

**METHODS OF TREATING PROSTATE CANCER WITH BISPECIFIC ANTI-PSMA x ANTI-CD3
ANTIBODIES AND BISPECIFIC ANTI-PSMA x ANTI-CD28 ANTIBODIES**

REFERENCE TO A SEQUENCE LISTING

[0001] This application incorporates by reference a computer readable Sequence Listing in ST.26 XML format, titled 11724WO01_Sequence, created on February 6, 2025 and containing 52,145 bytes.

FIELD OF THE INVENTION

[0002] The present invention relates to methods for treating cancer comprising administering to a subject in need thereof a bispecific antibody that specifically binds to prostate-specific membrane antigen (PSMA) and CD3 in combination with a bispecific antibody that specifically binds to PSMA and CD28.

BACKGROUND

[0003] Prostate-specific membrane antigen (PSMA), also known as FOLH1, glutamate carboxypeptidase II (GCPII), N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I), or N-acetyl-aspartylglutamate (NAAG) peptidase, is a homodimeric, enzymatic type II transmembrane protein encoded by the folate hydrolase 1 (FOLH1) gene. PSMA is an integral, non-shed membrane glycoprotein highly expressed on malignant prostate tissue and is a cell-surface marker for prostate cancer, but shows limited expression on normal tissue. Its expression is maintained in castrate-resistant prostate cancer, a condition with poor outcome and limited treatment options. Methods for treating prostate cancer by targeting PSMA have been investigated. For example, Yttrium-90 capromab is a radiotherapeutic comprising a monoclonal antibody to an intracellular epitope of PSMA. In another example, J591, a monoclonal antibody to an extracellular epitope of PSMA, is part of the radiotherapeutic Lutetium-177 J591 and in MLN2704, in which maytansinoid 1 (DM1, an antimicrotubule agent) is conjugated to J591. These therapies have been associated with toxicity. PSMA is also expressed within the neovasculature of other tumors such as bladder, renal, gastric, and colorectal carcinomas.

[0004] CD3 is a homodimeric or heterodimeric antigen expressed on T cells in association with the T cell receptor complex (TCR) and is required for T cell activation. Functional CD3 is formed from the dimeric association of two of four different chains: epsilon, zeta, delta and gamma. The CD3 dimeric arrangements include gamma/epsilon, delta/epsilon and zeta/zeta. Antibodies against CD3 have been shown to cluster CD3 on T cells, thereby causing T cell activation in a manner similar to the engagement of the TCR by peptide-loaded MHC molecules. Thus, anti-CD3 antibodies have been proposed for therapeutic purposes involving the activation of T cells. In

addition, bispecific antibodies that are capable of binding CD3 and a target antigen have been proposed for therapeutic uses involving targeting T cell immune responses to tissues and cells expressing the target antigen.

[0005] CD28 is a type I transmembrane protein, which has a single extracellular Ig-V-like domain assembled as a homodimer and which is expressed on the surface of T cells. CD28 is the receptor for the CD80 (B7.1) and CD86 (B7.2) proteins and is activated by CD80 or CD86 expressed on antigen-presenting cells (APCs). The binding of CD28 to CD80 or CD86 provides co-stimulatory signals important for T cell activation and survival. T cell stimulation through CD28, in addition to the T-cell receptor (TCR), provides a potent signal for the production of various interleukins. CD28 also potentiates cellular signals such as pathways controlled by the NFκB transcription factor after TCR activation. The CD28 co-signal is important for effective T-cell activation such as T cell differentiation, proliferation, cytokine release and cell-death. Anti-CD28 antibodies have been proposed for therapeutic purposes involving the activation of T cells. One particular anti-CD28 antibody, TGN1412 (anti-CD28 superagonist), was used in a clinical trial in 2006, in which six healthy volunteers were dosed intravenously with TGN1412 (anti-CD28 superagonist) at a dose of 0.1 mg/kg. Within two hours, all six patients had significant inflammatory responses (cytokine storm), and all patients were in multi-organ failure within sixteen hours. Subjects were treated with corticosteroids, and cytokine levels returned to normal within 2-3 days (Suntharalingam, *et al.*, Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412, NEJM 355:1018-1028 (2006)).

[0006] Programmed death-1 (PD-1) receptor signaling in the tumor microenvironment plays a key role in allowing tumor cells to escape immune surveillance by the host immune system. Blockade of the PD-1 signaling pathway has demonstrated clinical activity in patients with multiple tumor types, and antibody therapeutics that block PD-1 (*e.g.*, nivolumab and pembrolizumab) have been approved for the treatment of metastatic melanoma and metastatic squamous non-small cell lung cancer. Recent data has demonstrated the clinical activity of PD-1 blockade in patients with aggressive NHL and Hodgkin's lymphoma (Lesokhin, *et al.* 2014, Abstract 291, 56th ASH Annual Meeting and Exposition, San Francisco, Calif.; Ansell *et al.* 2015, *N. Engl. J. Med.* 372(4):311-9).

