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.
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Disclosure

• Compugen ltd. employee
DNAM-1 axis plays essential role in tumor immunology

- 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)

Modified from Alteber et al. Cancer Discov. 2021
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
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

Anti-PD-(L)1 expands a key population of PD-1$^{low}$ $T_{SCM}$ cells which also express TIGIT$^{low}$

Sadeh-Feldman et al., 2018, Cell

Modified from Chen and Mellman Nature 2017
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**

**PVRIG, TIGIT and PD-1 protein expression**

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

NSCLC: Non small cell lung cancer
PVRL2 has a dominant expression on dendritic cells

PVRL2 is expressed on DCs

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

PVRL2 protein expression on DCs in ovarian cancer

PVRL2 has a dominant expression on dendritic cells in ovarian cancer.

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

PVRL2 protein expression on DCs in ovarian cancer

PVRIG blockade may enhance T_{SCM} - DC interaction and induce potent T_{SCM} activation
Spatial transcriptomic analysis of immune aggregate niches shows enrichment of T_{SCM} and DCs, while exhausted cells localize to the tumor

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

![Graph showing expression levels of various genes in immune aggregates and tumors.](image-url)
Strong biological rationale for targeting PVRIG in cold tumors

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

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

$T_{\text{SCM}}$: Early differentiated stem like memory T cells
Confirmed PR in patient with primary peritoneal PD-L1\textsuperscript{neg} ovarian cancer treated with COM701 monotherapy

Patient received 3 prior lines of anti cancer therapy

PVRL2 & PD-L1

- 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 IFN\(\gamma\) induction and immune activation in peripheral blood

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

PVRL\(2\) PD\(-L1\)

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

Ophir E et al SITC 2022
COM701 monotherapy induces TME immune modulation in patients with ovarian cancer

- 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

Alteber et al, Oral presentation SITC 2022
TME modulation is induced by PVRIG blockade by COM701+nivolumab±anti-TIGIT (BMS-986207) in PROC patients

% of CD8 infiltration on treatment

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

Increase in peripheral CD8 T\textsubscript{EM} cells in patients treated with COM701+nivolumab

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

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

12 patients
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)
COM701 + nivolumab combination induces TME immune modulation
MSS CRC patients

**PD-L1 expression**

- Avg. fold change = 7.8
- 0.0403

**CD8 IHC**

- Avg. fold change = 3.5
- 0.0852

**IFNγ signature**

- Avg. fold change = 7.9
- 0.1271

- 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

**PR** = patient with partial response per RECIST

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Alteber et al, Oral presentation SITC 2022
Extensive TME modulation in MSS CRC patients partially responding to COM701 + nivolumab

Increased CD8 infiltration and immune modulation

<table>
<thead>
<tr>
<th>Pre</th>
<th>On</th>
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<tbody>
<tr>
<td>Responder 1</td>
<td>Responder 2</td>
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- IFN
- CD8+ Tcm
- CD8+ Tem
- CD8+ T cells

Increased TCR clonality and clonal expansion

<table>
<thead>
<tr>
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<th>Responder 2</th>
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<tr>
<td>TCRβ pre</td>
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<td>58</td>
<td>14</td>
</tr>
<tr>
<td>521</td>
<td>93</td>
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</table>

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

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

Personalis - ImmunoID NeXT™

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

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Compugen:


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Department of Pathology, Rabin Medical Center:

Abraham Avi Nathan

Gynecologic Oncology Division, Helen Schneider Hospital for Women, Rabin Medical Center:

Ram Eitan, Oded Raban
Synergistic T Cell activation with PVRIG, PD-1 and TIGIT blockade

**COM701 +/- anti-TIGIT**

- COM701 + α-TIGIT: +340%
- COM701 + α-PD-1: +41%

**COM701 +/- anti-PD-1**

- COM701 + α-PD-1: +136%
- COM701 + α-TIGIT: +57%

**Triple combination**

- COM701 + α-TIGIT + α-PD-1: +340%
- COM701 + α-TIGIT + α-PD-1: +293%
- COM701 + α-TIGIT + α-PD-1: +467%

Whelan, et al., Cancer Immunol Res. 2019
**COM701 shows clinical activity in PROC cancer**

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

<table>
<thead>
<tr>
<th>SOC 2L+</th>
<th>ORR %</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
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<tr>
<td>Single agent chemo</td>
<td>~8-12</td>
<td>~3-4</td>
<td>~13</td>
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<tr>
<th>Historical</th>
<th>ORR</th>
<th>PFS</th>
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<tr>
<td>PD(L)1 blockers/ Pembro + Vibostimab (aTIGIT)*</td>
<td>&lt;10%</td>
<td>2.1m</td>
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<table>
<thead>
<tr>
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<th>COM701 Mono*</th>
<th>COM701 + nivolumab</th>
<th>COM701 + BMS986207 + nivolumab</th>
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<tr>
<td>ORR</td>
<td>1 (16.6%)</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
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<tr>
<td>PR</td>
<td>2 (34%)</td>
<td>2** (10%)</td>
<td>4 (20%)</td>
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<tr>
<td>SD</td>
<td>3 (50%)</td>
<td>7 (35 %)</td>
<td>5 (25%)</td>
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<tr>
<td>DCR</td>
<td>4 (66%)</td>
<td>9 (45 %)</td>
<td>9 (45%)</td>
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* Keyvibe-001; 0% ORR in PDL1 CPS<1