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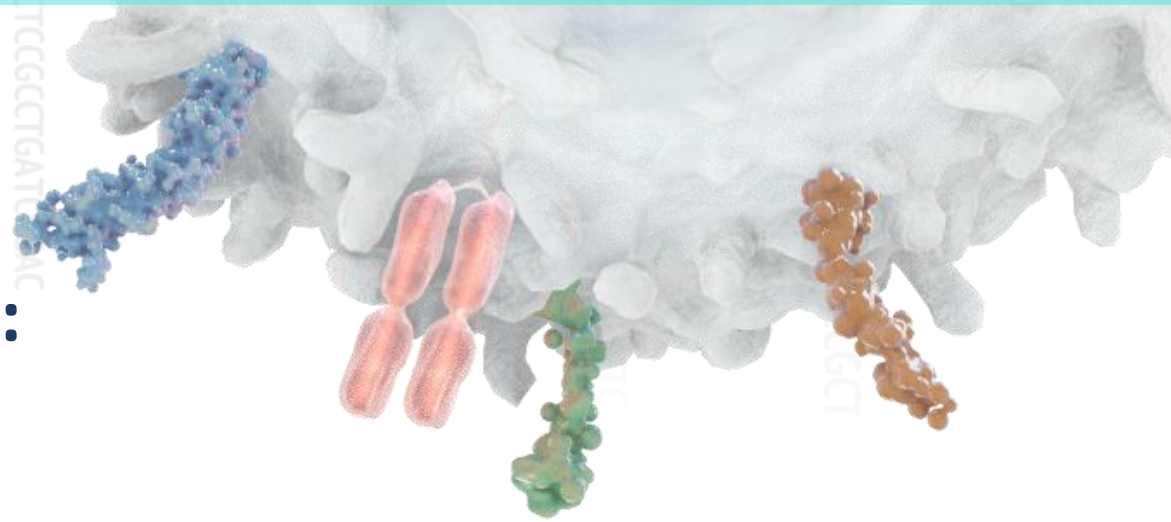

PVRIG and TIGIT immune checkpoint blockade in cancer: Emerging translational data from clinical trials

AIS 2022 – Montpellier – 28 June 2022

Pierre Ferré – VP Preclinical Development

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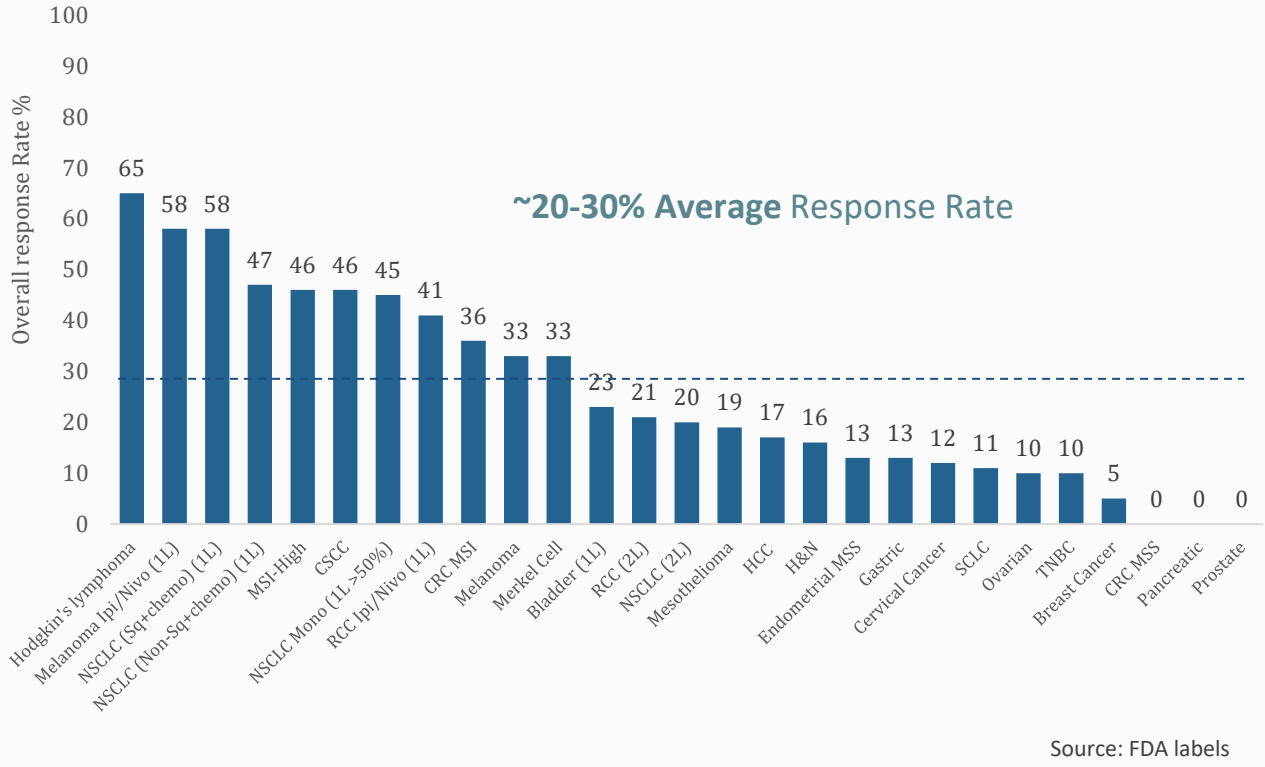
Opportunities to address a significant unmet need

70-80% of patients non-responsive to approved cancer immunotherapies

PD-1 monotherapy/combination activity across indications



Source: FDA labels

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- Clinical strategy primarily focused on PD-1 non-responsive cancer indications
- New drug targets and biological pathways aimed to address non-responsive patient populations
- Mechanism-driven first-in-class combinations
- Biomarker strategy to select patients based on pathway expression profile

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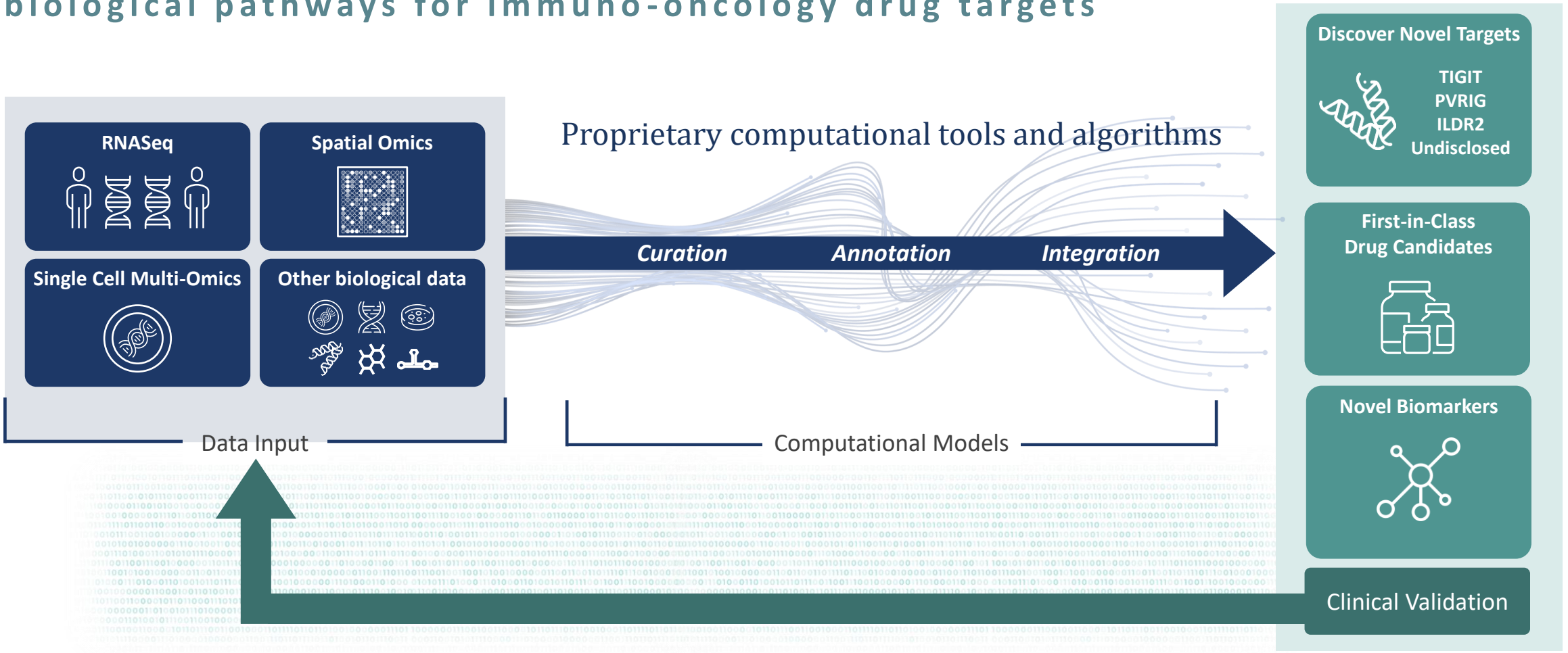
Pioneering predictive computational discovery platform

Proven computational approach to discover new biological pathways for immuno-oncology drug targets



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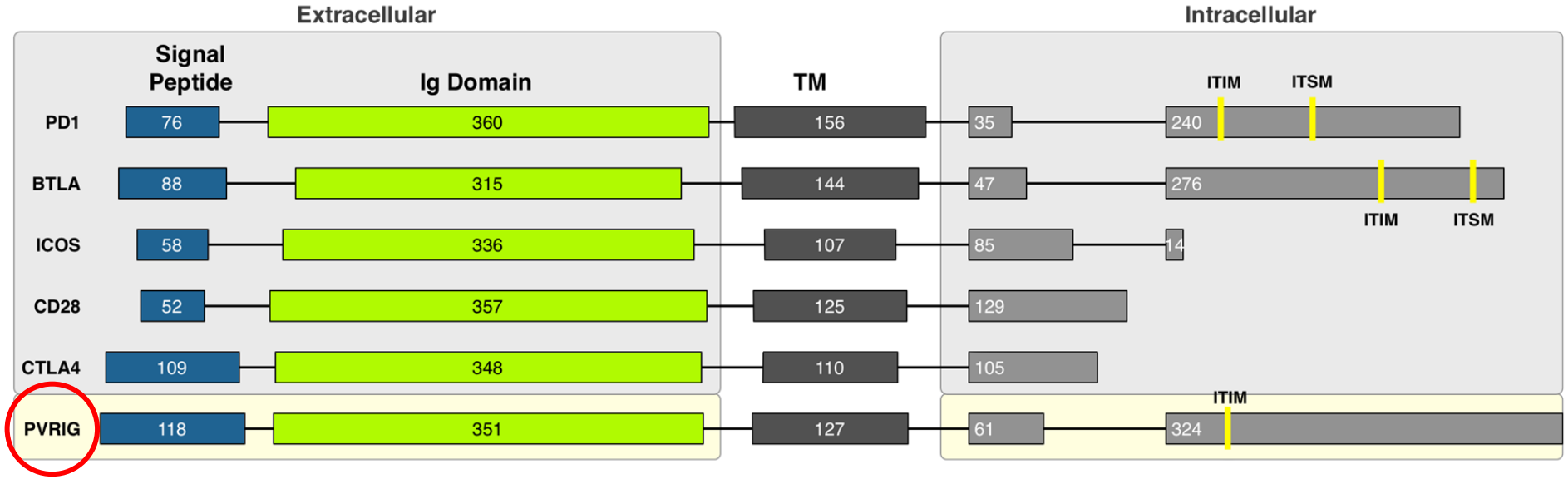
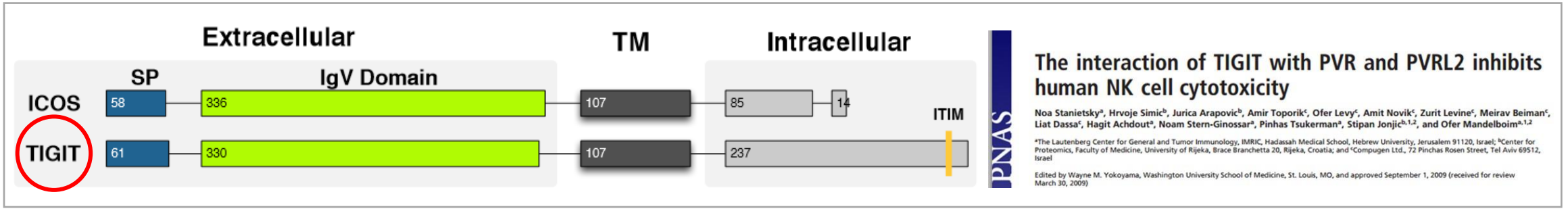
“Functional homology”: B7/CD28 immune checkpoints have a distinct extracellular gene structure



TIGIT identified by Compugen as a potential immune checkpoint in 2009



PNAS

The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity

Noa Stanietsky[a], Hrvoje Simic[b], Jurica Arapovic[b], Amir Toporik[c], Ofer Levy[c], Amit Novik[c], Zurit Levine[c], Meirav Beiman[c], Liat Dassa[c], Hagit Achdout[a], Noam Stern-Ginossar[a], Pinhas Tsukerman[a], Stipan Jonjic[b,1,2], and Ofer Mandelboim[a,1,2]

[a]The Lautenberg Center for General and Tumor Immunology, IMRIC, Hadassah Medical School, Hebrew University, Jerusalem 91120, Israel; [b]Center for Proteomics, Faculty of Medicine, University of Rijeka, Brace Branchetta 20, Rijeka, Croatia; and [c]Compugen Ltd., 72 Pinchas Rosen Street, Tel Aviv 69512, Israel

