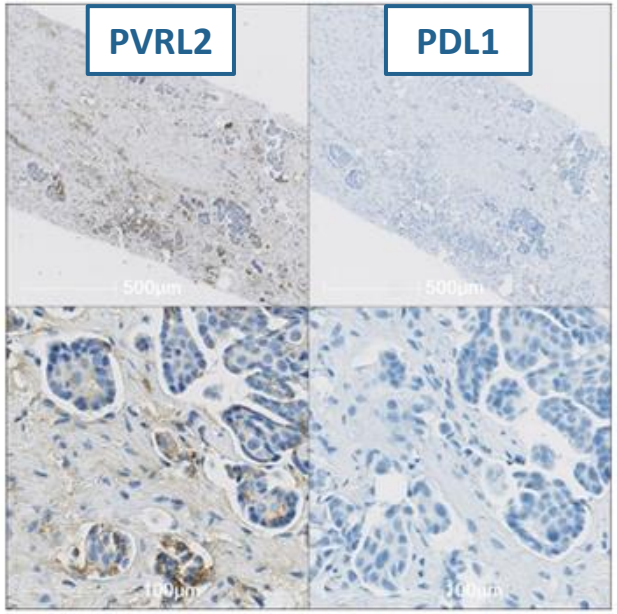
Confirmed PR in Patient with Primary Peritoneal PD-L1^{neg} Cancer Treated with COM701 Monotherapy

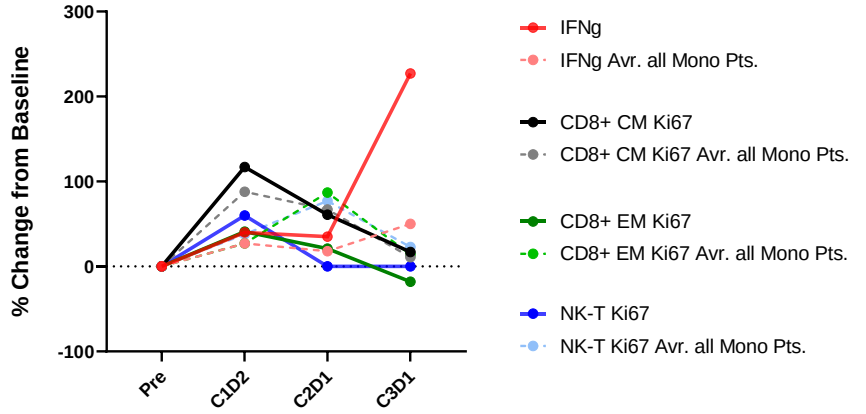


Patient received 3 prior lines of anti cancer therapy



- 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

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 following COM701 monotherapy

