FOCIS/SITC 2023
Combinatorial Therapeutics in Solid Tumors: PSMAxCD28 CoStimulatory Bispecific mAb (REGN5678) with Cemiplimab (anti-PD-1) in mCRPC

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Regeneron Pharmaceuticals

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Disclosures

1. Israel Lowy is Sr Vice President of Translational and Clinical Oncology, and an employee, officer and stockholder in Regeneron Pharmaceuticals
2. This presentation discusses off label/investigational uses of cemiplimab (anti-PD-1) and other therapeutic agents that have not received regulatory approvals

Unique flexibility of internally-developed pipeline drives potential for novel and differentiated combinations

CD3 Bispecifics: "Signal 1"

- Odronextamab (CD20xCD3) — R/R B-NHL, CLL
- BCMAxCD3 (REGN5458) — R/R Multiple Myeloma
- PSMAxCD3 (REGN4336) — Metastatic prostate cancer
- MUC16xCD3 (REGN4018) — Recurrent ovarian cancer
- PSMAxCD3 (REGN4336) + Cemiplimab (PD-1) — Metastatic prostate cancer
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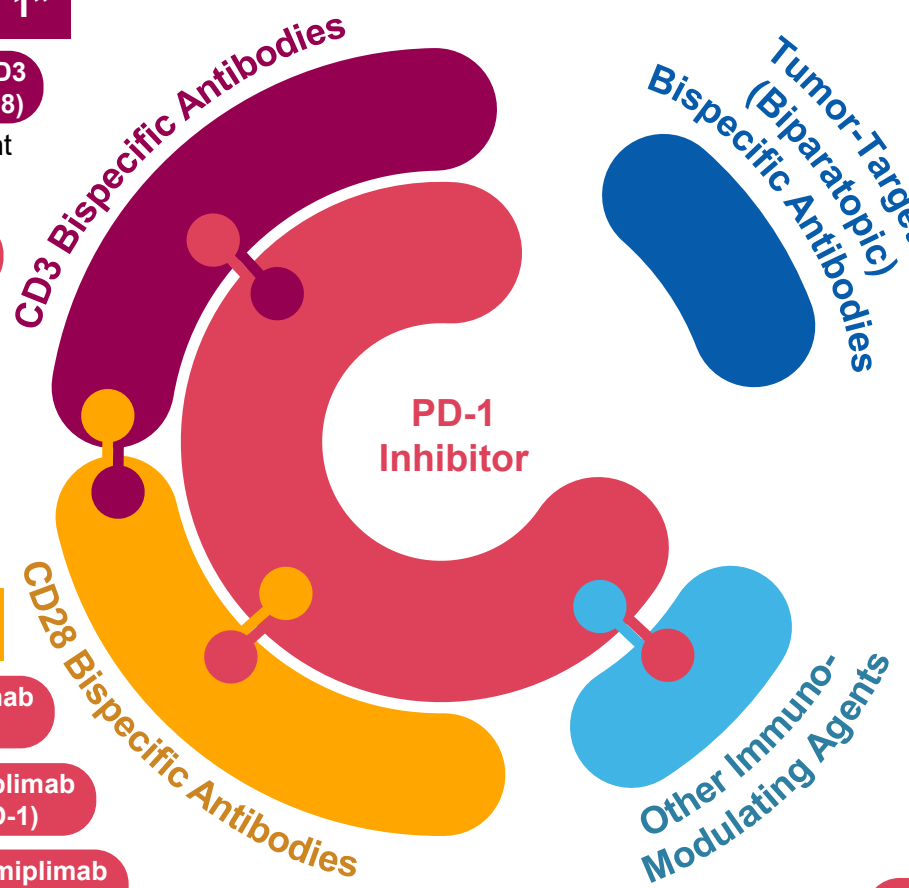
- MUC16xCD3 (REGN4018) + MUC16xCD28 (REGN5668) — Recurrent ovarian cancer
- PSMAxCD3 (REGN4336) + PSMAxCD28 (REGN5678) — Metastatic prostate cancer

CoStimulatory CD28 Bispecifics: "Signal 2"

- PSMAxCD28 (REGN5678) + Cemiplimab (PD-1) — Metastatic prostate cancer
- EGFRxCD28 (REGN7075) + Cemiplimab (PD-1) — Solid tumors
- MUC16xCD28 (REGN5668) + Cemiplimab (PD-1) — Recurrent ovarian cancer



Tumor-Targeted Biparatopics

- METxMET (REGN5093) — MET-altered advanced NSCLC
- METxMET ADC (REGN5093-M114) — MET over-expressing advanced NSCLC

Modulating immune response

- Cemiplimab (PD-1) + Fianlimab (LAG3) — Melanoma & other advanced malignancies
- Cemiplimab (PD-1) + GITR (REGN6569) — HNSCC
- Cemiplimab (PD-1) + vidutolimod (TLR9) — CSCC, Merkel cell carcinoma

EGFR, Epidermal growth factor receptor; MUC16, Mucin 16; PSMA, Prostate-specific membrane antigen; R/R, Relapse/refractory; B-NHL, B-cell Non-Hodgkin lymphoma; BCMA, B-cell maturation antigen; NSCLC, Non-small cell lung cancer; SCCHN, Squamous cell carcinoma of the head and neck; CSCC, Cutaneous squamous cell carcinoma; ADC, Antibody drug conjugate; LAG-3, Lymphocyte-activation gene 3; GITR, Glucocorticoid-induced TNFR-related protein

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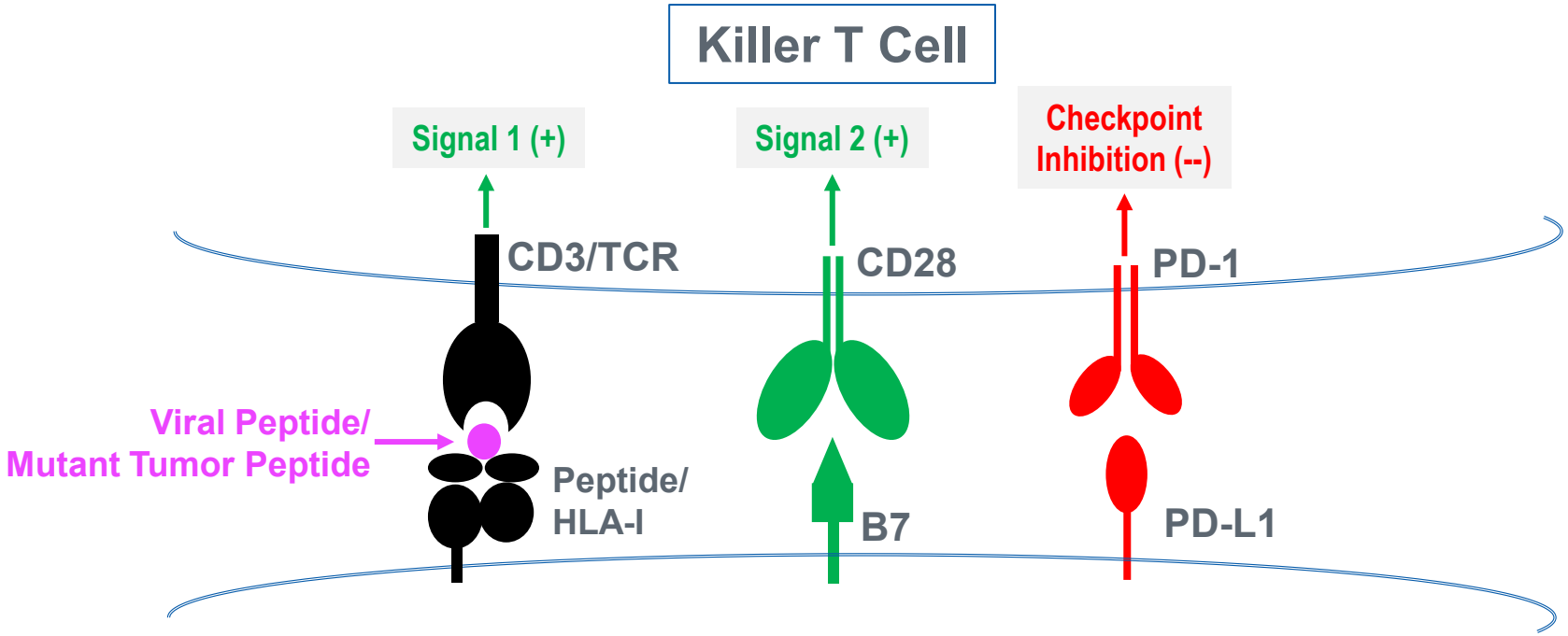
How Killer T cells recognize and attack target cells