Edited by Wayne M. Yokoyama, Washington University School of Medicine, St. Louis, MO, and approved September 1, 2009 (received for review March 30, 2009)

PVRIG and TIGIT functional gene structure matches known immune checkpoint receptors

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Innovative in-house discovered immuno-oncology portfolio

From Code to Cure® – Discovery to Clinical

PROGRAM TARGET	**PARTNER**	**INDICATION**	**STAGE OF DEVELOPMENT**
COM701 PVRIG		NSCLC, Breast, Ovarian, Endometrial and CRC (MSS)	Phase 1
COM701 + Opdivo® PVRIG, PD-1	**Bristol Myers Squibb**	Ovarian, Breast, Endometrial and CRC (MSS)	Phase 1
COM701 + Opdivo® + BMS-986207 PVRIG, PD-1, TIGIT	**Bristol Myers Squibb**	Ovarian, Endometrial, HNSCC and High PVRL-2 expressing tumors	Phase 1/2
COM902 TIGIT		Advanced Solid Tumors, Multiple Myeloma	Phase 1
COM902 + COM701 TIGIT, PVRIG		HNSCC, NSCLC, CRC (MSS)	Phase 1
Early-Stage Programs (including Myeloid Programs)		Undisclosed	Drug Discovery
Bapotulimab ILDR2*	**Bayer**	Advanced solid tumors	Phase 1
Bapotulimab + Keytruda® ILDR2, PD-1	**Bayer**	Head & Neck Squamous Cell Carcinoma	Phase 1
AZD2936 TIGIT x PD-1	**AstraZeneca**	Advanced or Metastatic Non-small Cell Lung Cancer	Phase 1/2

*Bapotulimab – previously BAY 1905254; BMS- Bristol Myers Squibb
*Dose escalation study

Compugen-owned programs Partner programs

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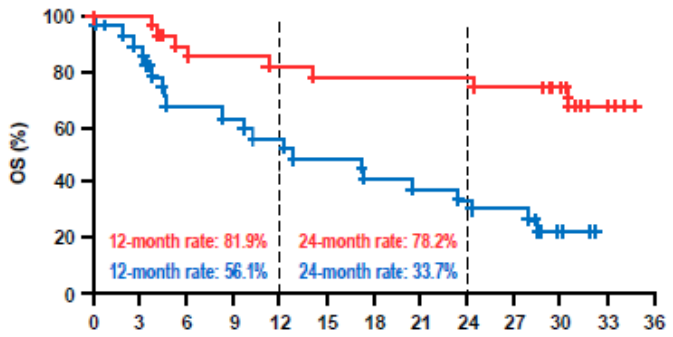
Combination of anti-TIGIT and anti-PD-L1 showed clinical efficacy only in patients with high PD-L1(≥50%)

Phase II CITYSCAPE Overall Survival

Overall survival: PD-L1 subgroups

PD-L1 TPS ≥50% (n=58)

	Events n (%)	Median OS, months (95% CI)	HR (95% CI)
Tira + atezo	8 (27.6)	NE (30.3–NE)	0.23*
Placebo + atezo	21 (72.4)	12.8 (4.7–24.2)	(0.10–0.53)

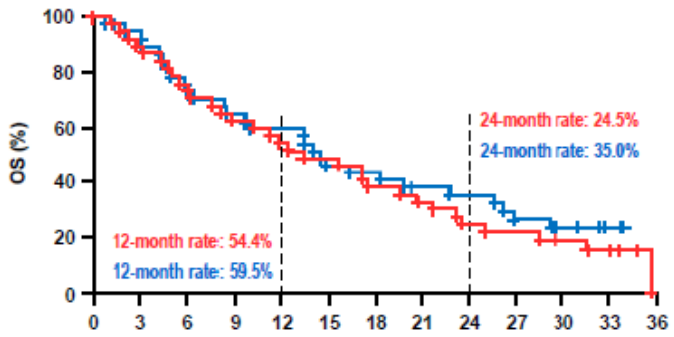


No. at risk

T + A	29	29	24	23	22	21	21	21	21	20	15	4	NE
P + A	29	25	18	17	15	13	11	10	9	8	3	NE	NE

PD-L1 TPS 1-49% (n=77)

	Events n (%)	Median OS, months (95% CI)	HR (95% CI)
Tira + atezo	32 (84.2)	13.3 (8.0–20.7)	1.16*
Placebo + atezo	28 (71.8)	14.5 (8.3–25.6)	(0.70–1.94)



No. at risk

T + A	38	34	28	23	20	18	14	12	9	8	5	4	NE
P + A	39	35	28	24	22	17	16	13	12	9	5	2	NE

ESMO IMMUNO-ONCOLOGY

*Unstratified

Updated analysis data cut-off: 16 August 2021 (median follow-up: 30.4 months)

Source: Roche; ESMO IO 2021

But no benefit of TIGIT in PD-L1 low patients

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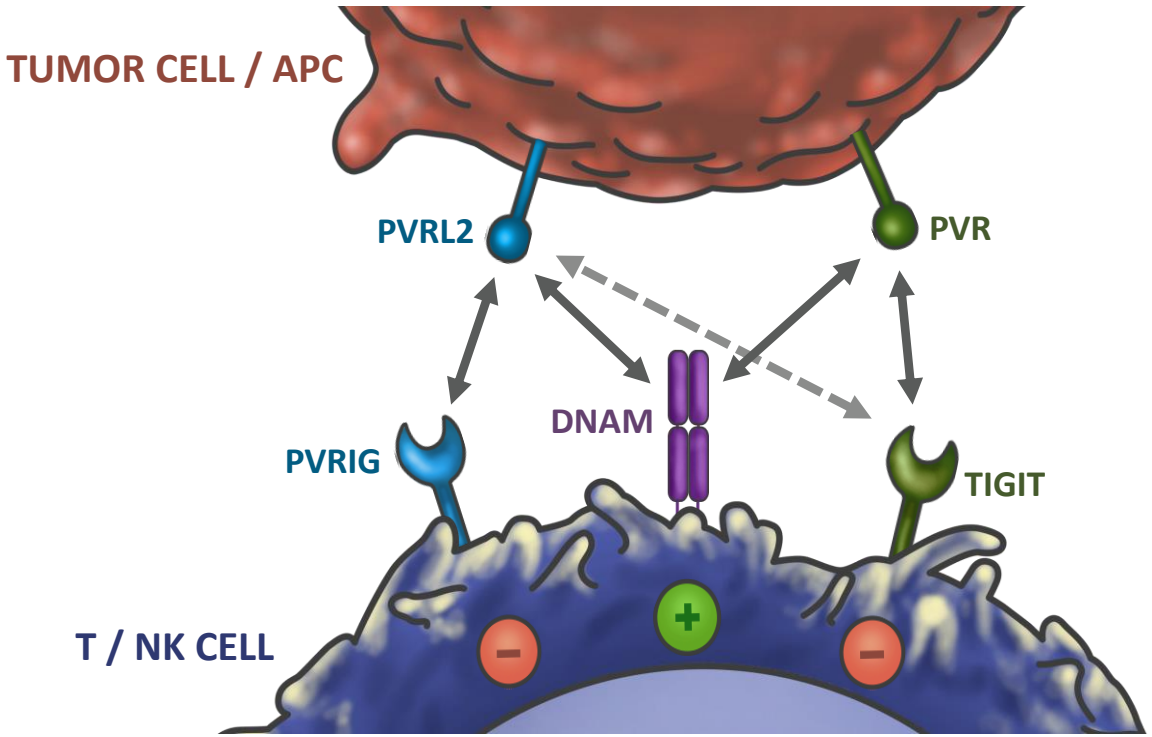
PVRIG and TIGIT biology

DNAM-1 axis plays 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 ; DNAM delivers activating signal
- TIGIT/PVRIG has higher affinity to PVR/PVRL2 than DNAM-1 (decoy effect)

Alteber *et al.* Cancer Discov. 2021

PVRIG blockade might be the missing piece to maximize the effect of TIGIT in non-responding patients

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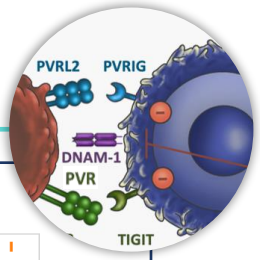
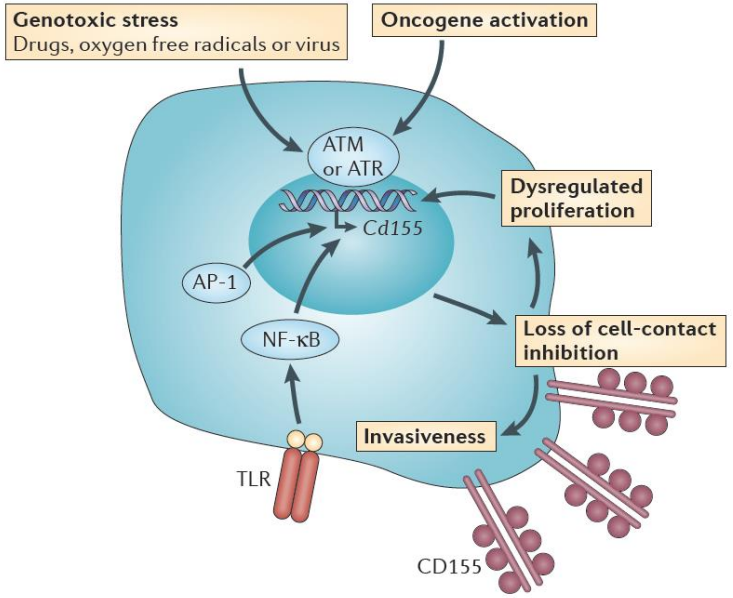
PVRL2 and PVR are expressed in both inflamed and non-inflamed tumors types



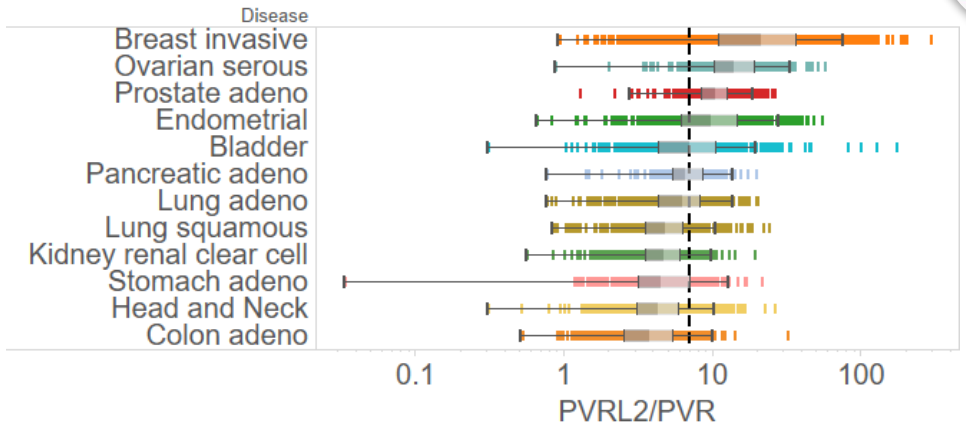
PVR/PVRL2 on tumor cells induced by:

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



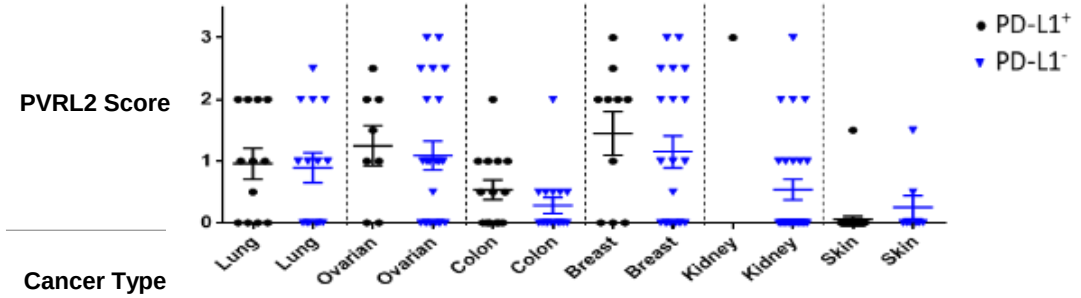
Martinet et al. Nature Rev. Imm. 2015

Cancer indications express higher PVRL2 relative to PVR



RNA (TCGA database)

