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

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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

**CoStimulatory CD28 Bispecifics: “Signal 2”**
- **PSMAxCD28** (REGN5678)
  - Metastatic prostate cancer
- **MUC16xCD28** (REGN5668)
  - Recurrent ovarian cancer
- **EGFRxCD28** (REGN7079)
  - Solid tumors
- **MUC16xCD28** (REGN5668)
  - Recurrent ovarian cancer

**Tumor-Targeted Biparatopics**
- **METxCD3** (REGN5093-M114)
  - MET-altered advanced NSCLC
- **METxCD3 ADC** (REGN5093-M114)
  - MET over-expressing advanced NSCLC

**Modulating immune response**
- **Cemiplimab** (PD-1)
  - EGFRxCD28 (REGN5678)
- **Fianlimab** (LAG3)
  - Cemiplimab (PD-1)
- **Cemiplimab** (PD-1)
  - GITR (REGN6569)
- **Cemiplimab** (PD-1)
  - vidutolimod (TLR9)
  - CSCC, Merkel cell carcinoma

**Other Immuno-Modulating Agents**
- Melanoma & other advanced malignancies

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

This slide contains investigational drug candidates that have not been approved by any regulatory authority.
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

Target Cell:
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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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Killer T Cell

- CD3/TCR
- CD28
- PD-1
- PD-L1

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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)

- Killer T Cell

- CD3/TCR
- CD28

- Tumor Antigen 1
- Tumor Antigen 2

- PD-1
- PD-L1

- CD3
- bispecific

- Costim
- bispecific

- Anti-PD-1

✓ 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
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 specific tumor targets
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

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

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Tumor-Targeted Bispecific Antibodies
- PD-1 Inhibitor

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

**Tumor Model**

- hCD3⁺/hCD28⁺/hPSMA⁺
- MC38/hPSMA 0.3e6 cells/ms SubQ

Dosing start day 9
1x/week (9, 16, 22)

Day 29: Collect tumor and spleen for ex vivo assays

**Ex vivo cell culture**

**Average tumor growth**

- Days Post Implant
- Tumor Volume (mm³)

Days: 0, 10, 20, 30

**Splenocytes**

- IFNγ

**Tumor infiltrating lymphocytes**

- IFNγ

Total spleen or tumor cells incubated overnight

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REGENERON
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:

  1. Dose Escalation
     - Combination R5678 + cemiplimab with 3-week R5678 lead-in
     - Primary endpoint: Safety, tolerability and PK
  2. Dose Expansion
     - R5678 RP2D + cemiplimab 350mg
     - Primary endpoint: ORR

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

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**DO NOT POST**
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)

<table>
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<th>Screening</th>
<th>‘pseudo-progression’</th>
<th>5/19/22</th>
<th>6/21/22</th>
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<tbody>
<tr>
<td>1/20/22</td>
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Investigator assessed target lesions sum of diameters & change from baseline

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<tr>
<td>75</td>
<td>103</td>
<td>65</td>
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<td>+37.3%, PD</td>
<td>-13.3%, SD</td>
<td>-34.7%, PR</td>
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PSMA PET/CT \(18^F\)-DCFPyL (representative images)

Last dose 6JUN2022. Discontinued due to autoimmune encephalitis

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

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

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

More data required to evaluate potential differentiation from Pluvicto™.
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
ACKNOWLEDGEMENTS

INVESTIGATORS AND COLLABORATORS
Mark Stein  Columbia University Medical Center
David Wise  Laura and Isaac Perlmutter Cancer Center (NYU Cancer Institute)
William Kelly  Thomas Jefferson University Hospital
Che-Kai Tsao  Icahn School of Medicine at Mount Sinai
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