Killer T cell activation requirements

Signal 1: Recognize target cell via T Cell Receptor (CD3/TCR)
Signal 2: Promote expansion of killing signal using costimulatory receptor (CD28) on APC
(Signal 3: Cytokine amplification: e.g., IL-2, IFNγ, IL-12)
Then: Rapid suppression, via checkpoint inhibition (e.g. PD-1 and LAG-3), to prevent auto-immunity

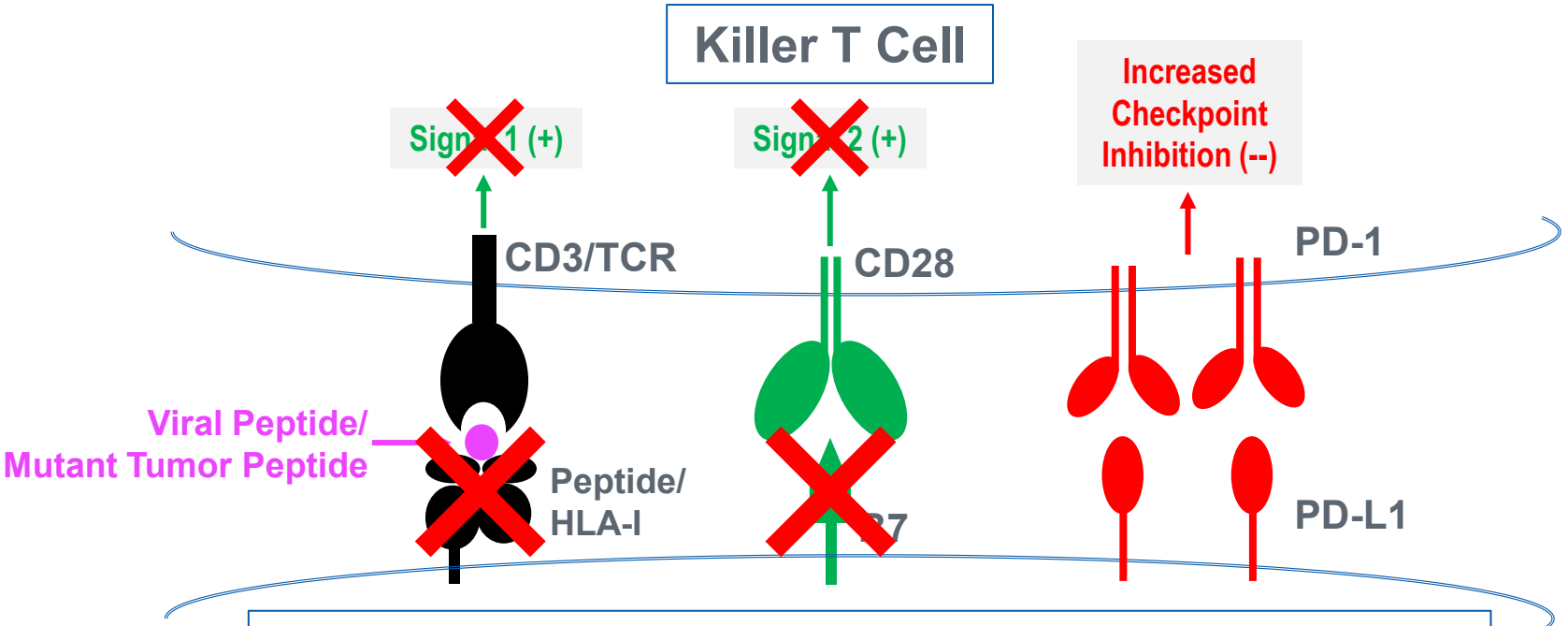


Target Cell:
Virally-infected or Tumor Cell or Antigen Presenting Cells (APCs):
"CD3/TCR" recognizes foreign viral peptide or mutated tumor peptide on HLA

“Cold tumors” can evade Killer T cells

Tumors eliminate Signal 1 and/or 2, and increase checkpoint inhibition

- **Signal 1: Tumors do not present any (or very few) mutant peptides**
- **Signal 2: Tumors do not present any (or little) costimulatory ligand (B7)**
- **Tumors over-express checkpoint (e.g. PD-1 and LAG-3) ligands**



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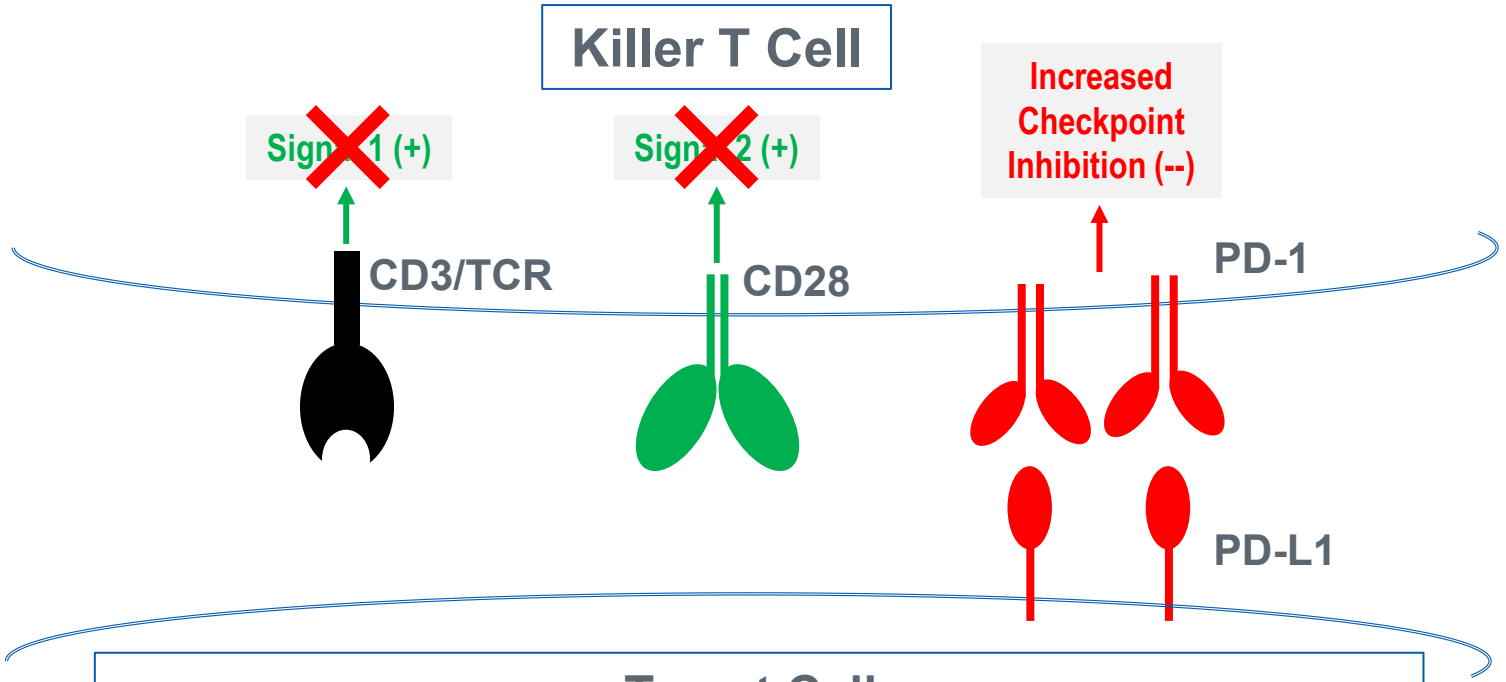