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} less-inflamed tumor types

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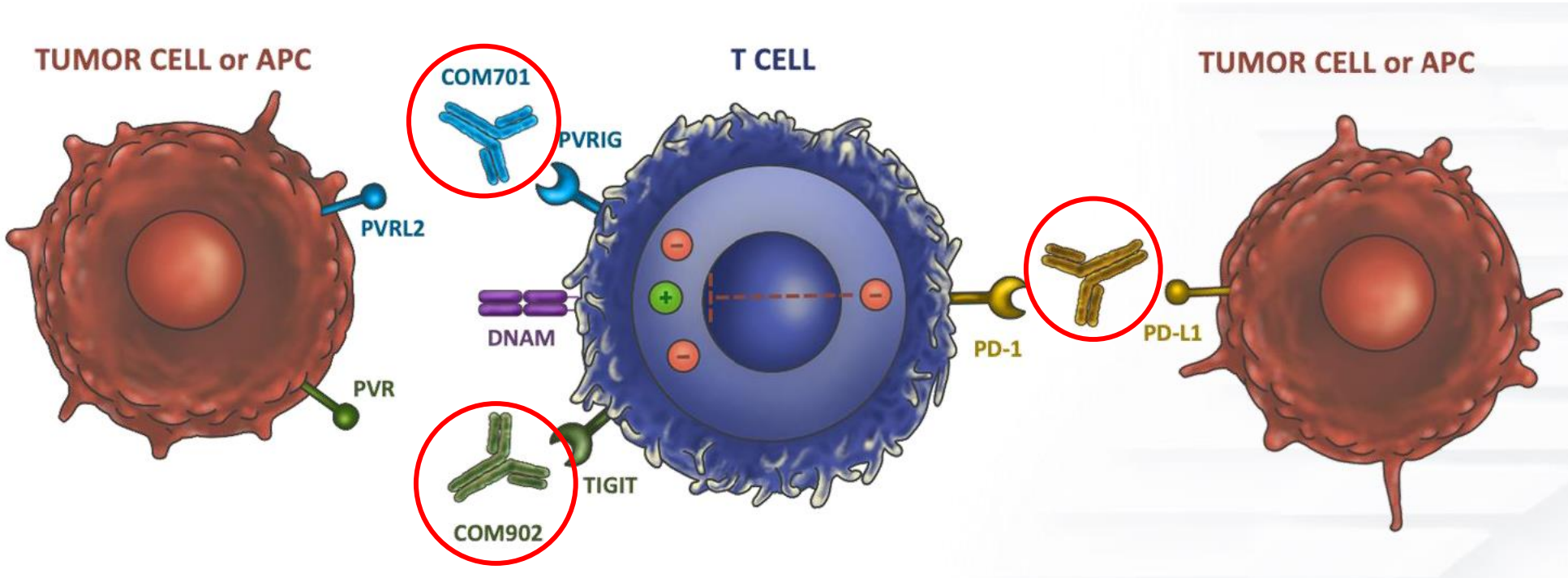
PVRIG, TIGIT and PD-1 are players in the DNAM-1 axis

PVRL2 and PVR are broadly expressed in PD-L1 positive and negative tumors



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

Intersection between TIGIT/PVRIG and PD-1 pathways support combination approach to overcome immunotherapy resistance

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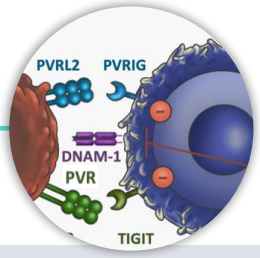
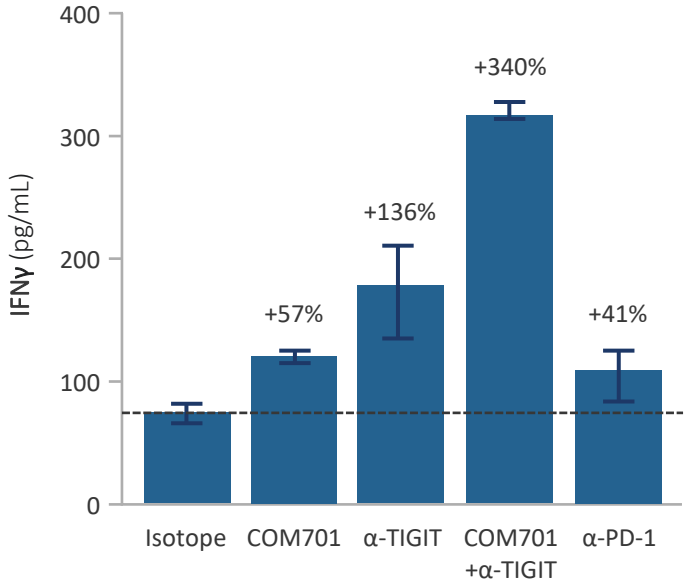
COM701 synergistic T cell activation

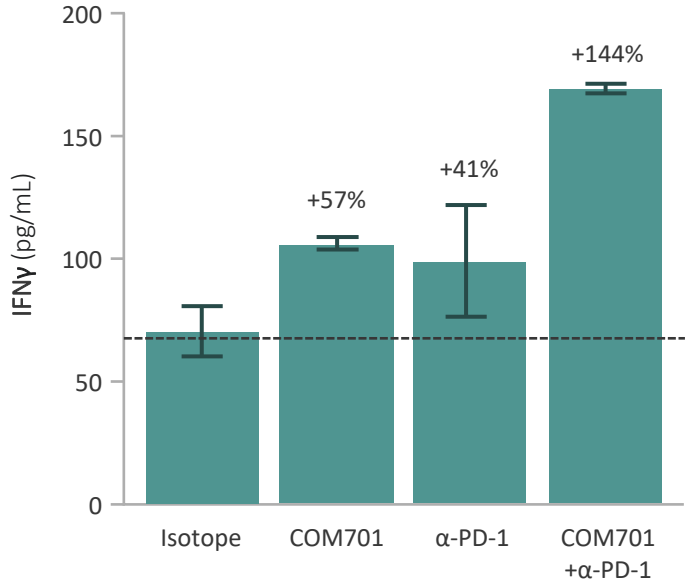
PVRIG with PD-1 and/or TIGIT inhibitors



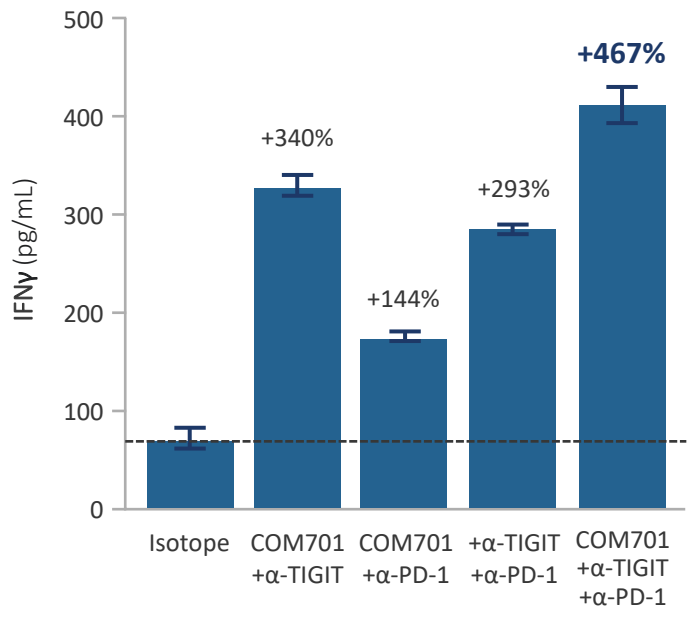
anti-PVRIG +/- anti-TIGIT



anti-PVRIG +/- anti-PD-1



Triple combination PVRIG / TIGIT / PD1 blockade



Whelan, et al., Cancer Immunol Res. 2019

CMV-specific Human CD8 T cells cocultured with CMV positive tumor cell lines

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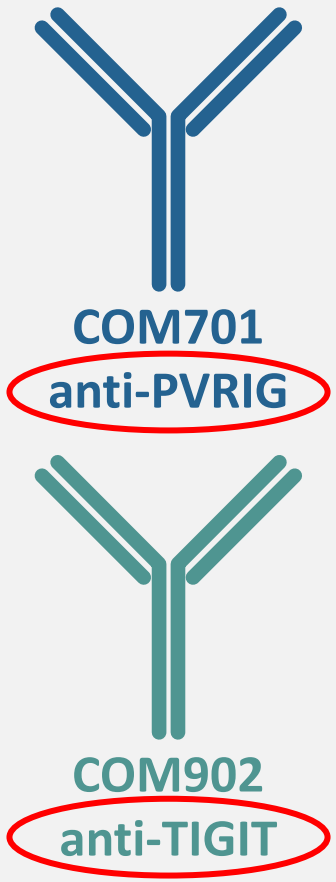
COM902 (TIGIT) and COM701 (PVRIG) clinical programs

COM701, COM902 clinical data reported

All comer patients progressed on standard of care



Open label design	COM701 dose escalation & expansion	COM701 + nivolumab dose escalation	COM701 + nivolumab + anti-TIGIT BMS-986207** dose escalation	COM902 dose escalation
Phase	1	1	1	1
# of patients	36	15	13	18
# prior therapies*	6	5	10	7
Primary endpoint	Safety & tolerability, PK/PD, preliminary anti-tumor activity			
Results presented	ASCO ‘21	ASCO ‘21	SITC ‘21	SITC ’21
CT identifier	NCT03667716	NCT03667716	NCT04570839	NCT04354246

*Median number of prior therapies

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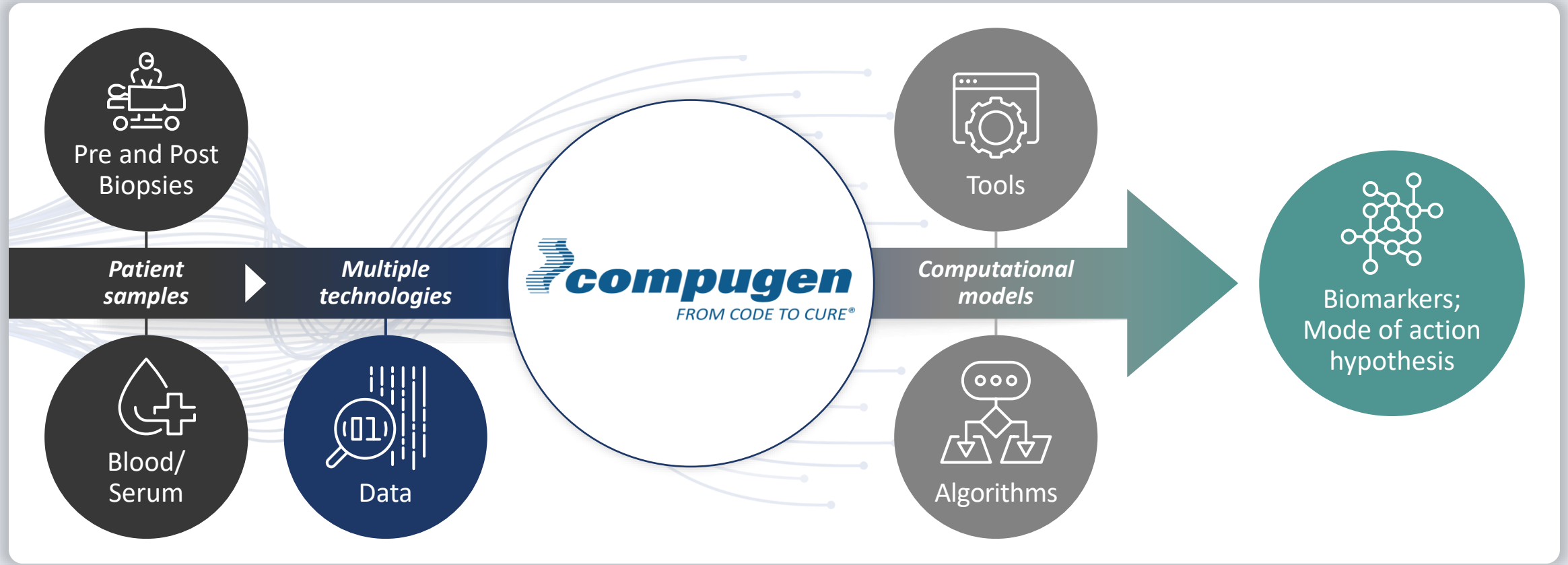
COM902 (TIGIT) and COM701 (PVRIG) clinical studies