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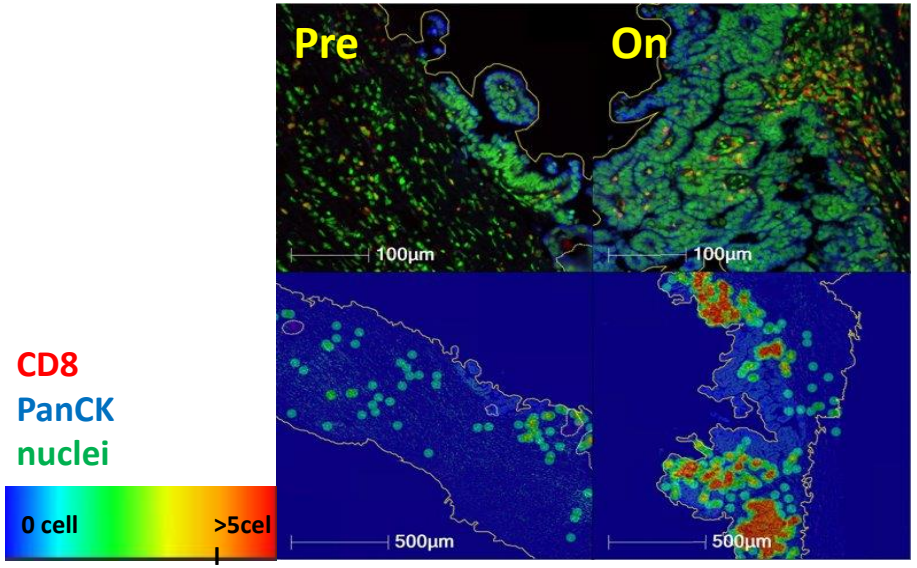
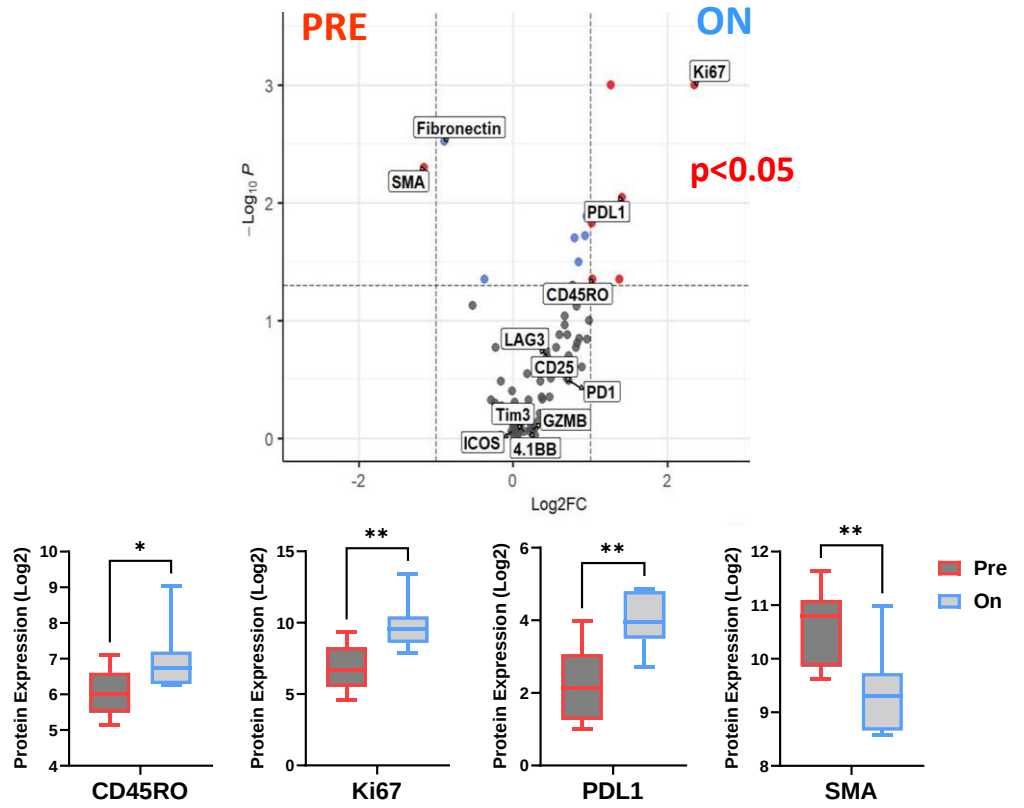
COM701 Monotherapy Induced Immune Activation in TME of Patient with Ovarian Cancer (Radiologically PD)

CD8 distribution in TME



% CD8 cells	1.4	5.9
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 PVRL2^{high} (H-score=250) PDL1 (8% TPS) ovarian cancer demonstrating shift from stromal markers towards immune activation in TME following COM701 monotherapy

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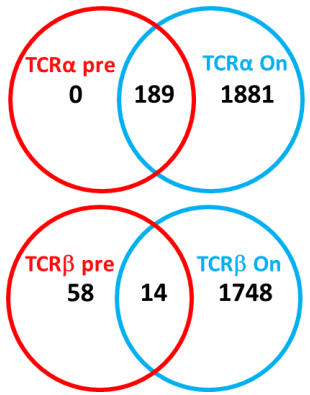
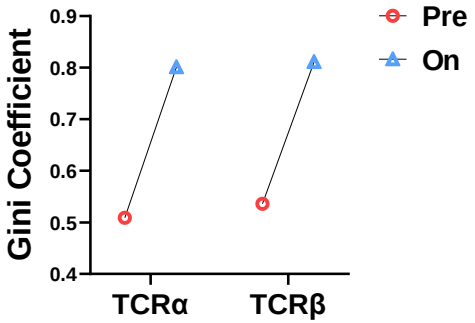
Increased TME Immune Activation and TCR Clonality in Patient with CRC (MSS) with PR to COM701+nivolumab Combination Therapy

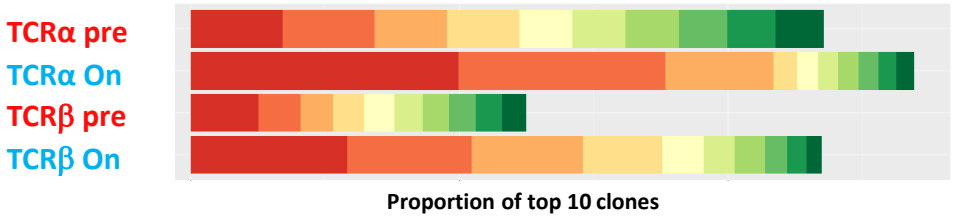
Patient received 4 prior lines of anti cancer therapy