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Turning “cold” tumors into “hot” tumors:
Restore signal 1 & 2 in killer T cells, block checkpoint inhibition

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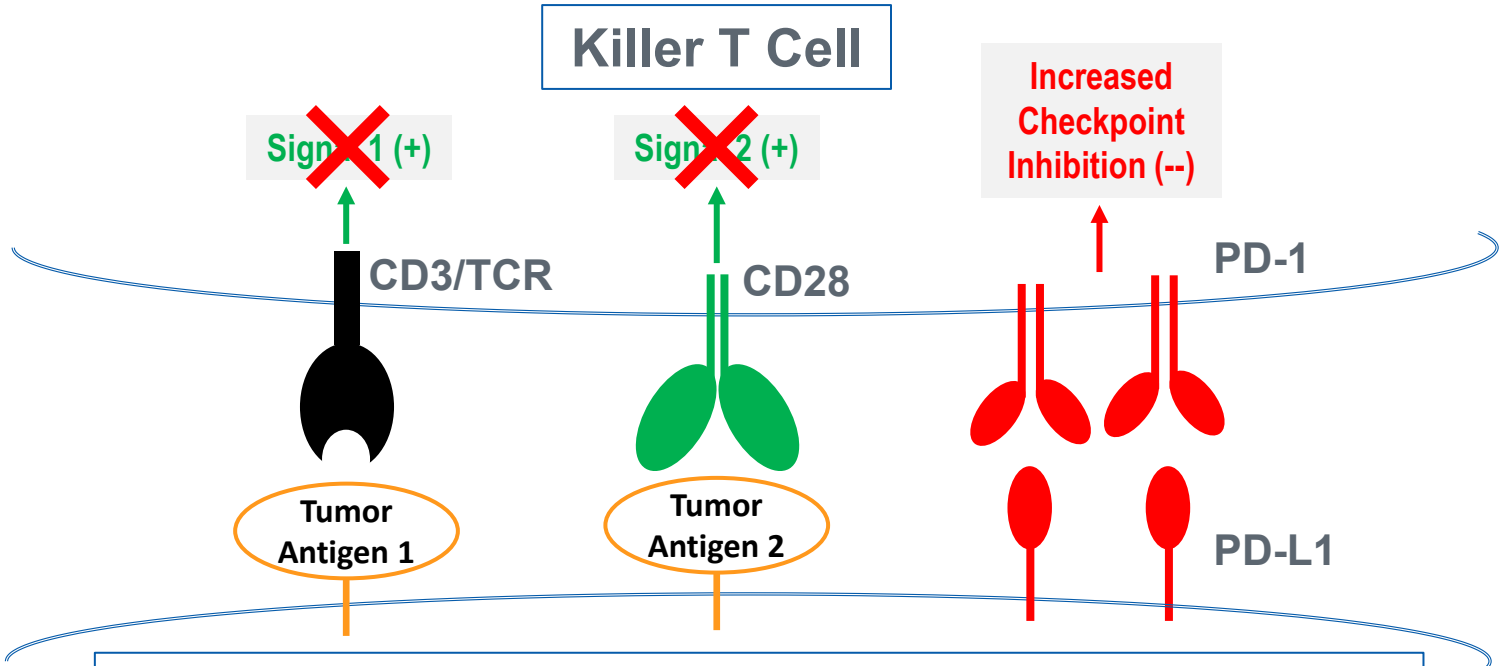

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Tumors do not present any (or very few) mutant peptides, and/or do not express any (or little) costimulatory ligand, and/or over-express checkpoint (e.g. PD-1 and LAG-3) ligands

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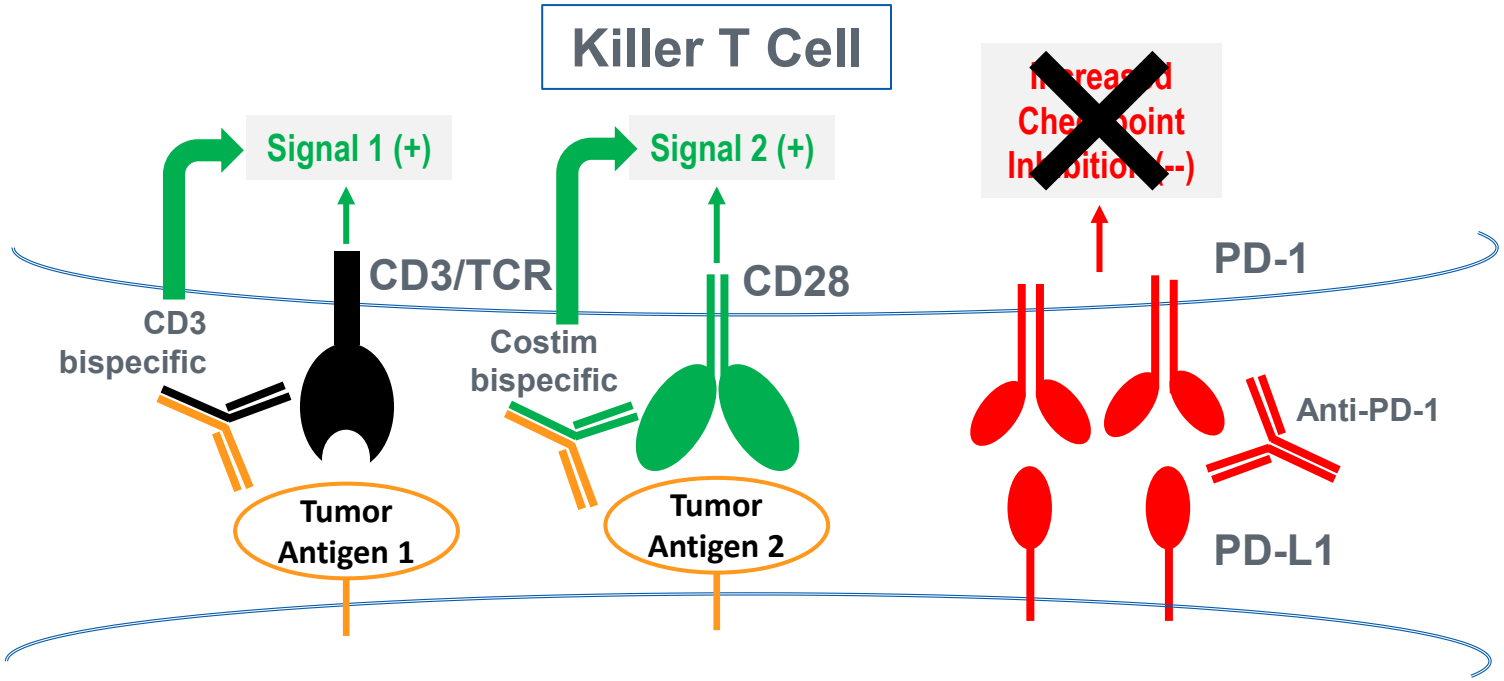
Turning “cold” tumors into “hot” tumors:
Restore Signal 1 & 2 in killer T cells, block checkpoint inhibition

Signal 1: Restore Signal 1 using “CD3 BiSpecific”
Signal 2: Restore Signal 2 using “CoStim BiSpecific”
Block “Checkpoint Inhibitors” using anti-PD1 (or anti-LAG-3)



- ✓ Regeneron has clinically validated its checkpoint blockers (anti-PD-1 and anti-LAG-3) and CD3-bispecifics
- ✓ First-in-class costimulatory bispecifics have minimal clinical activity as monotherapy
- ✓ Preclinical studies have shown profound synergy when any of these above agents are combined