Translational exploration



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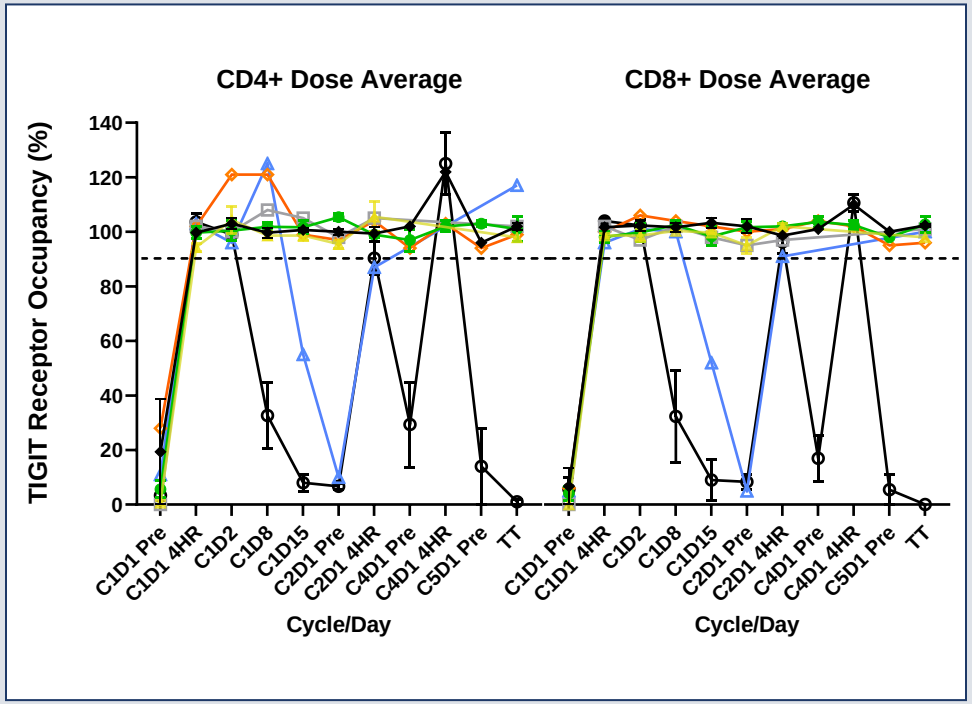
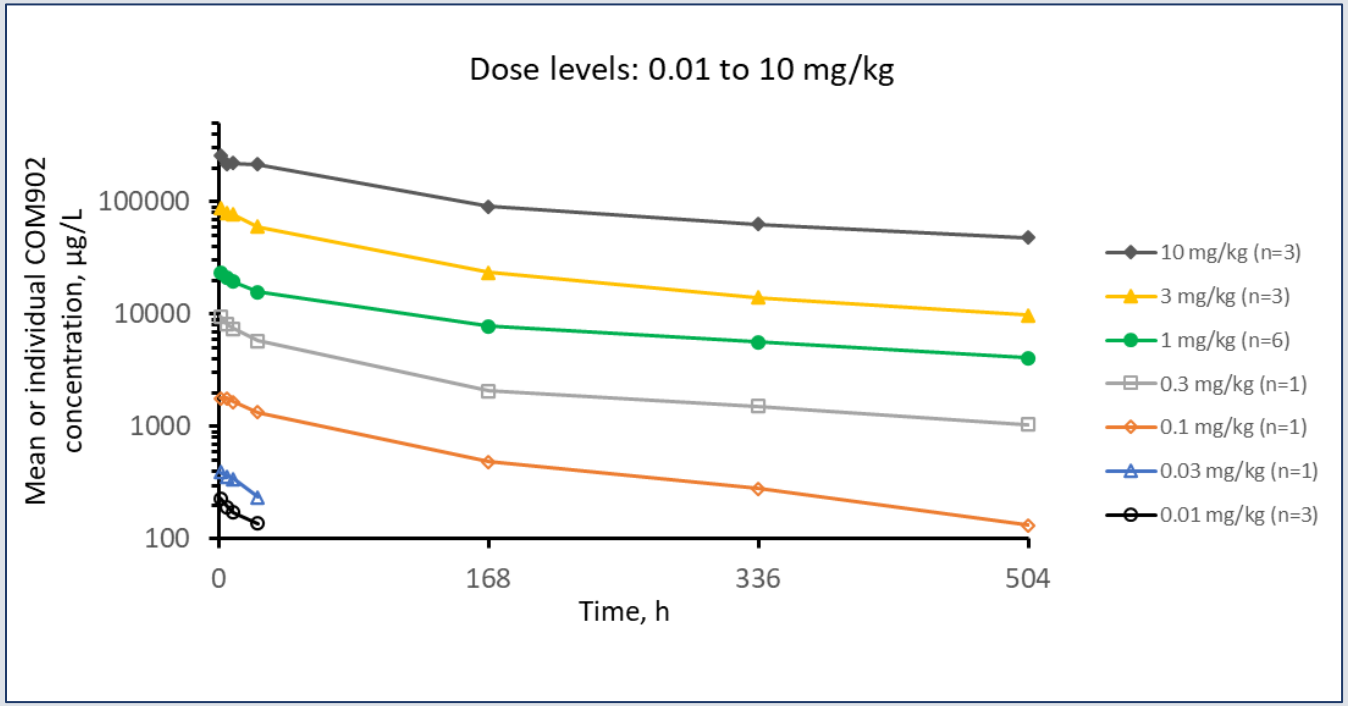
COM902 (TIGIT) translational results

COM902 (TIGIT) clinical study – receptor occupancy and PK



Mean COM902 PK serum concentration time profiles following COM902 IV Infusion in cancer patients at Cycle 1 Day 1 (study NCT04354246)



TIGIT receptor occupancy > 90% threshold over 21 days from 0.1 mg/kg ; linear pharmacokinetics

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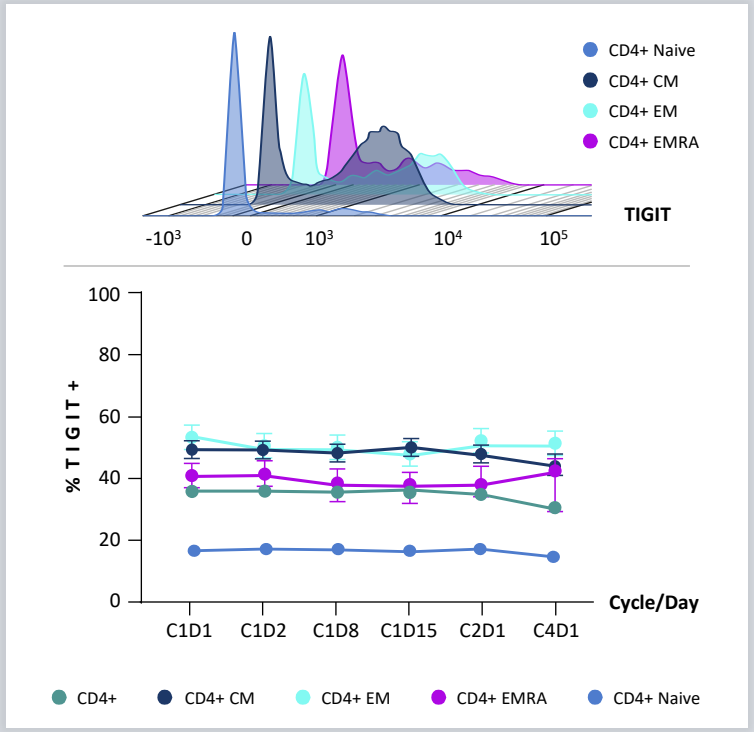
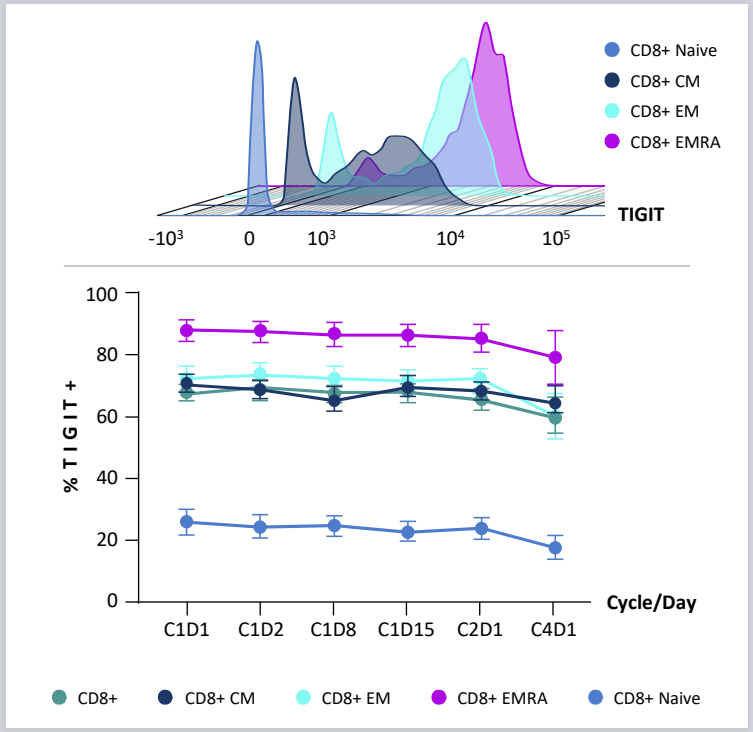
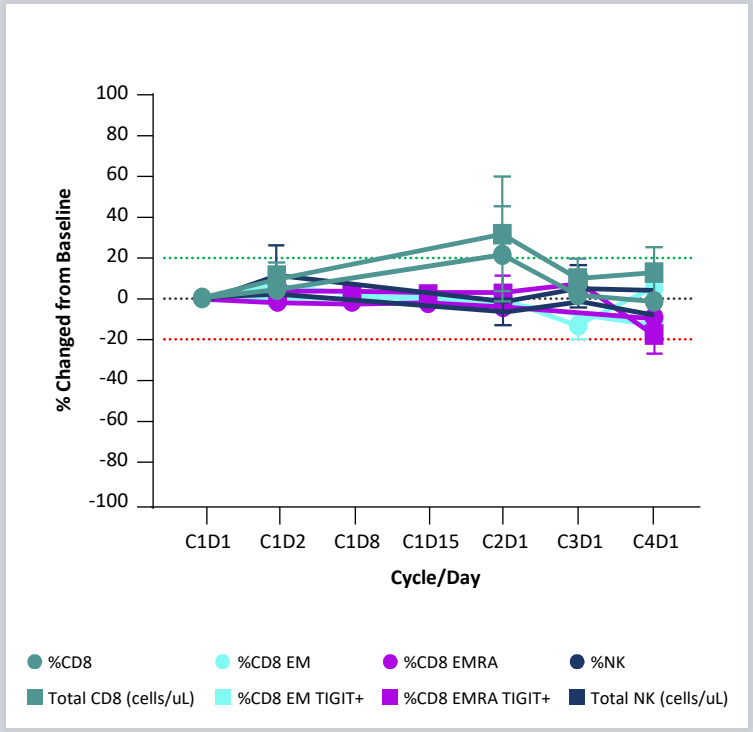
COM902 avoids depletion of major TIGIT+ expressing lymphocytes- NK, CD4 and CD8 T cells

Supporting rationale for selecting a high affinity anti-TIGIT antibody with an IgG4 backbone and low Fc effector function- COM902







Dumbrava et al, SITC November 2021 Poster Presentation, modified

COM902 avoids CD8+ T Cell depletion and potential associated risks

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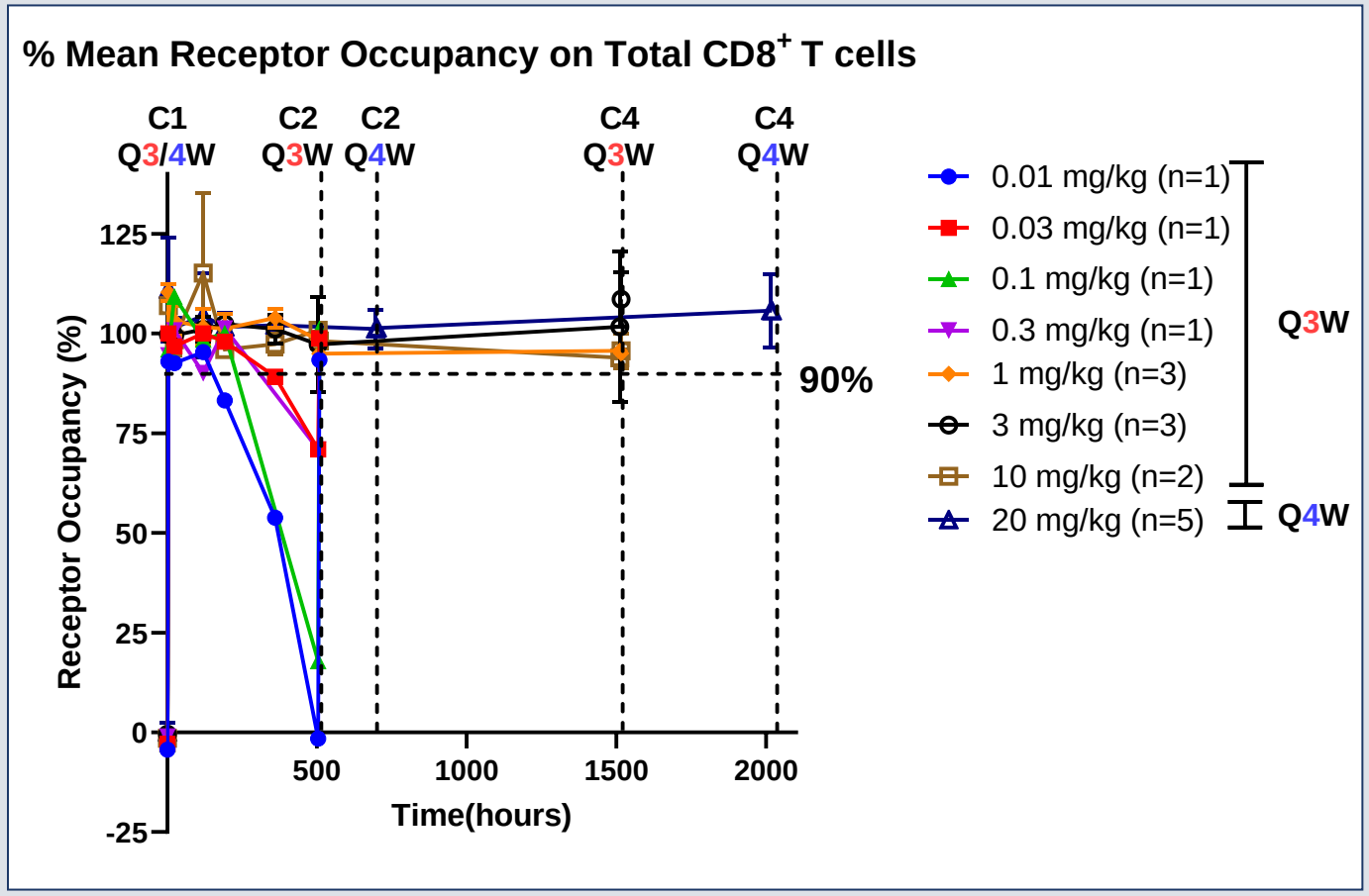
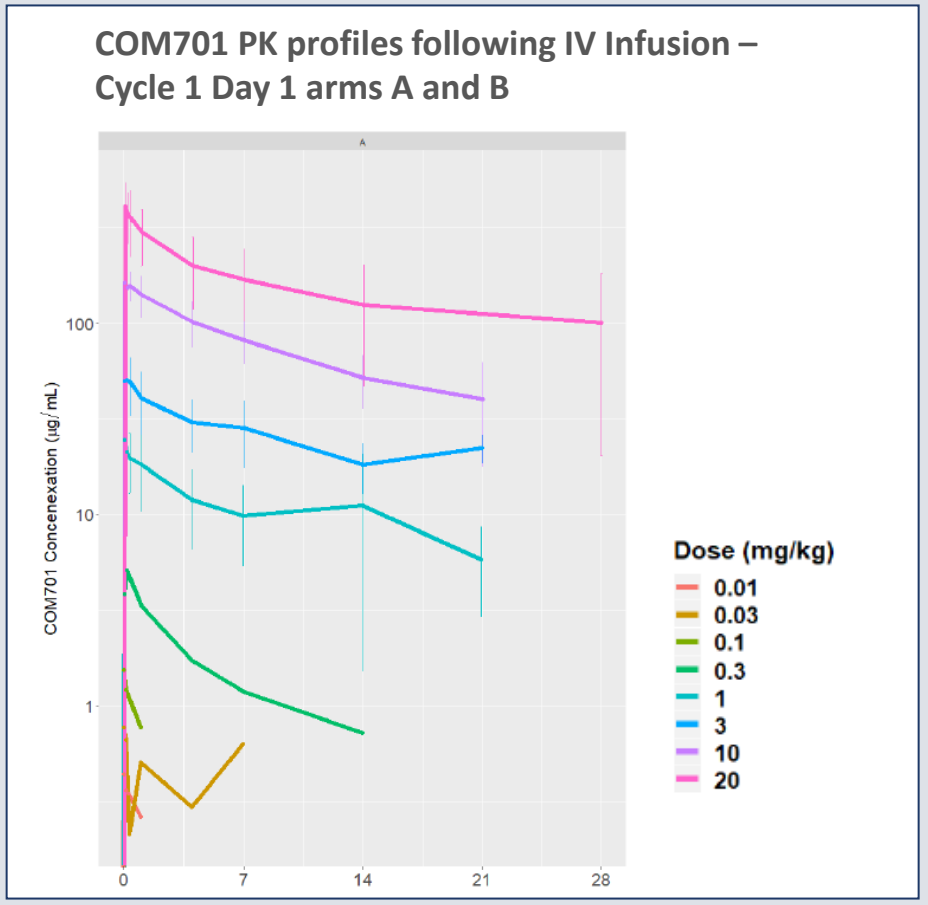
COM701 (PVRIG)translational results