[0007] Prostate cancer is the leading cause of new cancer diagnoses and the second most common cause of cancer-related death in men in the United States. There were 1.3 million new cases of prostate cancer and 358,989 deaths estimated worldwide in 2018. Therapies blocking androgen related pathways have been the standard for decades in treating prostate cancers. However, patients progress on androgen depletion and/or surgical castration and develop castration resistant prostate cancer. Prognosis is especially poor for men with metastatic castration resistant prostate cancer (mCRPC). mCRPC is characterized by an immunosuppressive tumor

microenvironment with few intratumoral effector T cells, leading to low response rates to immune checkpoint inhibitors. Currently, metastatic prostate cancers remain incurable and improvement in long-term survival remains a high unmet need.

BRIEF SUMMARY OF THE INVENTION

[0008] According to certain embodiments, the present disclosure provides methods for treating, ameliorating at least one symptom or indication, or inhibiting the growth of a PSMA-expressing cancer in a subject. The methods according to this aspect of the disclosure comprise administering a bispecific antibody that specifically binds to prostate specific membrane antigen (PSMA) and CD3 as monotherapy, or in combination with an antibody or antigen-binding fragment thereof that specifically binds to programmed death 1 (PD-1), or in combination with a bispecific antibody that specifically binds to PSMA and CD28 to a subject in need thereof. The methods provide increased anti-tumor efficacy and reduced toxicity (e.g., reduced cytokine release syndrome) in the subject.

[0009] In certain embodiments of the present disclosure, methods are provided for treating, ameliorating at least one symptom or indication, or inhibiting the growth of a PSMA-expressing cancer in a subject. In certain embodiments of the present disclosure, methods are provided for delaying the growth of a tumor or preventing tumor recurrence. The methods, according to this and other aspects of the disclosure, comprise sequentially administering one or more doses of a bispecific anti-PSMA x anti-CD3 antibody alone or in combination with one or more doses of an anti-PD-1 antibody or antigen-binding fragment thereof to a subject in need thereof. In certain other embodiments, the methods, according to this and other aspects of the disclosure, comprise sequentially administering one or more doses of the bispecific anti-PSMA x anti-CD3 antibody in combination with a bispecific anti-PSMA x anti-CD28 antibody. In one embodiment, the one or more doses of the bispecific anti-PSMA x anti-CD3 antibody is a subtherapeutic dose.

[0010] In one aspect, the present disclosure provides a method of treating a prostate-specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, comprising administering to the subject a bispecific anti-PSMA x anti-CD3 antibody in a dosing regimen, wherein the dosing regimen comprises: administering an initial dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during week 1 of the dosing regimen; administering at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject, wherein one transitional dose is administered during week 2 of the dosing regimen; and administering a target dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during a subsequent week of the dosing regimen, wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region

(HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 2, 3 and 4, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 6, 7 and 8, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively.

[0011] In one aspect, the present disclosure provides a method of treating a prostate-specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, comprising administering to the subject a bispecific anti-PSMA x anti-CD3 antibody in combination with an anti-PD-1 antibody that binds human programmed cell death-1 (PD-1) in a dosing regimen, wherein the dosing regimen comprises: administering an initial dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during week 1 of the dosing regimen; administering at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject, wherein one transitional dose is administered during week 2 of the dosing regimen; administering a target dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during a first subsequent week of the dosing regimen; and administering the target dose of the bispecific anti-PSMA x anti-CD3 antibody, and a dose of the anti-PD-1 antibody during a second subsequent week of the dosing regimen, wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 2, 3 and 4, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 6, 7 and 8, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the anti-PD-1 antibody comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 32, 33 and 34, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2

and LCDR3 comprising the amino acid sequences of SEQ ID NO: 36, 37 and 38. In certain embodiments, the target dose is a subtherapeutic dose.

[0012] In one aspect, the present disclosure provides a method of treating a prostate-specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, comprising administering to the subject a bispecific anti-PSMA x anti-CD3 antibody in combination with a bispecific anti-PSMA x anti-CD28 antibody in a dosing regimen, wherein the dosing regimen comprises: administering an initial dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during week 1 of the dosing regimen; administering at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject, wherein one transitional dose is administered during week 2 of the dosing regimen; administering a target dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during a first subsequent week of the dosing regimen; and administering the target dose of the bispecific anti-PSMA x anti-CD3 antibody, and a dose of the anti-PSMA x anti-CD28 antibody during a second subsequent week of the dosing regimen, wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 2, 3 and 4, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 6, 7 and 8, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the bispecific anti-PSMA x anti-CD28 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 17, 18 and 19, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 25, 26 and 27, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 21, 22 and 23, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and

LCDR3 comprising the amino acid sequences of SEQ ID NO: 25, 26 and 27, respectively. In certain embodiments, the target dose is a subtherapeutic dose.

[0013] In some embodiments, the first antigen-binding domain of the bispecific anti-PSMA x anti-CD3 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1 and a LCVR comprising the amino acid sequence of SEQ ID NO: 9, and the second antigen-binding domain of the bispecific anti-PSMA x anti-CD3 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 5 and a LCVR comprising the amino acid sequence of SEQ ID NO: 9.