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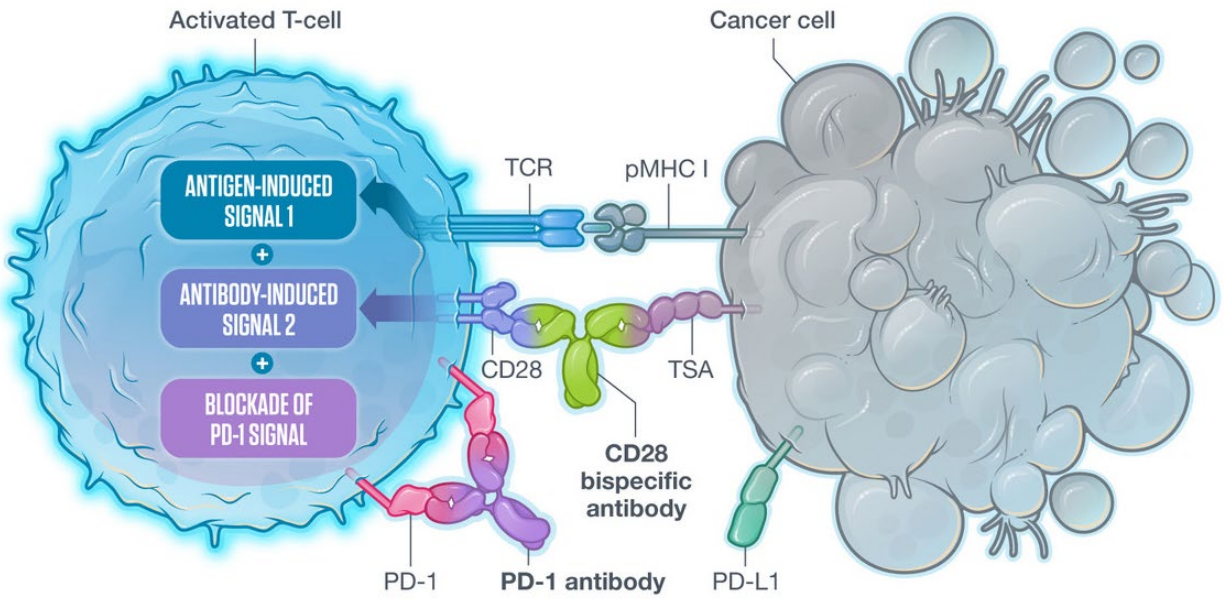
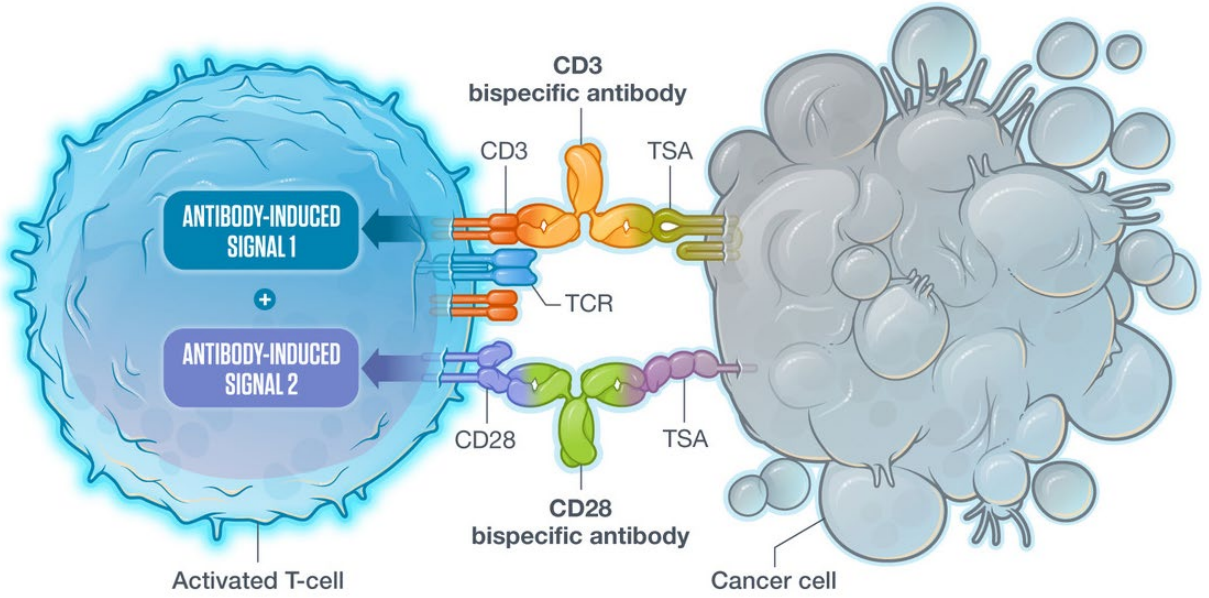
A NOVEL CLASS OF CD28 COSTIMULATORY ANTIBODIES may be combined with Anti-PD-1 and/or CD3 bispecific antibodies



Depends on pre-existing anti-tumor immunity



Requires <u>specific</u> tumor targets

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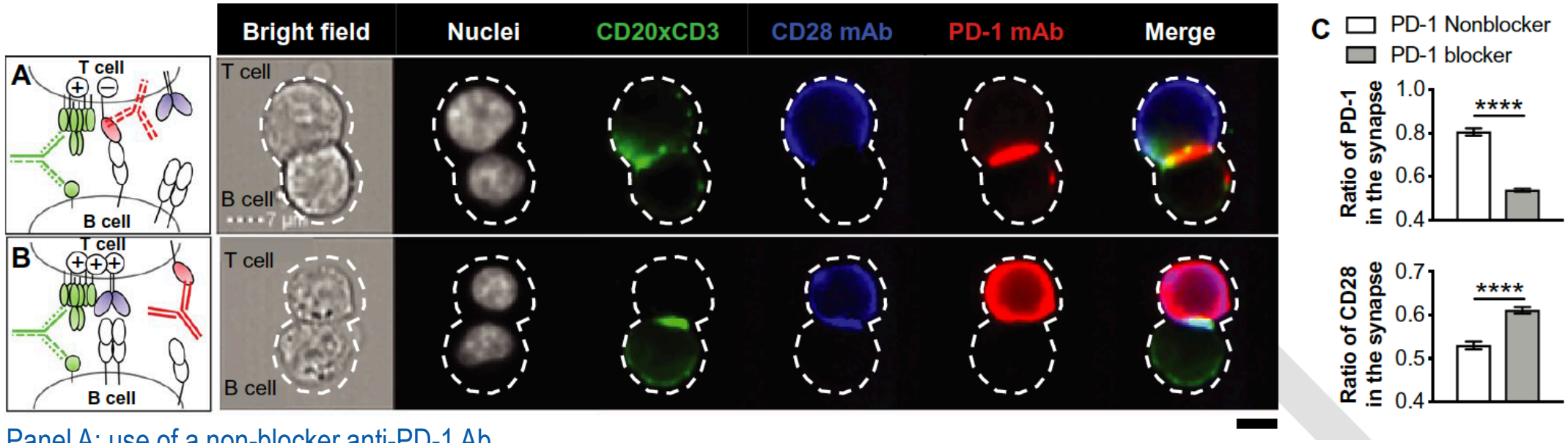
PD-1 can exclude CD28 from the synapse

- PD-1 inhibition decreases localization of PD-1 and enhances the accumulation of CD28 in the synapse



Panel A: use of a non-blocker anti-PD-1 Ab
Panel B: use of a blocker anti-PD-1 Ab

➢ PD-1 inhibition decreases localization of PD-1 and enhances the accumulation of CD28 in the synapse