COM701 (PVRIG) dose escalation – Receptor occupancy and PK





PVRIG receptor occupancy > 90% threshold over 21 days from 1 mg/kg ; linear pharmacokinetics

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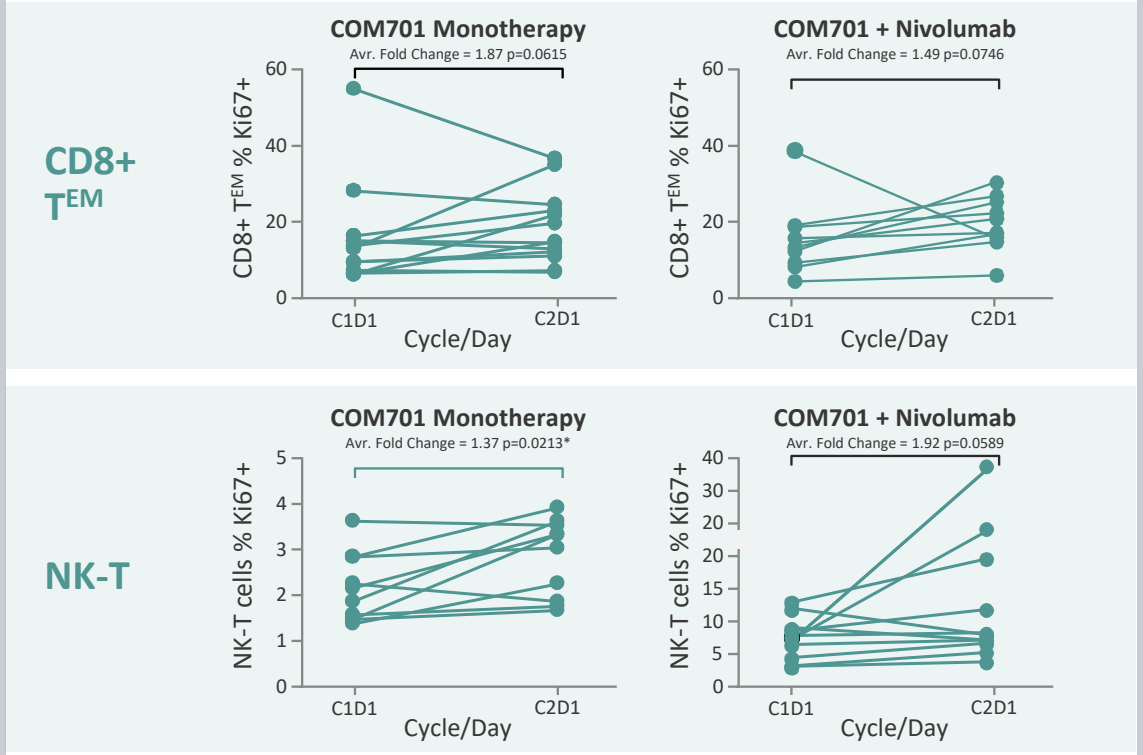
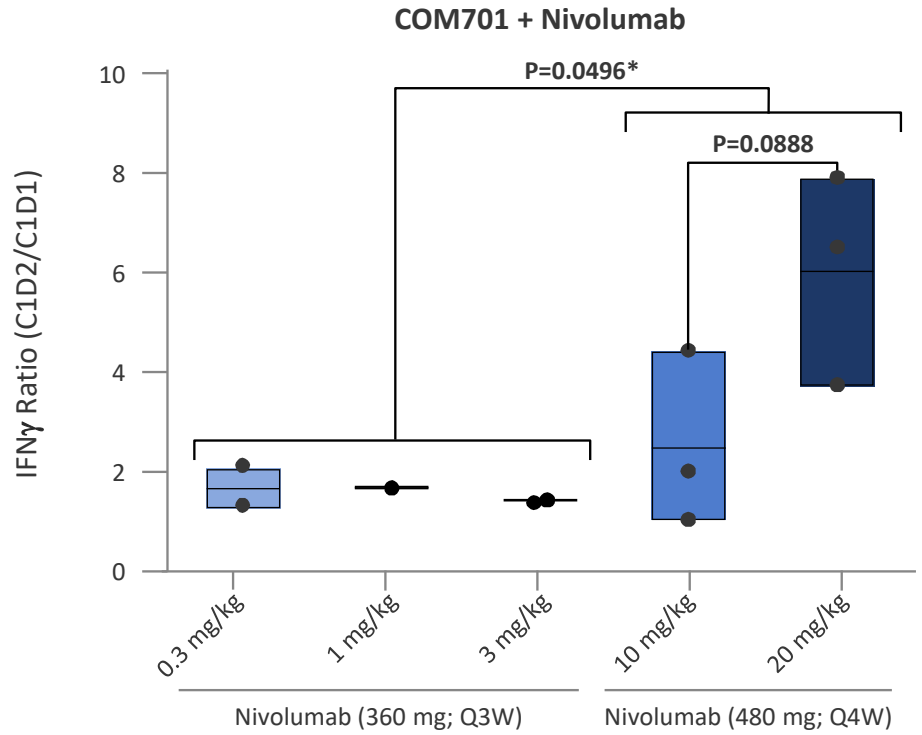
COM701 alone and with nivolumab associated with immune activation in peripheral blood

Trend of increasing proliferation of CD8+ T_{EM} (effector memory T cells) and NK-T cells



Increase in serum IFNγ with a trend for COM701 dose dependency



Modified from ASCO June 2021 Presentation

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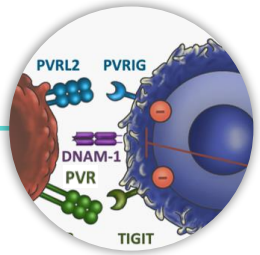
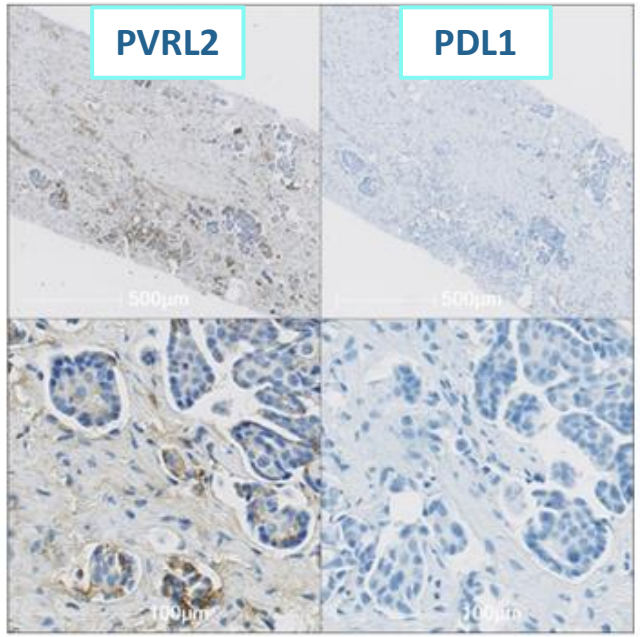
Partial response in patient with primary peritoneal cancer (platinum resistant, MSS, PD-L1^{neg})

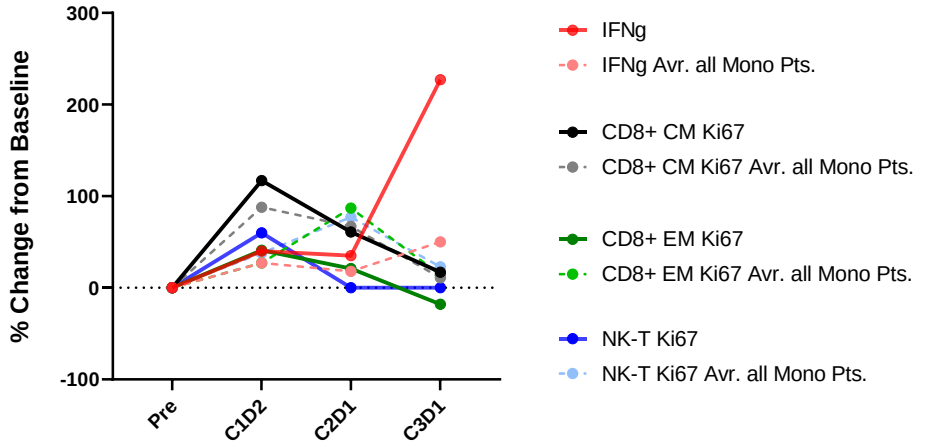
Treated with COM701 monotherapy, ongoing treatment 18 months





- 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

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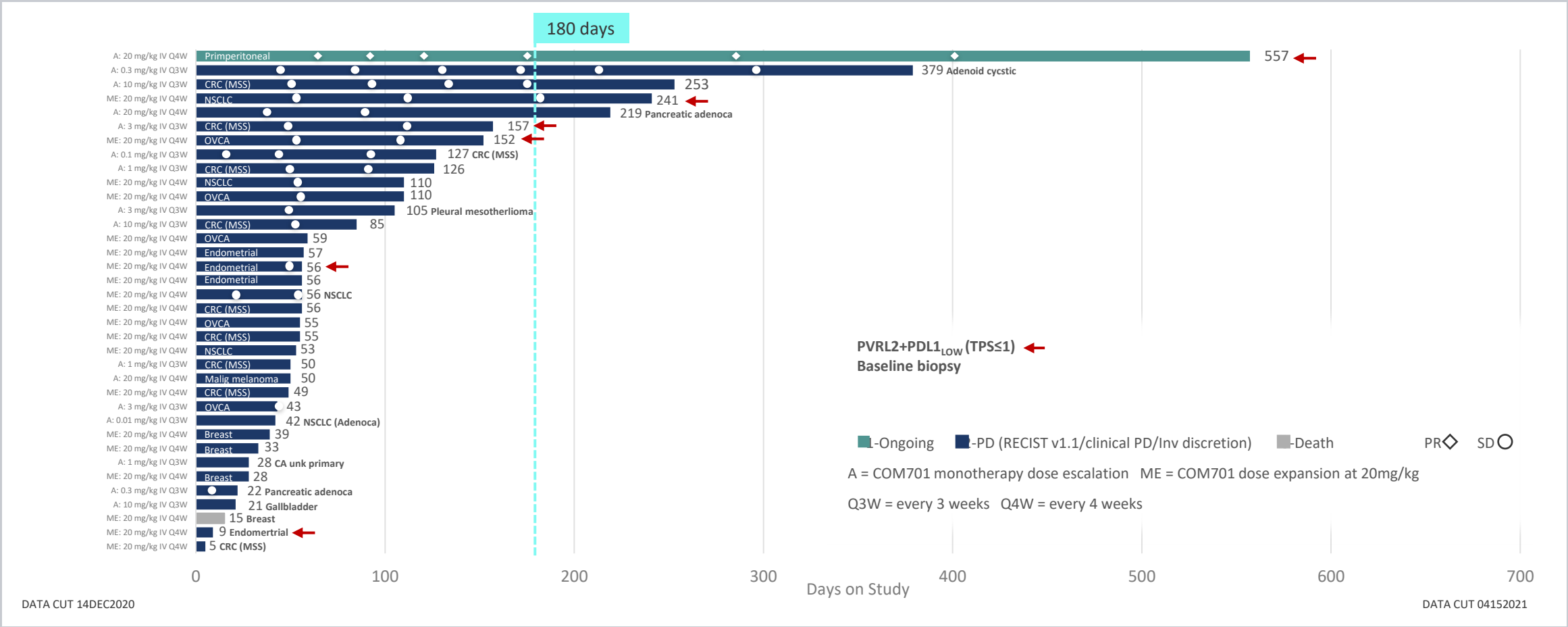
Swimmer plot COM701 monotherapy dose escalation and expansion Investigator assessed responses