[0014] In some embodiments, the anti-PD-1 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 31 and a LCVR comprising the amino acid sequence of SEQ ID NO: 35.

[0015] In some embodiments, the first antigen-binding domain of the bispecific anti-PSMA x anti-CD28 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 16 and a LCVR comprising the amino acid sequence of SEQ ID NO: 24, and the second antigen-binding domain of the bispecific anti-PSMA x anti-CD28 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 20 and a LCVR comprising the amino acid sequence of SEQ ID NO: 24.

[0016] In some embodiments, the bispecific anti-PSMA x anti-CD3 antibody, the bispecific anti-PSMA x CD28 antibody, and/or the anti-PD-1 antibody comprises a human IgG heavy chain constant region. In some cases, the human IgG heavy chain constant region is isotype IgG1. In some cases, the human IgG heavy chain constant region is isotype IgG4. In some embodiments, the bispecific anti-PSMA x anti-CD3 antibody, the bispecific anti-PSMA x CD28 antibody, and/or the anti-PD-1 antibody comprises a chimeric hinge that reduces Fcγ receptor binding relative to a wild-type hinge of the same isotype. In some embodiments, the bispecific anti-PSMA x anti-CD3 antibody and/or the bispecific anti-PSMA x CD28 antibody comprises a first heavy chain paired with a light chain, and a second heavy chain paired with a light chain, and wherein the first heavy chain or the second heavy chain, but not both, comprises a CH3 domain comprising a H435R (EU numbering) modification and a Y436F (EU numbering) modification.

[0017] In some embodiments, the bispecific anti-PSMA x anti-CD3 antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 13, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 14, and a common light chain comprising the amino acid sequence of SEQ ID NO: 15.

[0018] In some embodiments, the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 39, and a light chain comprising the amino acid sequence of SEQ ID NO: 40.

[0019] In some embodiments, the bispecific anti-PSMA x anti-CD28 antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 28, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 29, and a common light chain comprising the amino acid sequence of SEQ ID NO: 30.

[0020] In some embodiments, the PSMA-expressing cancer is prostate cancer. In some cases, the prostate cancer is metastatic prostate cancer. In some cases, the prostate cancer is castration-resistant prostate cancer. In some cases, the prostate cancer is metastatic castration-resistant prostate cancer.

[0021] In some embodiments, the PSMA-expressing cancer is prostate cancer, breast cancer, lung cancer, colorectal cancer, bladder cancer, renal cell carcinoma (RCC), a primary brain tumor, pancreatic cancer, breast adenocarcinoma, non-small-cell lung cancer, colorectal adenocarcinoma, transitional cell carcinoma, glioblastoma multiforme, pancreatic ductal adenocarcinoma, gastric adenocarcinoma, clear cell RCC, papillary RCC, chromophobe RCC, oncocytoma, angiomyolipoma, squamous cell carcinoma osteosarcoma, adenoid cystic carcinoma, cervical cancer, endometrial cancer, primary ovarian cancer, or metastatic ovarian cancer.

[0022] In some embodiments, the subject has received at least two prior therapies for metastatic and/or castration-resistant prostate cancer. In some embodiments, the subject has received at least one anti-androgen therapy. In some cases, the anti-androgen therapy is selected from abiraterone, enzalutamide, apalutamide, or darolutamide.

[0023] In some embodiments, the subject has histologically or cytologically confirmed adenocarcinoma of the prostate without pure small cell carcinoma. In some embodiments, the subject has metastatic castration-resistant prostate cancer with a prostate specific antigen (PSA) value of ≥ 4 ng/ml prior to treatment with the dosing regimen. In some embodiments, the subject's cancer has progressed within a six month period prior to treatment with the dosing regimen, wherein cancer progression is determined by: (a) a rising PSA level confirmed with an interval of ≥ 1 week between each assessment; (b) radiographic disease progression in soft tissue with or without a rise in PSA; and/or (c) radiographic disease progression in bone with an appearance of two or more bone lesions on bone scan with or without a rise in PSA. In some embodiments, the subject has had an orchiectomy. In some embodiments, the subject is receiving luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy, and has a serum testosterone level of < 50 ng/ml prior to treatment with the dosing regimen.

[0024] In some embodiments, the dosing regimen of any of the methods discussed above or herein further comprises administering an additional therapeutic agent or therapeutic regimen. In some embodiments, the additional therapeutic agent, therapy or regimen comprises surgery, radiation, chemotherapy or anti-androgen therapy.

[0025] In some embodiments, the subject is administered a steroid or an anti-IL-6R antibody before, after or concomitantly with a dose of the bispecific anti-PSMA x anti-CD3 antibody and/or the bispecific anti-PSMA x CD28 antibody.

[0026] In some embodiments, the subsequent week or the first subsequent week is week 3 of the dosing regimen. In some embodiments, the second subsequent week is week 4 of the dosing regimen.

[0027] In some embodiments, the at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody comprises the one transitional dose administered during week 2 of the dosing regimen and a second transitional dose administered during week 3 of the dosing regimen, wherein the second transitional dose is greater than the one transitional dose, but less than the target dose. In some cases, the subsequent week or the first subsequent week is week 4 of the dosing regimen. In some cases, the second subsequent week is week 5 of the dosing regimen.