Induced number of clones

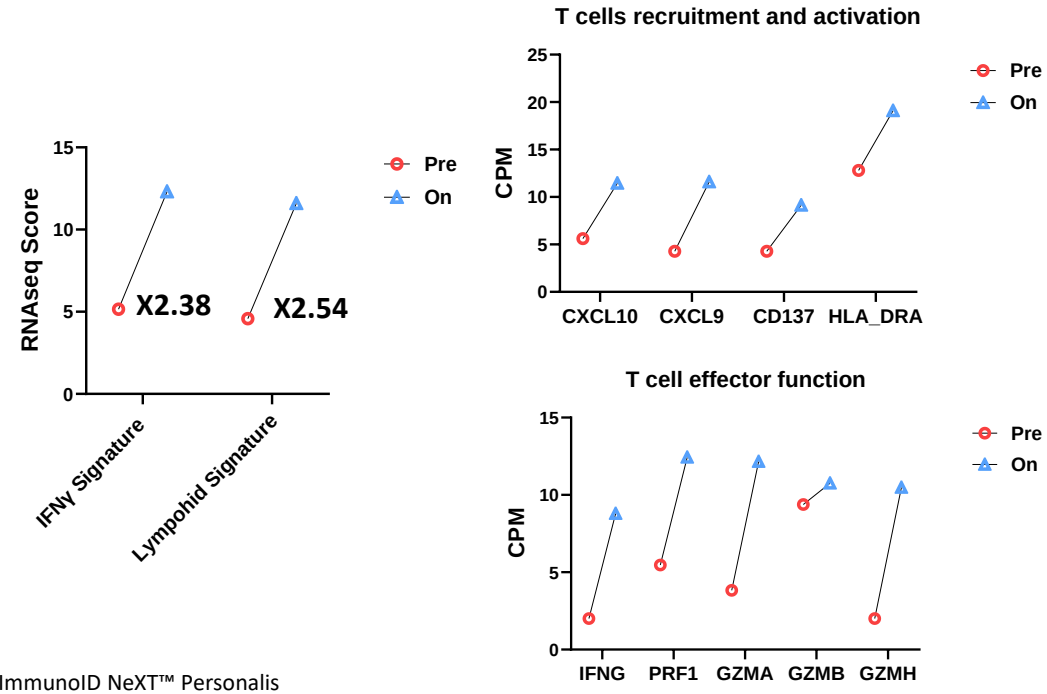


Increased clonal expansion





Increased Immune infiltration and activation



ImmunoID NeXT™ Personalis

Patient with PVRL2⁺ (H-score=25) PDL1^{low} (1% TPS) MSS-CRC demonstrating increase in TCR numbers and clonality and T cell infiltration and activation in TME following COM701+nivolumab combination

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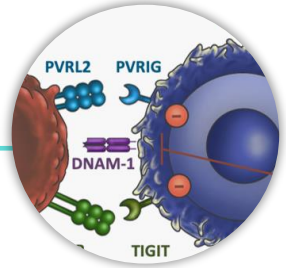
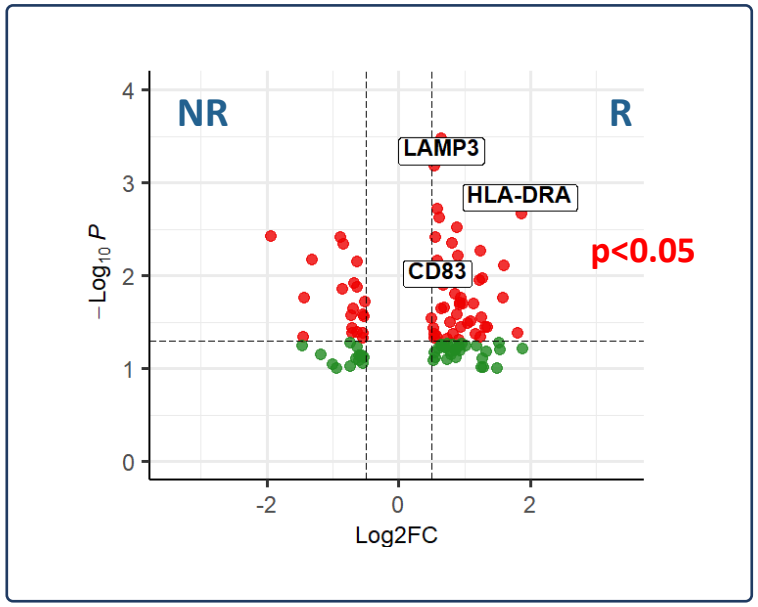
Combination of COM701+nivolumab Induced Markers of Activated DCs in Serum of 2 Responding Patients