Waite *et al.*, *Sci. Transl. Med. June 24, 2020*

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Applying our costimulatory bispecific based approach in various solid tumors: focus in prostate cancer

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- Recurrent ovarian cancer: MUC16xCD3 (REGN4018) + MUC16xCD28 (REGN5668)
- Metastatic prostate cancer: PSMAxCD3 (REGN4336) + PSMAxCD28 (REGN5678)

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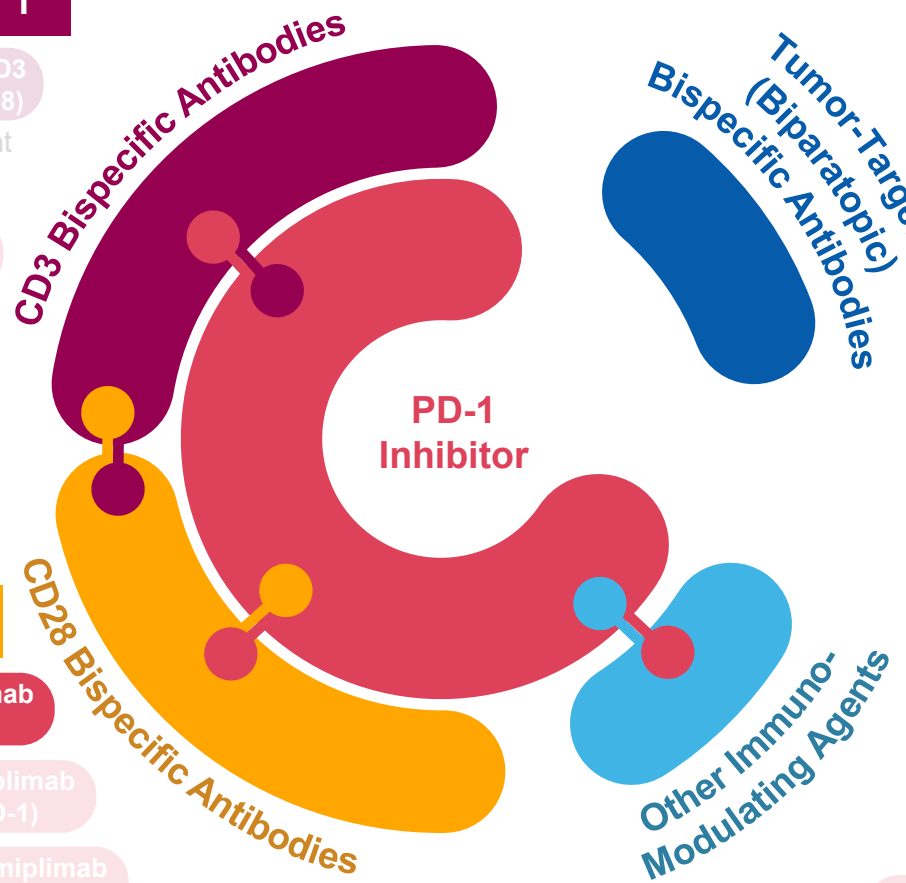

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Modulating immune response

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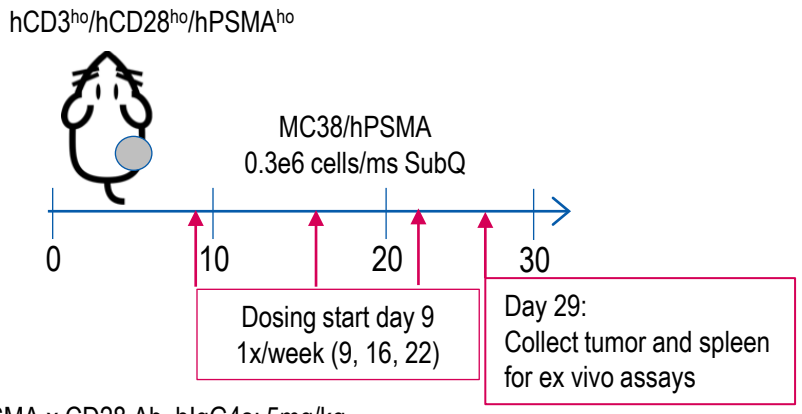
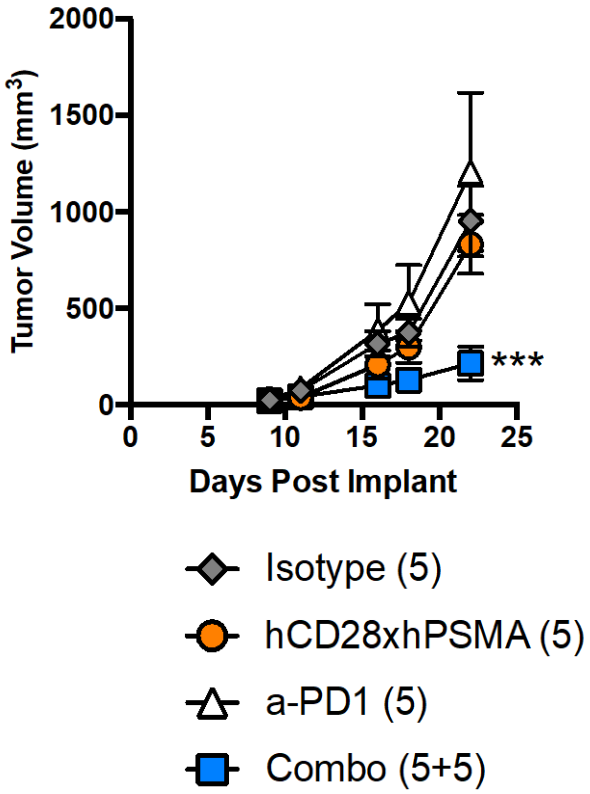
PSMAxCD28 + PD-1 MAB SPECIFICALLY ACTIVATES T CELLS & INDUCES PROINFLAMMATORY CYTOKINES WITHIN THE TUMOR