[0028] In some embodiments, the at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody comprises the one transitional dose administered during week 2 of the dosing regimen, a second transitional dose administered during week 3 of the dosing regimen, and a third transitional dose administered during week 4 of the dosing regimen, wherein the second transitional dose is greater than the one transitional dose, and the third transitional dose is greater than the second transitional dose, but less than the target dose. In some cases, the subsequent week or the first subsequent week is week 5 of the dosing regimen. In some cases, the second subsequent week is week 6 of the dosing regimen.

[0029] In some embodiments of the methods discussed above or herein, the initial dose of the bispecific anti-PSMA x anti-CD3 antibody is 0.01 mg to 100 mg, and the one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody is greater than the initial dose and is 0.03 mg to 300 mg. In some embodiments, the target dose of the bispecific anti-PSMA x anti-CD3 antibody is 0.03 mg to 900 mg.

[0030] In some embodiments of the methods discussed above or herein, the initial dose of the bispecific anti-PSMA x anti-CD3 antibody administered during week 1 of the dosing regimen, and the one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody administered during week 2 of the dosing regimen comprise, respectively: 0.01 mg and 0.03 mg; 0.01 mg and 0.04 mg; 0.01 mg and 0.05 mg; 0.013 mg and 0.07 mg; 0.017 mg and 0.08 mg; 0.02 mg and 0.08 mg; 0.02 mg and 0.11 mg; 0.022 mg and 0.11 mg; 0.029 mg and 0.14 mg; 0.03 mg and 0.15 mg; 0.03 mg and 0.03 mg; 0.03 mg and 0.1 mg; 0.04 mg and 0.13 mg; 0.04 mg and 0.2 mg; 0.045 mg and 0.1 mg; 0.05 mg and 0.15 mg; 0.05 mg and 0.16 mg; 0.05 mg and 0.23 mg; 0.05 mg and 0.25 mg; 0.06 mg and 0.2 mg; 0.06 mg and 0.21 mg; 0.06 mg and 0.3 mg; 0.07 mg and 0.25 mg; 0.07 mg and 0.33 mg; 0.07 mg and 0.34 mg; 0.09 mg and 0.3 mg; 0.09 mg and 0.43 mg; 0.09 mg and 0.45 mg; 0.11

mg and 0.4 mg; 0.12 mg and 0.59 mg; 0.135 mg and 0.45 mg; 0.14 mg and 0.45 mg; 0.14 mg and 0.6 mg; 0.15 mg and 0.5 mg; 0.15 mg and 0.76 mg; 0.18 mg and 0.6 mg; 0.18 mg and 0.8 mg; 0.19 mg and 0.65 mg; 0.2 mg and 0.65 mg; 0.2 mg and 0.9 mg; 0.2 mg and 0.99 mg; 0.24 mg and 0.8 mg; 0.26 mg and 1.3 mg; 0.3 mg and 0.9 mg; 0.3 mg and 1.35 mg; 0.39 mg and 1.8 mg; 0.4 mg and 1.1 mg; 0.45 mg and 1.35 mg; 0.45 mg and 2 mg; 0.5 mg and 1.5 mg; 0.51 mg and 2.3 mg; 0.6 mg and 1.8 mg; 0.6 mg and 2.7 mg; 0.65 mg and 1.9 mg; 0.65 mg and 2 mg; 0.66 mg and 3 mg; 0.68 mg and 3 mg; 0.84 mg and 2.4 mg; 0.86 mg and 3.9 mg; 0.9 mg and 3 mg; 0.9 mg and 4 mg; 1.1 mg and 4 mg; 1.2 mg and 5.2 mg; 1.35 mg and 4.5 mg; 1.4 mg and 6 mg; 1.5 mg and 5 mg; 1.5 mg and 6.8 mg; 1.8 mg and 6 mg; 1.8 mg and 8 mg; 1.9 mg and 6.5 mg; 2 mg and 6.5 mg; 2 mg and 8.8 mg; 2 mg and 9 mg; 2.4 mg and 8.4 mg; 2.6 mg and 11.4 mg; 3 mg and 9 mg; 3 mg and 12 mg; 3.9 mg and 11.7 mg; 3.9 mg and 15.5 mg; 4.5 mg and 13.5 mg; 4.5 mg and 18 mg; 5.1 mg and 15.2 mg; 5.1 mg and 20.3 mg; 6 mg and 18 mg; 6 mg and 24 mg; 6.6 mg and 19.8 mg; 6.6 mg and 26.4 mg; 6.75 mg and 20.25 mg; 6.8 mg and 27 mg; 8.6 mg and 25.7 mg; 8.6 mg and 34.3 mg; 10 mg and 30 mg; 10 mg and 36 mg; 13 mg and 39 mg; 15 mg and 45 mg; 17 mg and 50.7 mg; 20 mg and 60 mg; 22 mg and 66 mg; 22.5 mg and 67.5 mg; 28.6 mg and 85.7 mg; 30 mg and 100 mg; 39 mg and 130 mg; 45 mg and 150 mg; 50.7 mg and 169 mg; 60 mg and 200 mg; 66 mg and 222 mg; 67.5 mg and 225 mg; 85.7 mg and 286 mg; or 100 mg and 300 mg. In some embodiments, the initial dose is from 0.01 to 0.15 mg, and the transitional dose is from 0.7 to 1.5 mg. In some embodiments, the initial dose is from 0.01 mg to 0.15 mg. In some embodiments, the transitional dose is from 0.7 mg to 1.5 mg.