Activity also seen in PD-L1 low tumors



ASCO June 2021 presentation, modified

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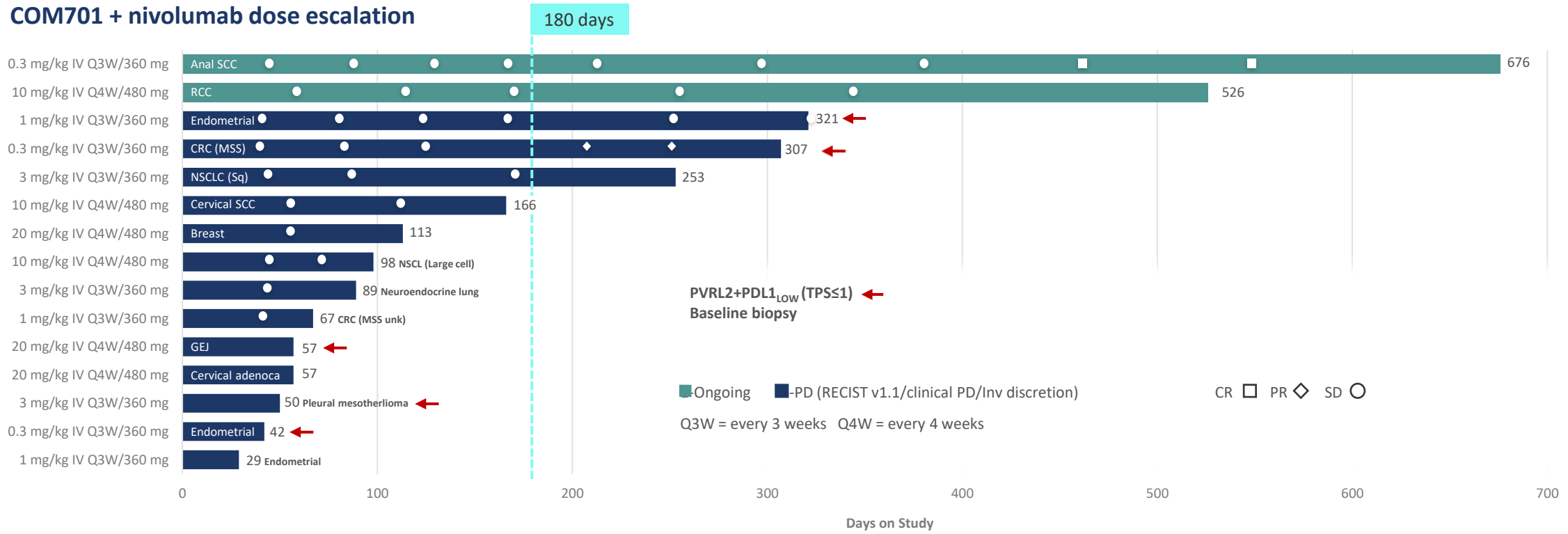
Swimmer plot COM701 with nivolumab Investigator assessed responses

Activity also seen in PD-L1 low tumors



ASCO June 2021 presentation, modified

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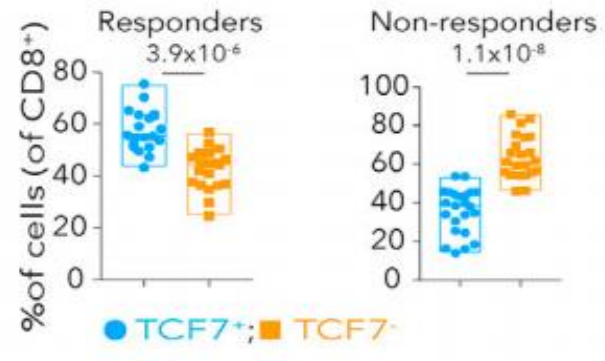
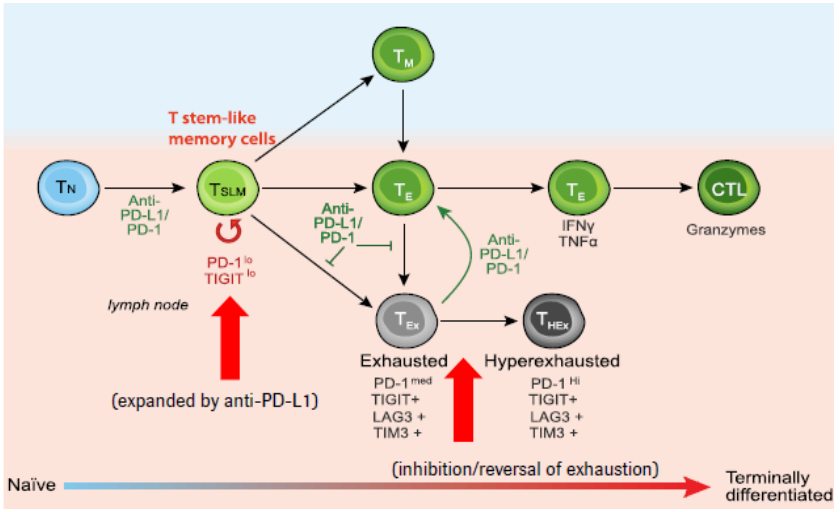
Growing evidence of early differentiated T stem-like memory cells importance in response to checkpoint blockade

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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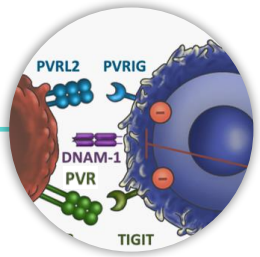
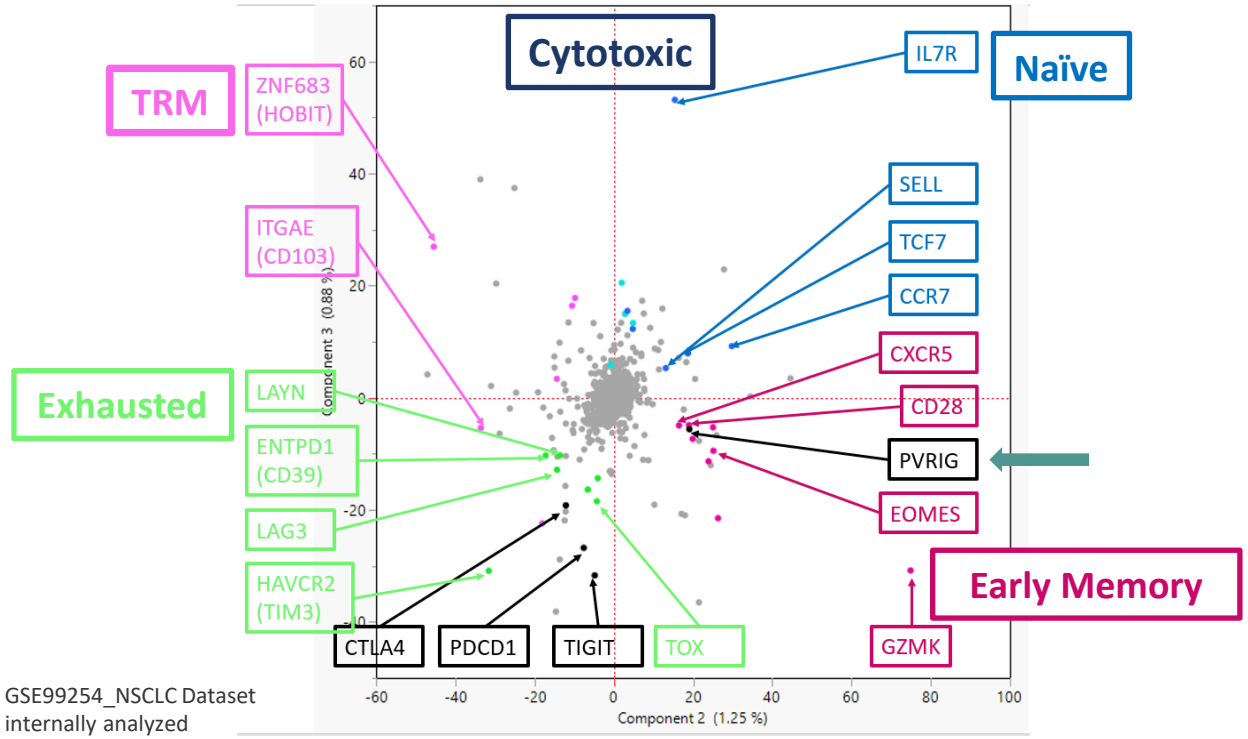
PVRIG uniquely clusters with early memory differentiation/stem-like genes



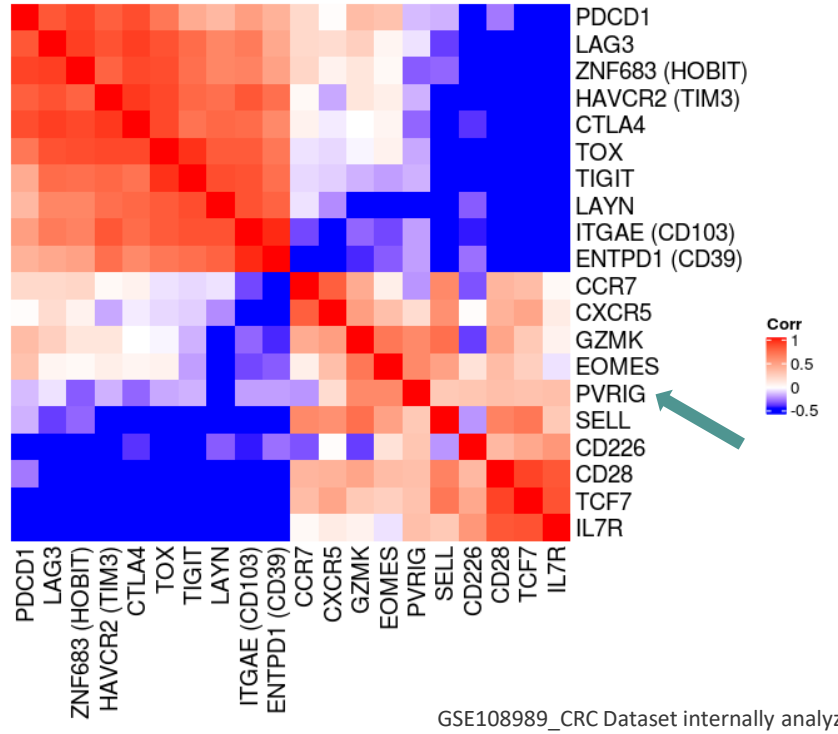
Potential for optimal Tscm activation, expansion and generation of effector T cells

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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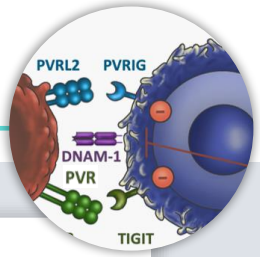
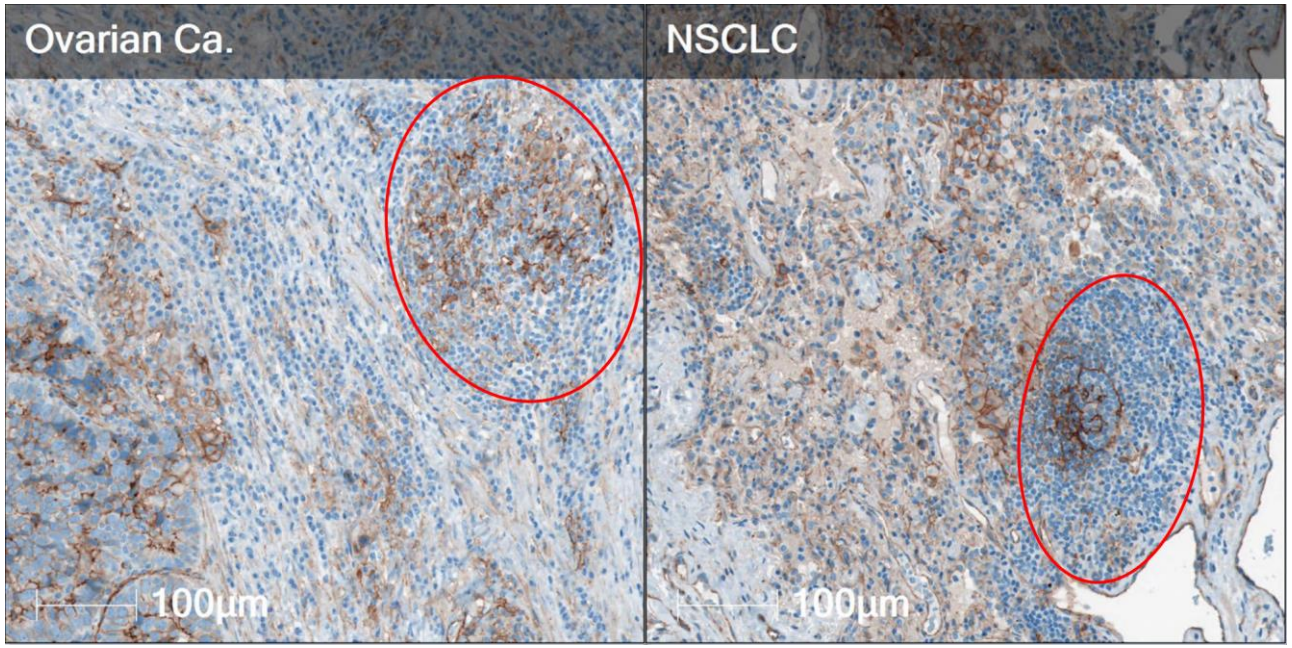
PVRL2 is expressed in tertiary lymphoid structures