Tumor Model

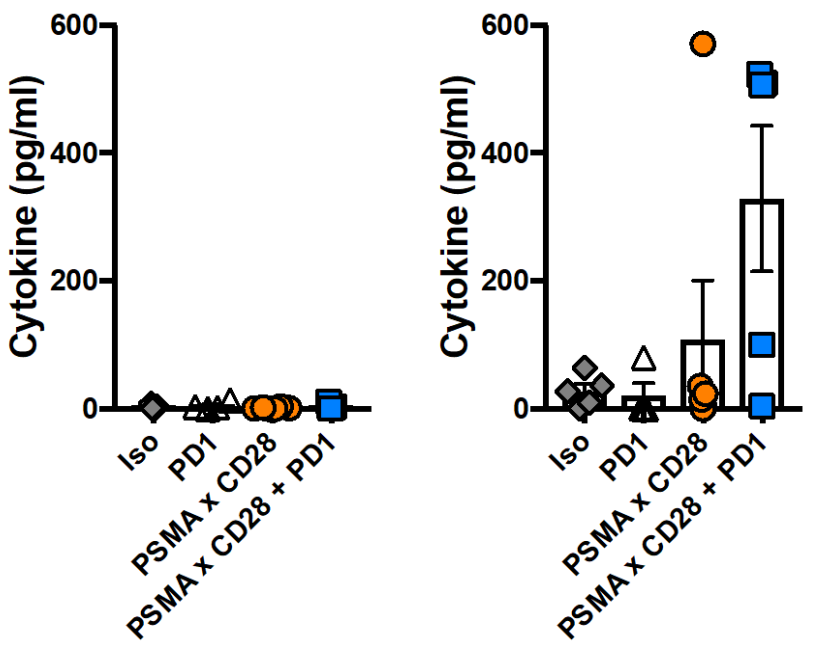


PSMA x CD28 Ab, hIgG4s: 5mg/kg
Anti-msPD1, rIgG2a: 5mg/kg

Average tumor growth



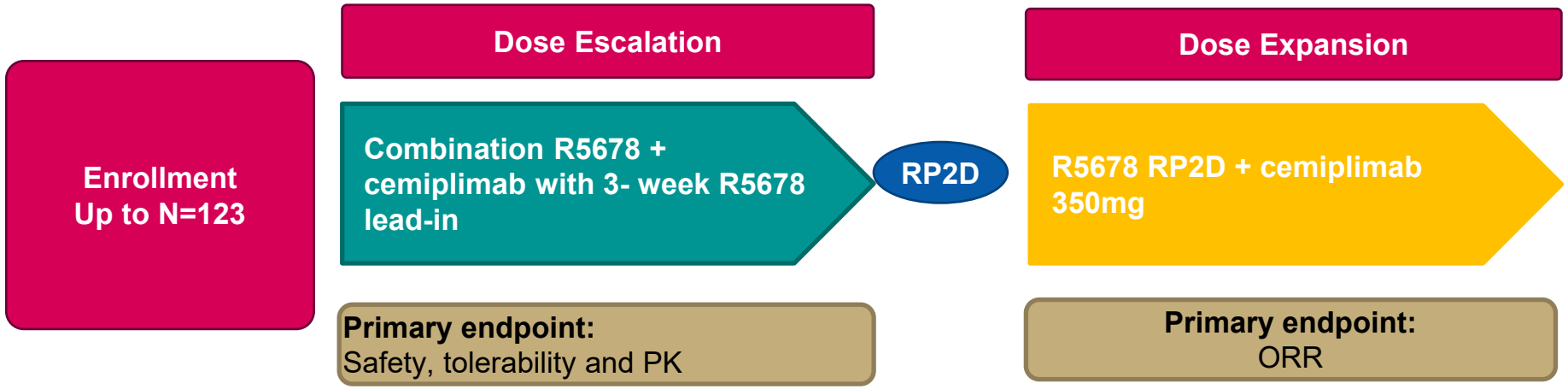
Ex vivo cell culture



Total spleen or tumor cells incubated overnight

First-in-class costim bispecific PSMAxCD28 + cemiplimab in development for late-stage prostate cancer

- REGN5678-ONC-1879 is an open label, phase 1/2, first-in-human (FIH) study evaluating safety, tolerability, PK and preliminary anti-tumor activity of REGN5678 (PSMAxCD28 bsAB) alone and in combination with cemiplimab (anti-PD-1 mAb) in treatment-experienced mCRPC. There are two parts:



Key inclusion:

mCRPC that has progressed within 6 months prior to screening based on prostate specific antigen progression and/or radiographic progression.

Received ≥2 lines of prior systemic therapy approved for metastatic and/or castration-resistant disease, including an NHA

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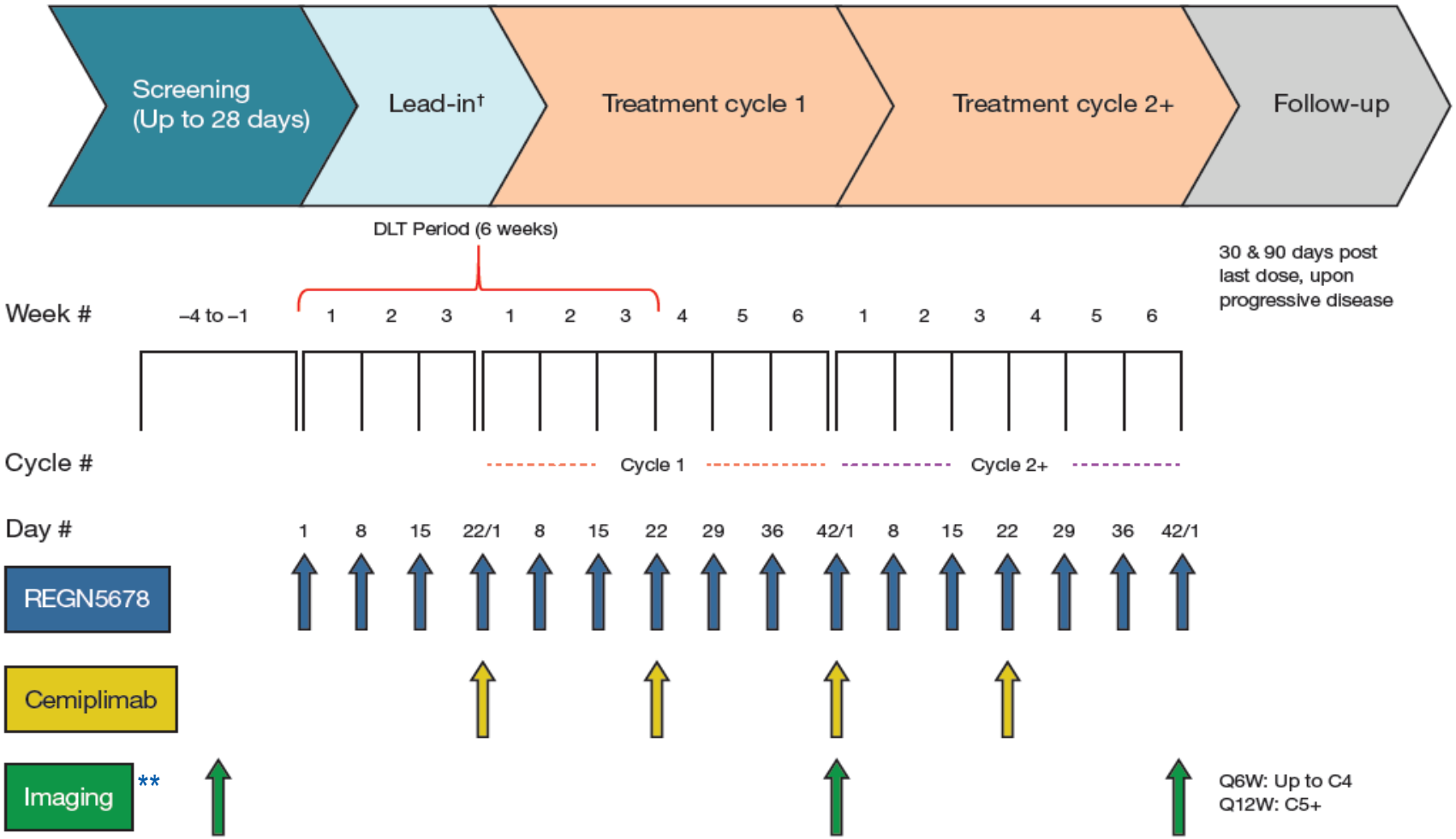
Study Schema: R5678-ONC-1879 (NCT03972657)



**Standard imaging assessment will be performed, in addition to PSMA PET (18F-DCFPyL) at select centers and time points

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PSMAxCD28 + Cemiplimab: Initial Clinical Data Supporting Synergy with CoStim BiSpecs & anti-PD-1

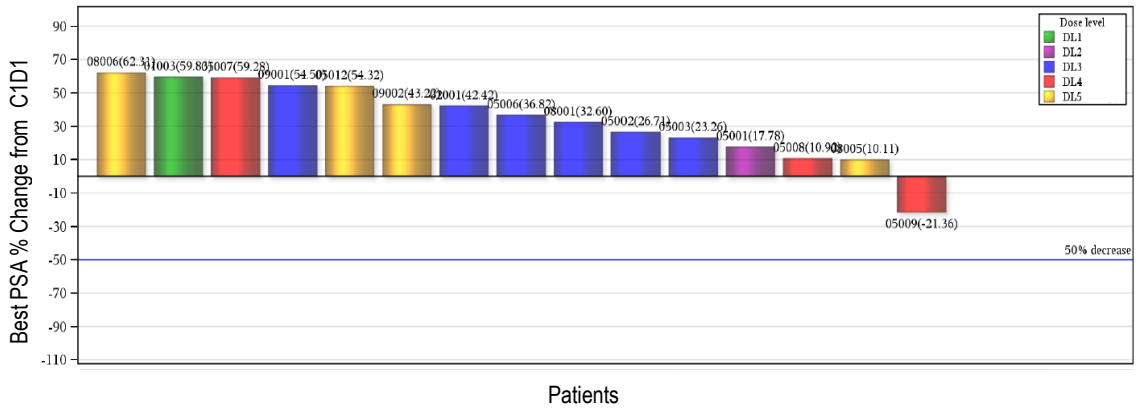
Proof-of-principle for the broader costimulatory bispecific platform