[0031] In some embodiments of the methods discussed above or herein, the target dose of the bispecific anti-PSMA x anti-CD3 antibody is 0.03 mg, 0.3 mg, 0.39 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.51 mg, 0.6 mg, 0.66 mg, 0.7 mg, 0.86 mg, 0.9 mg, 1 mg, 1.1 mg, 1.3 mg, 1.35 mg, 1.5 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.9 mg, 3 mg, 3.9 mg, 4 mg, 4.5 mg, 5 mg, 5.1 mg, 6 mg, 6.5 mg, 6.6 mg, 6.8 mg, 8.4 mg, 8.6 mg, 9 mg, 11 mg, 11.7 mg, 13.5 mg, 15 mg, 15.2 mg, 18 mg, 19 mg, 19.8 mg, 20 mg, 20.3 mg, 24 mg, 25.7 mg, 30 mg, 39 mg, 45 mg, 50.7 mg, 51 mg, 60 mg, 65.9 mg, 66 mg, 67.5 mg, 85.7 mg, 86 mg, 100 mg, 130 mg, 150 mg, 169 mg, 200 mg, 220 mg, 225 mg, 286 mg, 300 mg, 390 mg, 450 mg, 507 mg, 600 mg, 659 mg, 675 mg, 857 mg or 900 mg.

[0032] In some embodiments of the methods discussed above or herein, the initial dose of the bispecific anti-PSMA x CD3 antibody is 0.1 mg to 0.18 mg (*e.g.*, 0.14 mg), the transitional dose is 0.9 mg to 1.3 mg, and the target dose is selected from the group consisting of 5-10 mg, 10-15 mg, 15-20 mg, 20-25 mg, 25-30 mg, 30-35 mg, 35-40 mg, 40-45 mg, 45-50 mg, 50-55 mg, 55-60 mg, 60-65 mg, 65-70 mg, 70-75 mg, 75-80 mg, 80-85 mg, 85-90 mg, 90-95 mg, and 95-100 mg. In some cases, administration of the bispecific anti-PSMA x CD3 antibody (*e.g.*, weekly or once every

three weeks) may be combined with a dose of 300 mg to 400 mg (*e.g.*, 350 mg) of the anti-PD-1 antibody (*e.g.*, administered Q3W), as discussed herein. In some cases, administration of the bispecific anti-PSMA x CD3 antibody may be combined with a dose of 20 mg to 40 mg (*e.g.*, 30 mg), 75 mg to 125 mg (*e.g.*, 100 mg), or 275 mg to 325 mg (*e.g.*, 300 mg) of the bispecific anti-PSMA x CD28 antibody (*e.g.*, administered weekly or once every three weeks), as discussed herein.

[0033] In some embodiments, one or more target doses of the bispecific anti-PSMA x anti-CD3 antibody are administered to the subject weekly, or once every three weeks (Q3W), after the first target dose in the dosing regimen.

[0034] In some embodiments, the anti-PD-1 antibody is administered to the subject at a dose of 300 to 400 mg. In some cases, the anti-PD-1 antibody is administered to the subject at a dose of 350 mg. In some cases, the anti-PD-1 antibody is administered to the subject once every three weeks after the first dose of the anti-PD-1 antibody in the dosing regimen.

[0035] In some embodiments, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 20 mg to 40 mg. In some cases, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 30 mg. In some embodiments, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 50 mg to 150 mg. In some cases, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 100 mg. In some embodiments, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 250 mg to 350 mg. In some cases, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 300 mg. In some cases, the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject weekly, or once every three weeks (Q3W), after the first dose of the bispecific anti-PSMA x anti-CD28 antibody in the dosing regimen.

[0036] In some embodiments, the bispecific anti-PSMA x anti-CD3 antibody, the anti-PD-1 antibody and/or the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject subcutaneously. In some embodiments, the bispecific anti-PSMA x anti-CD3 antibody, the anti-PD-1 antibody and/or the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject intravenously.

[0037] In some embodiments, the subject has stable disease, a partial response, or a complete response following administration of the dosing regimen.

[0038] In some embodiments, the subject is subjected to radiographic imaging following administration of one or more doses of the bispecific antibody. In some cases, the radiographic imaging comprises a Fluorine F18 DCFPyL PET/CT scan. In some cases, the radiographic imaging comprises a Gallium Ga PSMA-11 PET/CT scan.

[0039] In some embodiments, the subject has previously received an androgen deprivation therapy and a taxane chemotherapy, optionally wherein the androgen deprivation therapy comprises abiraterone, enzalutamide, apalutamide, and/or darolutamide, and optionally wherein the taxane chemotherapy comprises docetaxel.