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



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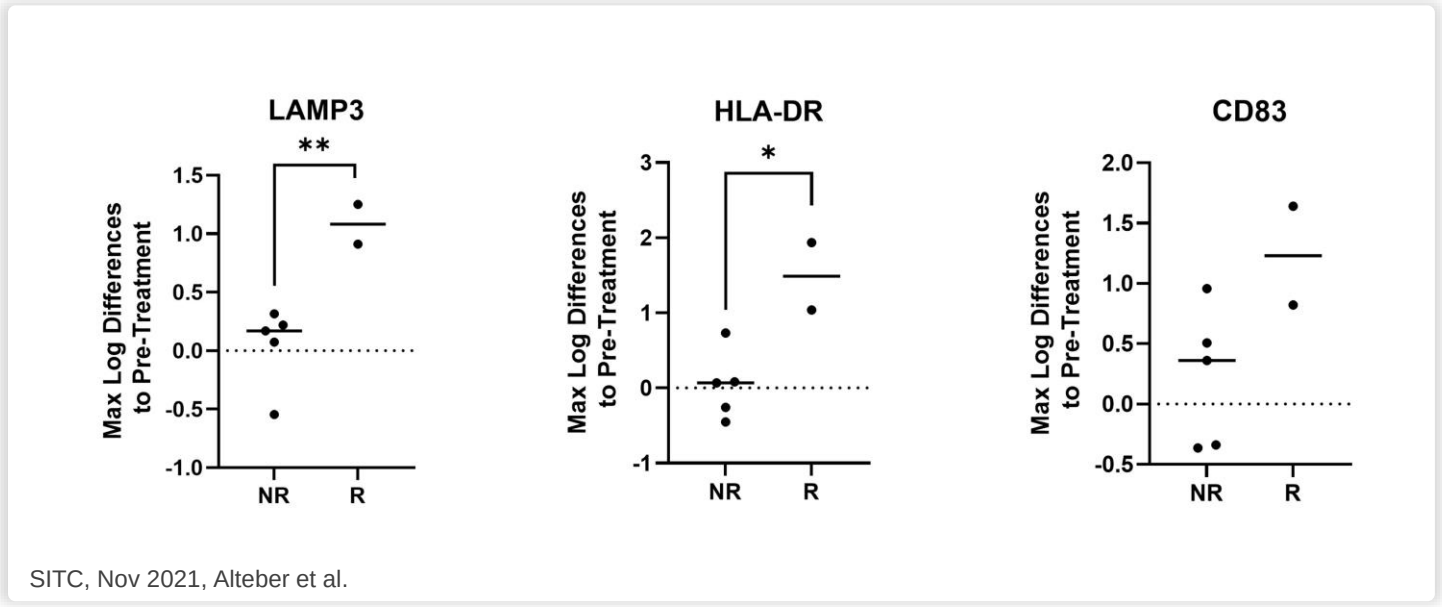

SITC, Nov 2021, Alteber et al.

Induction of activated-DC markers in serum of 2 patients that clinically responded to COM701+nivolumab, compared to non-responders

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Summary

- PVRIG, a novel checkpoint in the DNAM-1 axis, expressed on stem-like and exhausted T cells but has a unique dominant expression on early differentiated Tscm
- PVRL2 (ligand for PVRIG) and PVR (ligand for TIGIT) are expressed in PD-L1^{low} and PD-L1^{high} tumor types
- PVRL2 is dominantly expressed across DC types and in Tertiary Lymphoid Structures
- PVRIG blockade may enhance Tscm activation by DCs, resulting in their increased expansion and differentiation. A potential mechanism which could lead to increased T cell expansion and infiltration into less 'inflamed' tumors
- Preliminary data shows that COM701 (anti-PVRIG) monotherapy induced immune activation in periphery and signs of anti-tumor activity in patients with PVRL2^{+}PD-L1^{low} tumors
- Data shows increased infiltration and activation of T cells in TME of patient treated with COM701 monotherapy
- Dual (PVRIG & PD-1) blockade resulted in increased T cell clonality and activation in TME of CRC (MSS) responding patient and increased induction of activated DC markers in serum of 2 patients responding to this therapy
- Dual (PVRIG & TIGIT or PVRIG & PD-1) and triple blockade (PVRIG & TIGIT & PD-1) clinical trials are ongoing

Thank you.

Our Vision

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

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