Note: Prostate cancer shows ~5% response rates to anti-PD-1 monotherapy
First clinical data from ongoing Phase 1/2 trial showed first evidence of anti-tumor activity for REGN5678 (PSMAxCD28) when combined with standard dose cemiplimab, suggesting potential to overcome mCRPC resistance to PD-1 inhibition

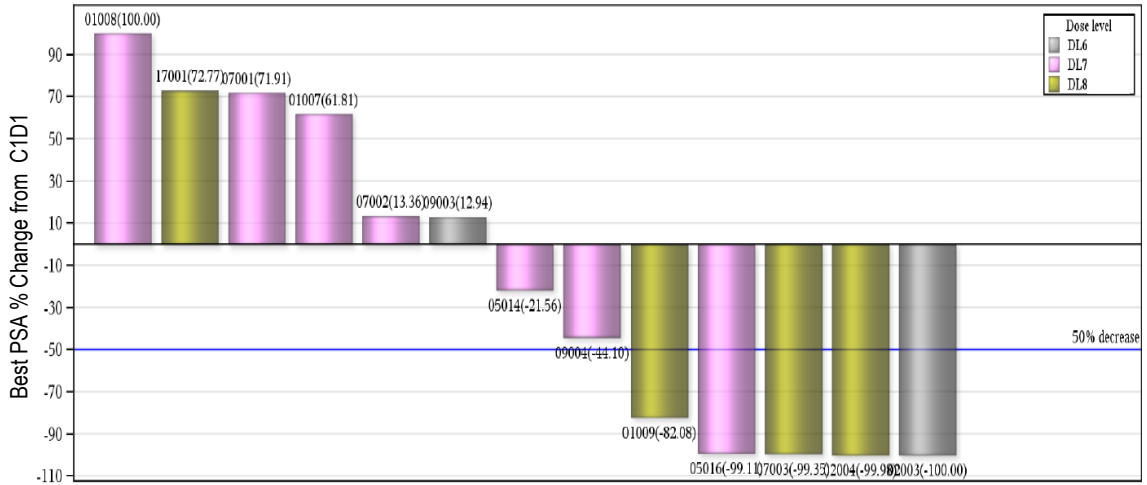
Efficacy and safety:

- **Dose Levels 1-5 (n=17): Minimal anti-tumor activity and no ≥Gr3 immune-mediated adverse events (imAEs)**
  - 1/17 with PSA decline across these 5 dose levels
- **Dose Levels 6-8 (n=18): Early signs of efficacy associated with imAEs**
  - DL6: 1/4 patients had response -- a 100% decrease in PSA and a complete response in target lesions, maintained for ~12 months
    - Responder discontinued therapy due to a Gr3 imAE of skin; CR maintained over 1 year off therapy, with resolution of identifiable disease including bone lesions
  - DL7: 3/8 patients had PSA declines -- >99%, 44% and 22% respective decrease in PSA on combination therapy
    - Two pts with PSA decline had a Gr3 treatment related AE, which resolved
  - DL8: 3/4 patients had PSA responses -- >99%, 99% and 82% respective decreases in PSA on combination therapy
    - One pt with PSA response had an imAE resulting in death
- **No additional Gr4 imAEs or ≥Gr2 CRS have been observed in the trial to date**
- **All ≥Gr3 imAEs occurred in patients with anti-tumor activity**

Patients from Dose Levels 1 to 5:
1/17 with PSA decline



Patients from Dose Levels 6 to 8:
7/16 with PSA decline



PSA, prostate-specific antigen; CR, complete response; Gr, grade; CRS, cytokine release syndrome.
Preliminary data.

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PSMAxCD28 + Cemiplimab demonstrated 75% PSA response at dose level 8

Advanced metastatic castration-resistant prostate cancer shows ~5% response rates to anti-PD-1 monotherapy

Dose Level 8: 3/4 patients had clinical responses while on combination treatment

- **Patient 1009: 82% reduction in PSA at week 9**
  - PSA at baseline >30 ng/mL; PSA continued to rise to >50 ng/mL until cemiplimab initiated at week 3
- **Patient 7003: 99% reduction in PSA at week 9**
  - PSA at baseline >200 ng/mL; PSA continued to rise until cemiplimab initiated at week 3
- **Patient 2004: >99% reduction in PSA at week 6**
  - PSA at baseline >500 ng/mL; PSA continued to rise to >600 ng/mL until cemiplimab initiated at week 3
  - Developed Gr3 case of acute inflammatory demyelinating polyradiculopathy (AIDP) shortly after initial cemiplimab administration
  - AIDP developed into hemophagocytic lymphohistiocytosis (HLH) at week 9 and patient passed away at week 13

Graphs of three PSA responders at dose level 8

Prostate-Specific Antigen (PSA) vs. time (weeks)

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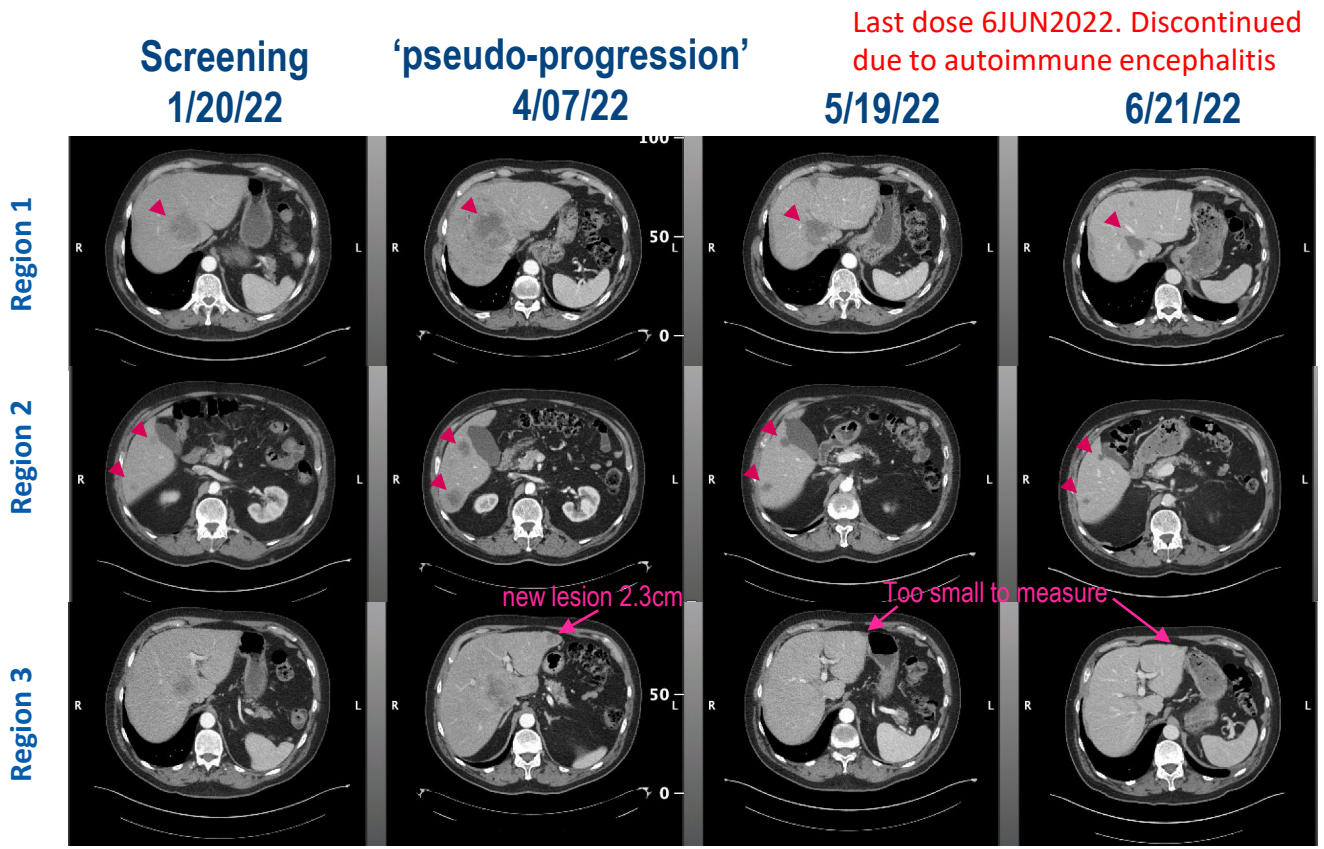
Pt in DL7 with PSA response (decrease by 99%): 'pseudo-progression' in liver followed by response, PSMA PET positive lesion signal decreased in several lesions