PVRL2



Helmink et al Nature 2020

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

- **Predictive of PD-1 response**

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

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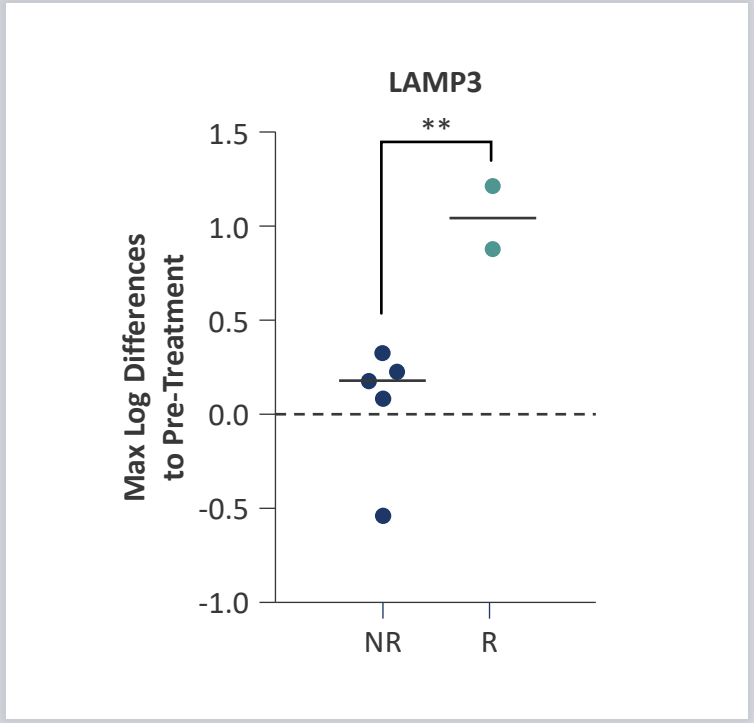
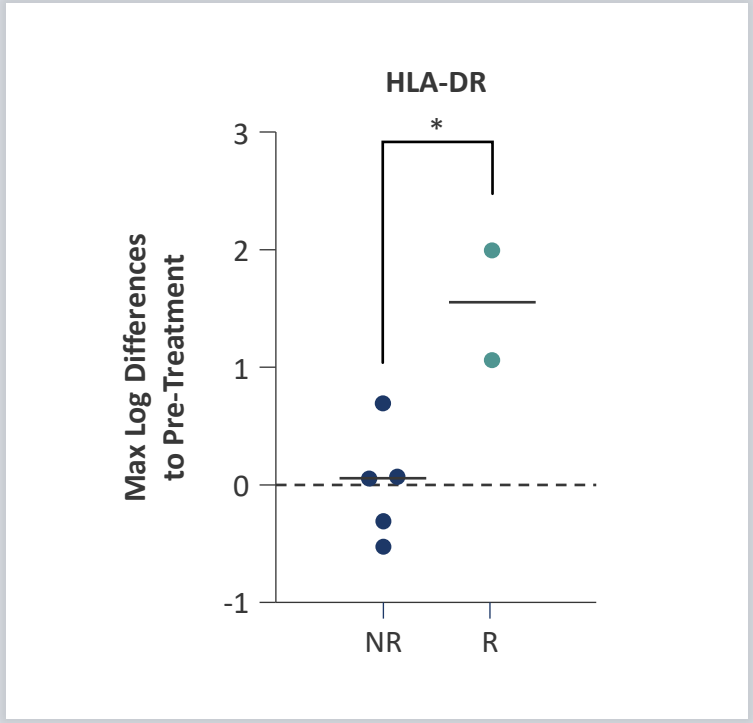
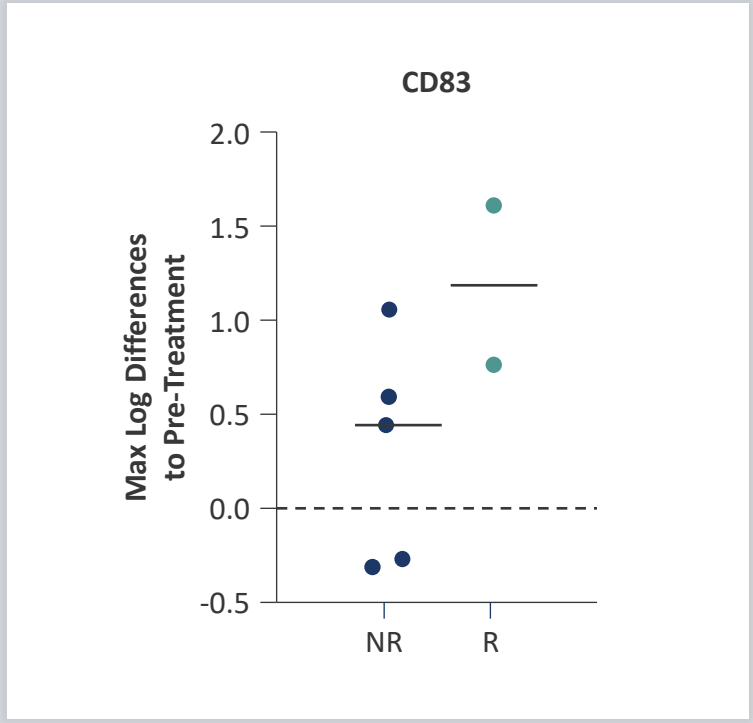
Induction of activated DC markers in serum of patients responding to COM701 + nivolumab

2 patients who responded to treatment with COM701 + nivolumab had a higher induction of activated DC markers in their serum compared to non-responders







Alteber et al, SITC November 2021 Poster Presentation, modified

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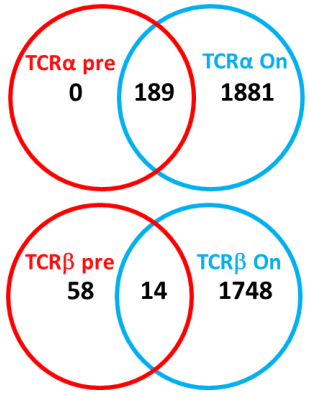
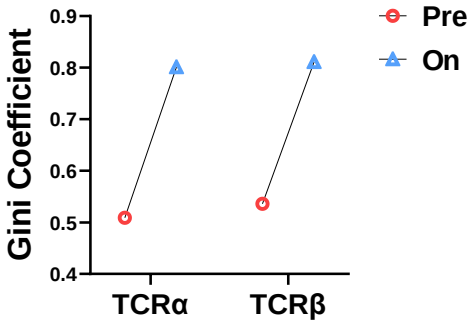
Increased TME immune activation and TCR clonality in patient with CRC (MSS) with PR to COM701+nivolumab combination therapy

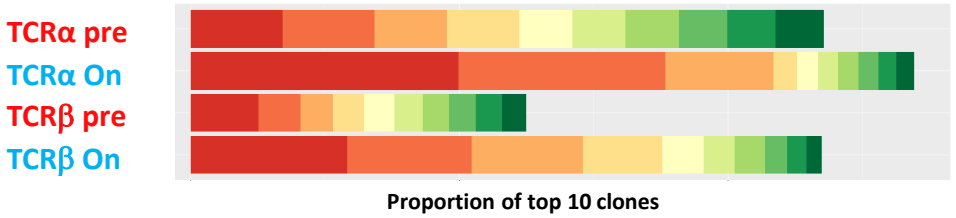
Patient received 4 prior lines of anti cancer therapy

Induced number of clones

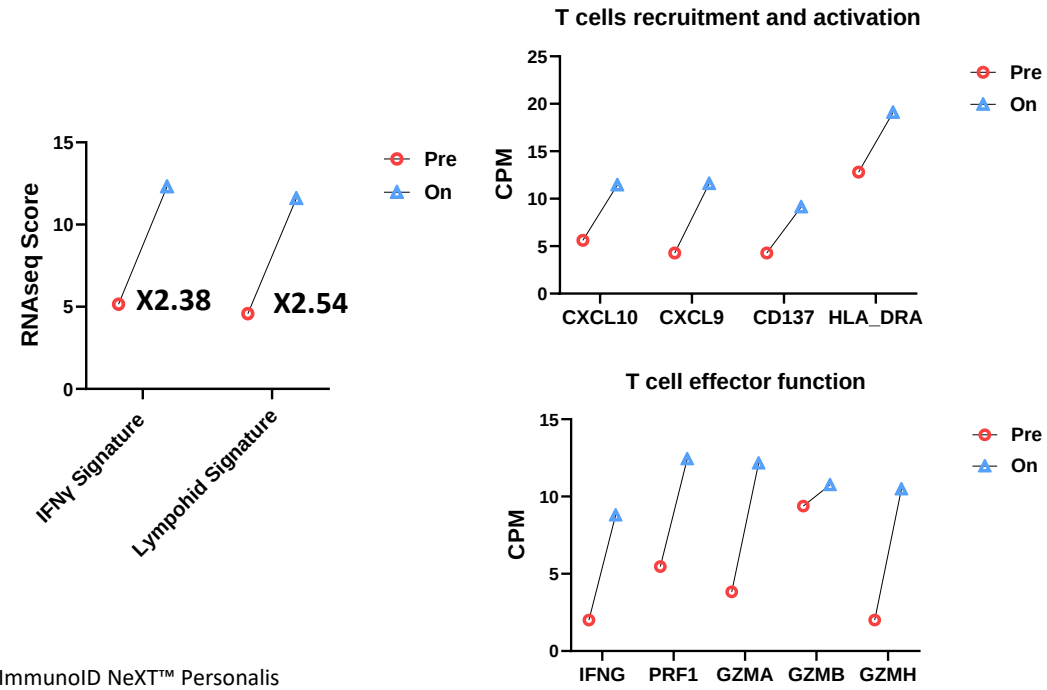


Increased clonal expansion





Increased Immune infiltration and activation



Ophir E - TIGIT summit 2021

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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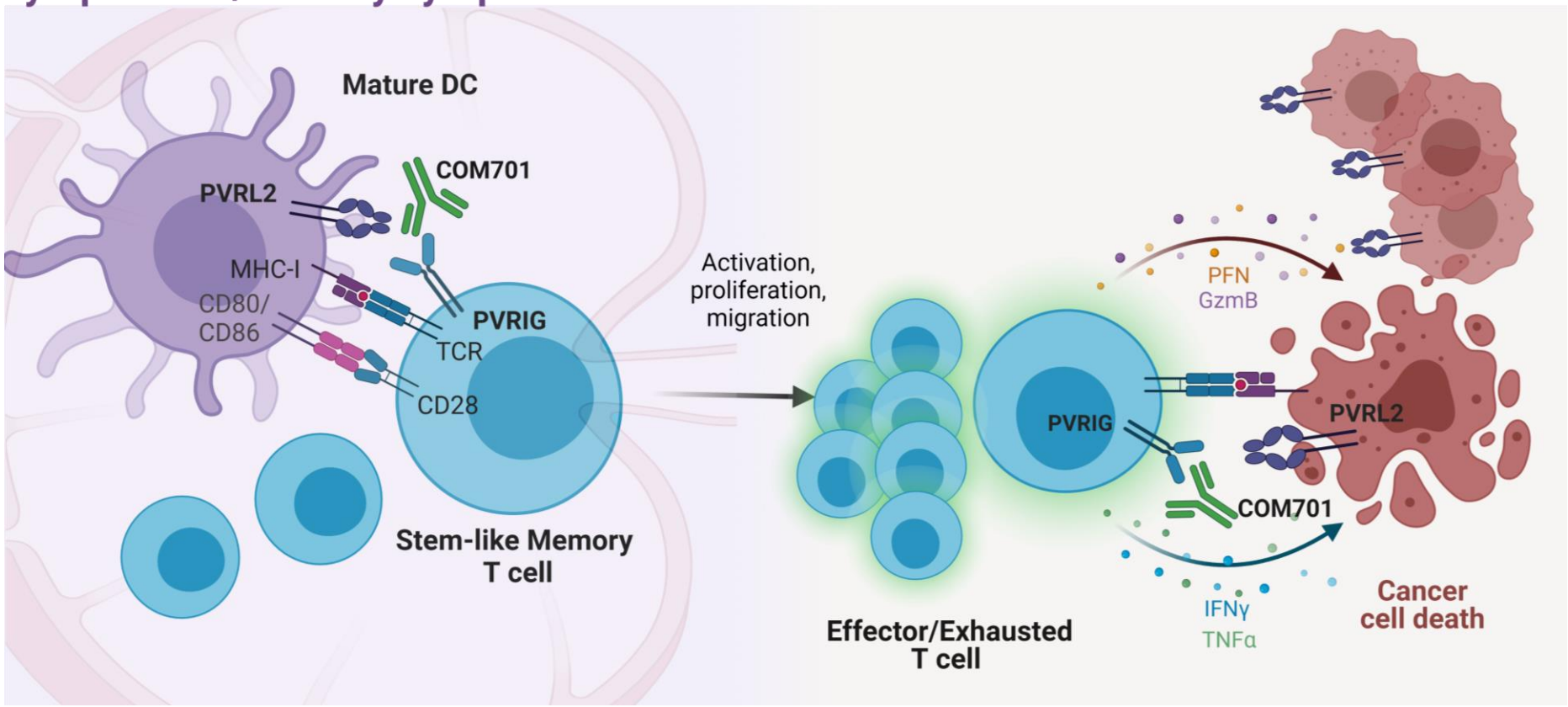
PVRIG+ stem-like memory T cells interaction with PVRL2+ DCs hypothesis support PVRIG activity in less inflamed PDL1 low tumors



SITC, Nov 2021, Alteber et al.