[0040] In some embodiments, the subject has previously received a radioligand therapeutic agent, optionally wherein the radioligand therapeutic agent is lutetium Lu 177 vipivotide tetraxetan.

[0041] In some embodiments, the subject has not previously received a therapy for treatment of the PSMA-expressing cancer.

[0042] In various embodiments, any of the features or components of embodiments discussed above or herein may be combined, and such combinations are encompassed within the scope of the present disclosure. Any specific value discussed above or herein may be combined with another related value discussed above or herein to recite a range with the values representing the upper and lower ends of the range, and such ranges are encompassed within the scope of the present disclosure.

[0043] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0044] Figure 1 illustrates the inhibition of PSMA-expressing tumor growth *in vivo* with low dose REGN4336 in combination with REGN5678. CD, Cluster of differentiation; h (as a prefix), Human; PSMA, Prostate-specific membrane antigen; PTI, Post-tumor implantation; TAA, Tumor-associated antigen; TRAMPC2, Transgenic adenocarcinoma of mouse prostate C2. Symbols on the graphs represent group means and error bars represent standard error of the mean.

[0045] Figures 2A and 2B illustrate the lower cytokine release resulting from low dose administration of REGN4336 in combination with REGN5678 relative to the cytokine release from administration of high dose REGN4336 monotherapy. CD, Cluster of differentiation; h (as a prefix), Human; IFNG, Interferon gamma; IL, Interleukin; KC-GRO, Keratinocyte chemoattractant/human growth-regulated oncogene; PSMA, Prostate-specific membrane antigen; TAA, Tumor-associated antigen; TNFA, Tumor necrosis factor alpha; TRAMPC2, Transgenic adenocarcinoma of mouse prostate C2. Symbols on the graphs represent individual mice and error bars represent standard error of the mean.

[0046] Figure 3 illustrates the survival of mice administered low dose REGN4336 in combination with REGN5678 relative to survival of mice administered high dose REGN4336 monotherapy. CD, Cluster of differentiation; h (as a prefix), Human; PSMA, Prostate-specific membrane antigen; PTI, Post-tumor implantation; TAA, Tumor-associated antigen; TRAMPC2, Transgenic adenocarcinoma

of mouse prostate C2. Tumor volume was measured, and mice were euthanized when the tumor size reached $>2000 \text{ mm}^3$. Percentage survival is plotted over time. Results for survival were analyzed using a Log-rank (Mantel-Cox) test for significance. “&” symbol indicates a significant difference between the group dosed with non-TAAxCD3 + IgG4^{P-PVA} isotype control compared with REGN4336 (5 mg/kg) + IgG4^{P-PVA} isotype control; “#” symbol indicates a significant difference between the group dosed with non-TAAxCD3 + IgG4^{P-PVA} isotype control compared with REGN4336 (0.02 mg/kg) + REGN5678. Increasing numbers of symbols represent increasing significance: 1x= $P<0.05$, 2x= $P<0.001$.

[0047] Figure 4 illustrates the minimization of IFNG release resulting from administration of a low dose of REGN4336 in combination with REGN5678. CD, Cluster of differentiation; h (as a prefix), Human; IFNG, Interferon gamma; PSMA, Prostate-specific membrane antigen; TAA, Tumor-associated antigen; TRAMPC2, Transgenic adenocarcinoma of mouse prostate C2. Symbols on the graphs represent individual mice and error bars represent standard error of the mean. Data were analyzed using an ordinary 1-way analysis of variance and Tukey’s multiple comparisons test. “**” symbols indicate significant differences compared with all other groups. Number of “**” symbols represent increasing significance: 4x= $P<0.0001$.

[0048] Figures 5A and 5B illustrate re-challenge tumor rejection rate (Fig. 5A), and the presence of tumor-specific T cells in the spleens of re-challenged mice (Fig. 5B). In Fig. 5A, bars represent the frequency of tumor-free mice 21 days after re-challenge tumor implant. Statistical significance was determined using Chi-square test. N=31 mice per group combined from 4 separate experiments. In Fig. 5B, the results of a SPAS-1 Trampc2 neoantigen ELISPOT assay are shown. IFNg ELISPOT was performed with 200,000 spleens cells incubated with 1 μ M of peptide overnight. The numbers of SPAS-1 TrampC2 neoantigen (SNC9-H8 S-T-H-V-N-H-L-H-C) were normalized to negative control OVA OT1 peptide (S-I-I-N-F-E-K-L). Symbols represent the number of SPAS-1 specific T cells counted from individual mice. Statistical significance was determined using an Unpaired T test. Data was combined from 2 separate experiments.

[0049] Figure 6 illustrates an embodiment of the patient-level study schema for Module 1, as discussed in Example 4.

[0050] Figure 7 illustrates an embodiment of the patient-level study schema for Module 2, as discussed in Example 4.

[0051] Figure 8 illustrates an embodiment of the patient-level study schema for Module 3, as discussed in Example 4.