Diagnostic CT (representative images)

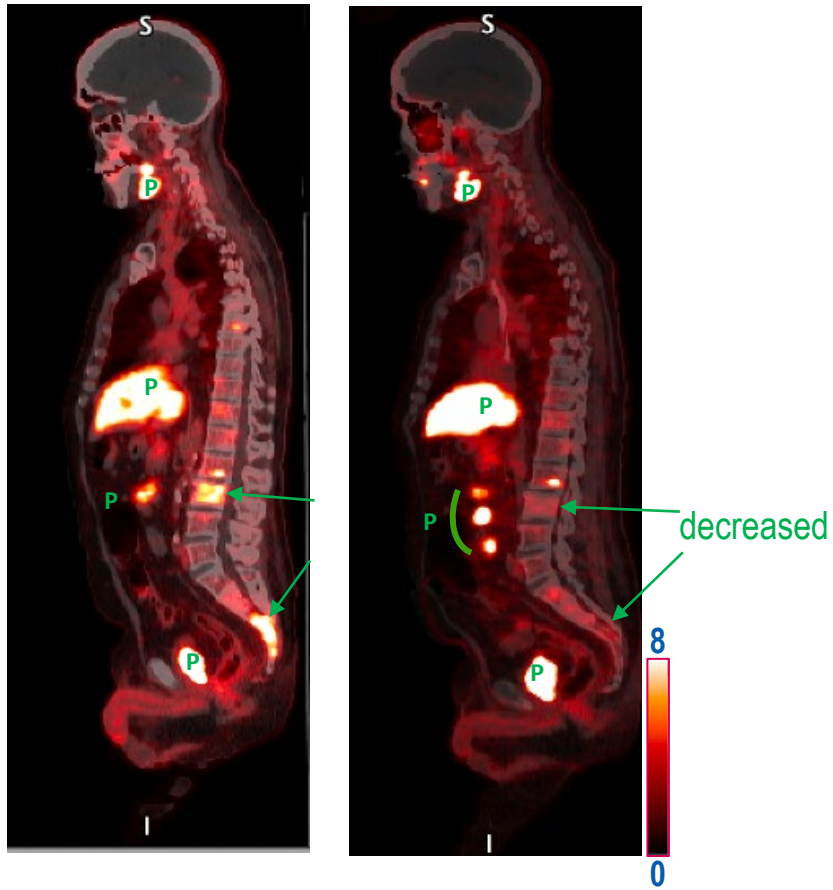
Last dose 6JUN2022. Discontinued due to autoimmune encephalitis



Investigator assessed target lesions sum of diameters & change from baseline

75	103 +37.3%, PD	65 -13.3%, SD	49 -34.7%, PR

PSMA PET/CT ^{18}F-DCFPyL (representative images)



P = physiological uptake (salivary glands, liver, GI, bladder)

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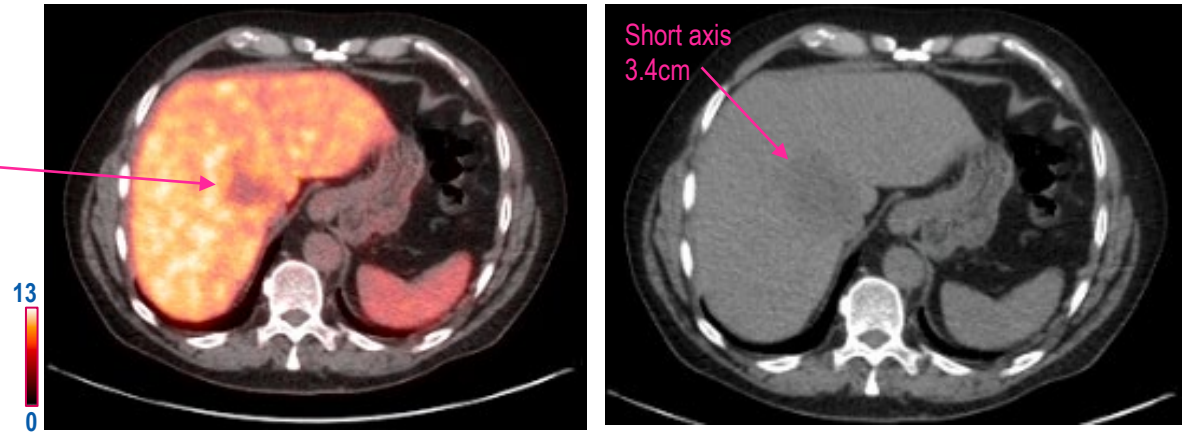
Tumor lesions with low PSMA PET signal responded to R5678 + cemi
These lesions are not expected to respond to Pluvicto™ (177Lu-PSMA-11)

Screening scans of patient on previous slide (representative images)

PSMA PET signal in tumor less than liver



More data required to evaluate potential differentiation from Pluvicto™

Pluvicto™ (177Lu-PSMA-11) eligibility criteria – all non-bone tumor lesions meeting size criteria must be positive on PSMA PET scan

- Size criteria = organ tumor lesions and bone lesion soft tissue component short axis ≥1cm, nodal lesions short axis ≥ 2.5cm
- PSMA PET visual assessment
  - positive = tumor signal greater than normal liver
  - negative = tumor signal equal to or less than liver

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Summary

1. Preliminary data on PSMAxCD28 (REGN5678) plus cemiplimab (anti-PD-1) in patients with mCRPC provide first evidence of clinical activity of a CD28 co-stimulatory bispecific antibody in solid tumors
2. Clinical activity was observed at doses of DL6-DL8 in combination with cemiplimab
3. ≥G3 imAEs occurred in patients with PSA declines, suggesting a possible association
4. Mitigation strategies under investigation to decouple imAEs from clinical activity
   - IL-6R blockade has been shown to mitigate both acute CRS with CART and CD3 bispecifics, as well as imAEs with dual checkpoint blockade
5. Study is ongoing to determine the maximum tolerated and recommended Phase 2 doses
   - Companion study is underway to explore PSMAxCD3 +/- cemiplimab and potential to combine with PSMAxCD28

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INVESTIGATORS AND COLLABORATORS

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Jingsong Zhang	Moffitt Cancer Center
Benedito Carneiro	Lifespan Cancer Institute
Gerald Falchook	Sarah Cannon Research Institute SCRI
Xin Gao	Massachusetts General Hospital
Joseph Kim	Yale University Hospital
Sumit Subudhi	MD Anderson Cancer Center
Bilal Siddiqui	MD Anderson Cancer Center
Christopher Logothetis	MD Anderson Cancer Center

THANK YOU TO ALL OF THE PATIENTS AND THEIR FAMILIES

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