This hypothesis may support PVRIG activity in less inflamed PDL1^{low} tumor types

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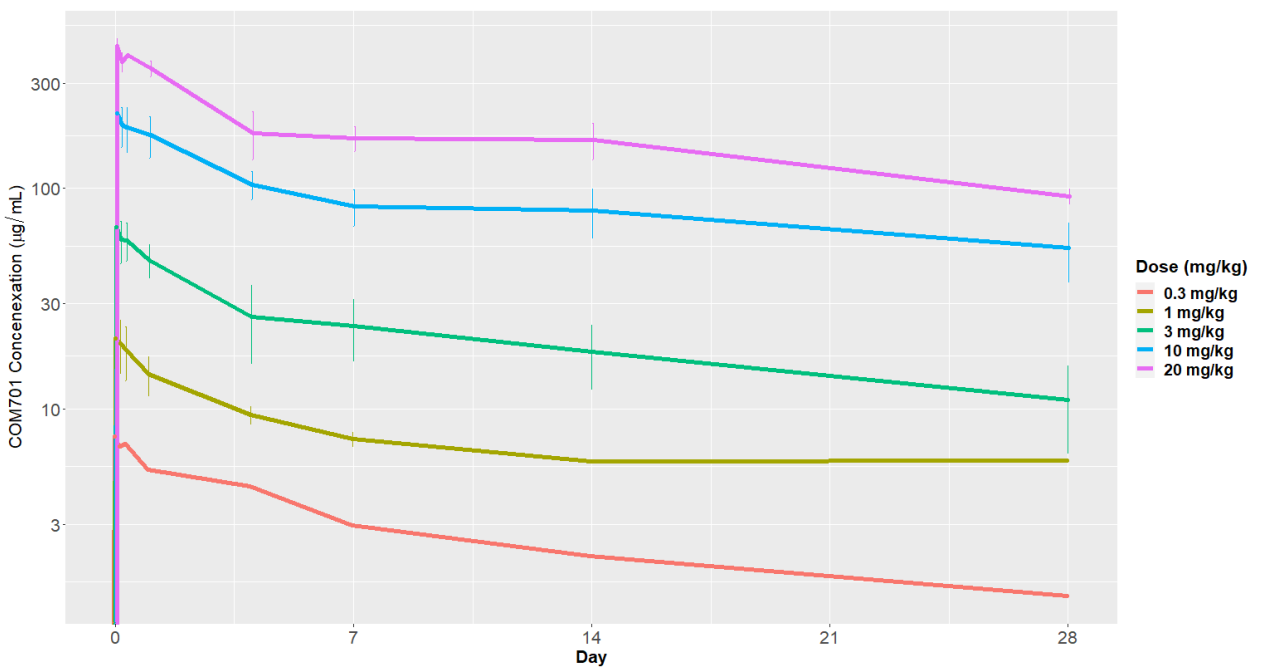
COM701, nivolumab and BMS-986207 combination well tolerated in dose escalation study

- Favorable safety and tolerability
- A maximum tolerated dose was not reached
  Favorable PK confirmed
- Best response of stable disease in a heavily pretreated all-comer patient population



Dumbrava et al, SITC November 2021 Poster Presentation, modified
Datacut 03 September 2021

Study clears the path to a comprehensive evaluation of Compugen's DNAM-1 axis hypothesis in select expansion cohorts

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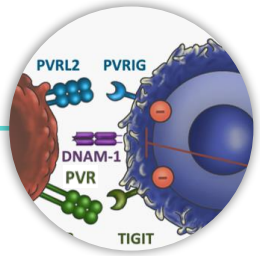
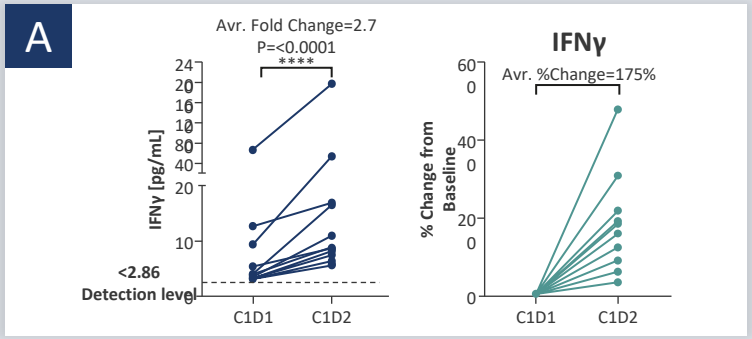
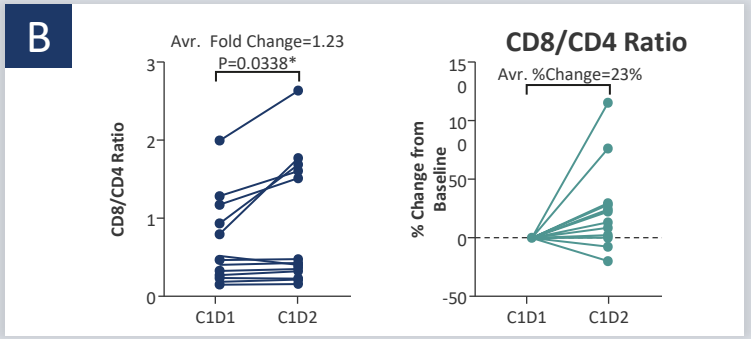
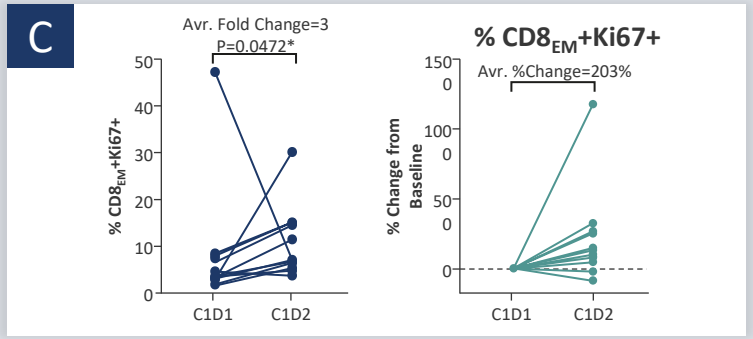
Potent activation of the immune system with “triple blockade”*

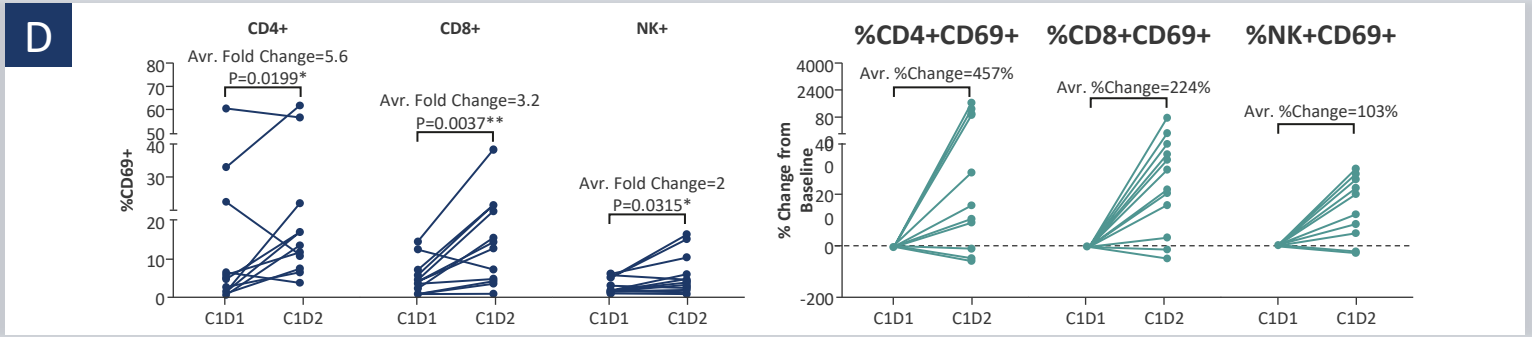
Increased T and NK cell activation, memory T Cell proliferation and IFNγ induction in blood











- **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

***PVRIG + TIGIT + PD1 blockade = COM701 + anti-TIGIT BMS-986207 + nivolumab (NCT04570839)**

Dumbrava et al, SITC November 2021 Poster Presentation, modified

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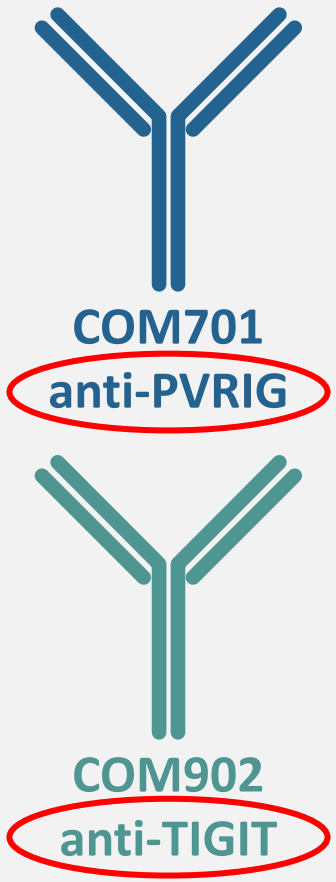
COM701, COM902 ongoing clinical cohort expansion program

Patients who have progressed on standard of care



Open label design	COM701 + nivolumab	COM701 + nivolumab + anti-TIGIT BMS-986207	COM902 RDFE	COM701 + COM902 both at RDFE
Phase	1	1/2	1	1
# of patients	20 per cohort	20 per cohort	10	20 per cohort
Tumor type	OC, BC, EC, CRC (MSS)	OC, EC, HNSCC, PVRL2 high tumors	Adv. Solid tumors MM	HNSCC, NSCLC, CRC (MSS)
Primary endpoint	Safety & tolerability, PK/PD, preliminary anti-tumor activity			
Status	First patient dosed Q2 ‘21	First patient dosed Q3 ’21	Enrolling	First patient dosed Q4 ‘21
CT identifier	NCT03667716	NCT04570839	NCT04254246	NCT04354246

HNSCC: Head and neck squamous cell cancer; 2 cohorts: IO-naïve cohort and cohort with prior IO therapy
OC: Ovarian Cancer; BC: Breast Cancer; EC: Endometrial Cancer; CRC (MSS): Colorectal Cancer Microsatellite Stable; NSCLC: Non-Small Cell Lung Cancer; MM: Multiple Myeloma
RDFE: Recommended Dose for Expansion

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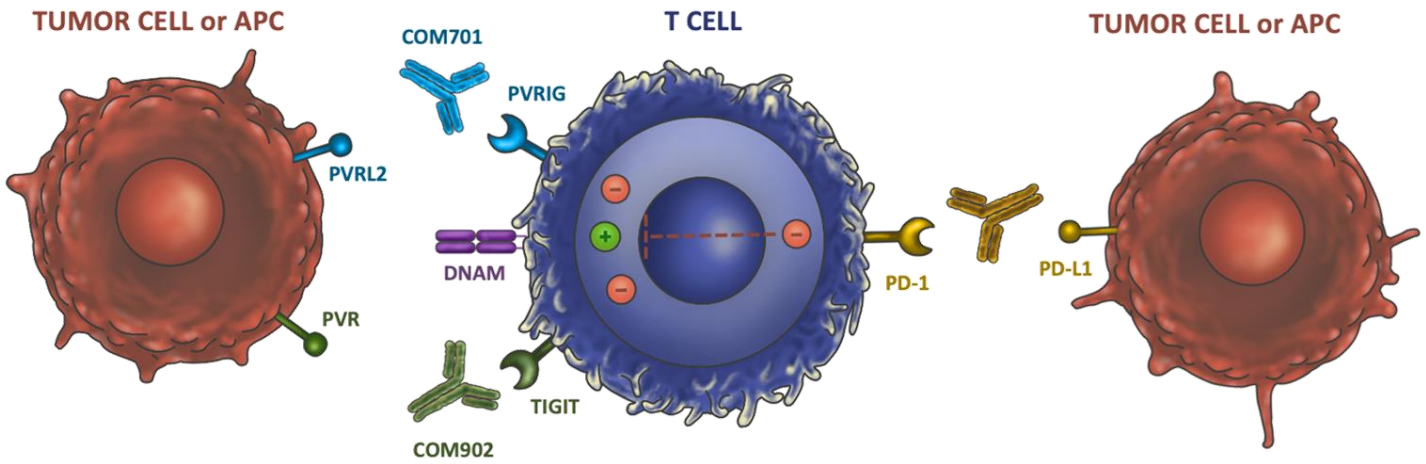
Conclusion

COM701 and COM902 potential game changers in cancer

COM701 (PVRIG) may be the missing piece for cancer patients when current checkpoint inhibitors fail



Dual blockade (PVRIG & TIGIT or PD-1) and triple blockade (PVRIG & TIGIT & PD-1) clinical trials are ongoing

- PVRIG and TIGIT discovered by Compugen's discovery platform as distinct complementary pathways
- Unique biology to address cancer indications where current immunotherapy fails, eg PDL1 low
- Robust translational data emerging from COM701 and COM902 clinical trials confirm Compugen hypothesis

Adapted from Alteber et al. Cancer Discov. 2021

Thank you