[0052] Figure 9 illustrates an embodiment of the patient-level study schema for Module 3, as discussed in Example 4, including premedication options. The dexamethasone premedication is optional in an embodiment, and in an embodiment the dexamethasone doses beginning with cycle

2 are optional. In an embodiment, sarilumab may also be administered prior to the initial dose of the PSMA x CD3 antibody. The starred doses may be administered as detailed in Figure 8.

DETAILED DESCRIPTION

[0053] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims. Any embodiments or features of embodiments can be combined with one another, and such combinations are expressly encompassed within the scope of the present invention. Any specific value discussed above or herein may be combined with another related value discussed above or herein to recite a range with the values representing the upper and lower ends of the range, and such ranges are encompassed within the scope of the present disclosure.

[0054] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0055] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All patents, applications and non-patent publications mentioned in this specification are incorporated herein by reference in their entireties.

[0056] A high unmet need is present for patients with metastatic castration-resistant prostate cancer (mCRPC). Prostate cancer is the second leading cause of cancer death in men in the United States (In 2020, the American Cancer Society estimated around 192,000 new cases and 33,000 deaths of patients with mCRPC). Therapies blocking androgen related pathways have been the standard for decades in treating prostate cancers. However, patients progress on androgen depletion and/or surgical castration and develop castrate resistant prostate cancer.

[0057] The standard-of-care for treating mCRPC has rapidly evolved with several recent therapies including second generation androgen receptor pathway targeting agents (abiraterone acetate, enzalutamide), chemotherapy (docetaxel, cabazitaxel), immunotherapy (Sipuleucel-T) and bone-targeted agents (radium-223). Although these agents have improved survival, metastatic prostate cancers remain incurable and improvement in long-term survival is of urgent need.

[0058] The study discussed in Example 4, below includes 3 separate modules with the goal of determining which of three immunotherapeutic-based approaches may provide the greatest potential benefit versus risk for patients with mCRPC.

[0059] Module 1 will evaluate REGN4336 (PSMAxCD3) monotherapy. Module 1 began by evaluating REGN4336 administered subcutaneously (SC) and will also evaluate REGN4336 administered intravenously (IV) based on observations that: (i) cytokine release syndrome (CRS) has been observed despite SC dosing requiring steroid prophylaxis; (ii) SC dosing results in injection site reactions (ISRs) also requiring steroid prophylaxis (which may negatively impact anti-tumor activity); and (iii) experience with several PSMAxCD3 programs suggests that immunogenicity may be problematic with PSMAxCD3 bispecific antibodies and might be mitigated by IV administration.

[0060] Module 2 will evaluate REGN4336 in combination with cemiplimab, an anti-PD-1 monoclonal antibody, based on the hypothesis that release from PD-1 checkpoint inhibition may foster the proliferation and cytolytic activity of CD3-positive killer T-cells.

[0061] Module 3 will evaluate REGN4336 in combination with REGN5678, a PSMAxCD28 bispecific antibody, based on preclinical data demonstrating that 1) co-stimulation through CD28 enhances the proliferation and cytolytic activity of CD3-positive killer T cells activated by a PSMAxCD3 bsAb in PSMA+ tumors and 2) this combination may allow for administration of lower doses of the PSMAxCD3 bsAb and hence less cytokine secretion. In particular, Module 3 will evaluate enhanced activation of T-cells through the administration of PSMA-directed exogenous signal 1 (provided by REGN4336) in combination with exogenous signal 2 (provided by REGN5678). After T-cells recognize and bind target cells through the CD3/TCR complex (signal 1), their activation and proliferation can be further enhanced when T-cell costimulatory receptors such as CD28 engage their cognate ligands (CD80, CD86, B7-H2) on professional antigen-presenting cells or target cells (signal 2). In preclinical studies, the addition of a PSMAxCD28 bispecific antibody markedly increased the ability of a PSMAxCD3 bispecific antibody to expand and activate CD4+ and CD8+ T-cells and to induce T-cell killing of PSMA-expressing tumor cells in prostate cancer models *in vitro* and *in vivo*. In a syngeneic triple humanized mouse model (TrampC2/hPSMA tumors implanted in hCD3/hCD28/hPSMA mice), subtherapeutic doses of the PSMAxCD3 bispecific (0.02 mg/kg) in combination with the PSMAxCD28 bispecific (0.5-5 mg/kg) achieved comparable (and near complete) suppression of tumor growth similar to the higher monotherapy doses of PSMAxCD3 that demonstrate activity *in vivo* (5 mg/kg). However, whereas PSMAxCD3 monotherapy (5 mg/kg) was associated with significant cytokine release as measured 4 hours post-dose in serum of treated mice (IFN- γ 200 pg/mL), lower-dose, subtherapeutic PSMAxCD3 (0.02 mg/kg) combined with PSMAxCD28 (0.5-5 mg/kg) induced near-negligible cytokine release. These

findings suggest that combining subtherapeutic doses of PSMAxCD3 with PSMAxCD28 may provide anti-tumor activity and reduce toxicity, particularly cytokine release syndrome, which may be a dose-limiting toxicity of CD3-directed bispecific antibodies (REGN4336). In a study in which patients received a combination of REGN5678 IV QW with cemiplimab 350 mg IV Q3W, several high-grade iAEs were observed, which primarily occurred after the addition of PD-1 blockade. Notably, these events occurred primarily in patients with evidence of anti-tumor activity. Without intending to be bound, it is hypothesized that these events may relate to breaking self-tolerance of potentially auto-reactive T-cells that were enriched in the tumor tissue and recognized self-antigens presented by MHC on tumor cells or within draining lymph nodes. These auto-reactive T-cells located in proximity to PSMA may have been previously rendered tolerant through the combined activity of PD-1 signaling and absence of CD28 costimulation. Systemic (non-targeted) PD-1 blockade may also contribute to activation of auto-reactive T cells in healthy tissue. As discussed above, animal models suggest that the combination of the PSMAxCD28 bispecific antibody with low doses of the PSMAxCD3 bispecific antibody do not require the addition of checkpoint (PD-1/PD-L1) inhibition to induce substantial anti-tumor immunity. Thus, in contrast to the combination of costimulation plus checkpoint inhibition used in study mentioned above, the use in Module 3 of low-dose REGN4336 (PSMAxCD3) to activate T-cells in a non-cognate manner together with conservative doses of the costimulatory antibody REGN5678 (PSMAxCD28), in the absence of anti-PD-1, may result in anti-tumor activity without the activation of T-cells whose cognate receptors react with self-antigen presented by MHC. Thus, it is hypothesized that the combination of REGN5678 with REGN4336 at low doses may result in anti-tumor effects while avoiding the high-grade iAEs observed in the study mentioned above. Consistent with these observations, an in-house *in vitro* study showed that REGN4336-mediated cytotoxicity against C4-2 cells was accompanied by IFN-gamma, IL6, IL10, and tumor necrosis factor α (TNF- α) release from human PBMCs. Administration of the non-target-antigenxCD3 bispecific antibody did not mediate cytokine release from human PBMCs.

Methods for Treating or Inhibiting the Growth of Cancers

[0062] The present disclosure includes methods for treating, ameliorating or reducing the severity of at least one symptom or indication, or inhibiting the growth of a PSMA-expressing cancer (*e.g.*, metastatic castration-resistant prostate cancer) in a subject. The methods according to this aspect of the disclosure comprise administering a bispecific antibody against PSMA and CD3 alone, or in combination with an antibody or antigen-binding fragment thereof that specifically binds PD-1, or in combination with a bispecific antibody against PSMA and CD28 to a subject in need thereof. As used herein, the terms "treat", "treating", or the like, mean to alleviate symptoms, eliminate the

causation of symptoms either on a temporary or permanent basis, to delay or inhibit tumor growth, to reduce tumor cell load or tumor burden, to promote tumor regression, to cause tumor shrinkage, necrosis and/or disappearance, to prevent tumor recurrence, and/or to increase duration of survival of the subject.

[0063] As used herein, references to cancer include PSMA-expressing cancers, and include any cancer comprising cells expressing PSMA (*e.g.*, human PSMA) or for which PSMA (*e.g.*, human PSMA) is expressed in the tumor vascular endothelium, PSMA-expressing cancers include, without limitation, prostate cancer, breast cancer, lung cancer, colorectal cancer, bladder cancer, renal cell carcinoma (RCC), primary brain tumors, and pancreatic cancer, and more specifically metastatic prostate cancer, metastatic castration-resistant prostate cancer, breast adenocarcinoma, non-small-cell lung cancer, colorectal adenocarcinoma, transitional cell carcinoma, glioblastoma multiforme, pancreatic ductal adenocarcinoma, gastric adenocarcinoma, clear cell RCC, papillary RCC, chromophobe RCC, oncocytoma, angiomyolipoma, squamous cell carcinoma osteosarcoma, adenoid cystic carcinoma, cervical cancer, endometrial cancer, or primary or metastatic ovarian cancer.

[0064] As used herein, the expression "a subject in need thereof" means a human or non-human mammal that exhibits one or more symptoms or indications of cancer, and/or who has been diagnosed with cancer, including a prostate cancer (*e.g.*, metastatic castration-resistant prostate cancer) and who needs treatment for the same. In many embodiments, the term "subject" may be interchangeably used with the term "patient". For example, a human subject may be diagnosed with a primary or a metastatic tumor and/or with one or more symptoms or indications including, but not limited to, enlarged lymph node(s), swollen abdomen, unexplained pain, unexplained weight loss, fever, night sweats, persistent fatigue, loss of appetite, and/or enlargement of spleen. The expression includes subjects with primary or established prostate tumors. In specific embodiments, the expression includes human subjects that have and need treatment for prostate cancer or another tumor expressing PSMA. In other specific embodiments, the expression includes subjects with PSMA+ tumors (*e.g.*, a tumor with PSMA expression as determined by flow cytometry). In certain embodiments, the expression "a subject in need thereof" includes patients with a prostate cancer that is resistant to or refractory to or is inadequately controlled by prior therapy (*e.g.*, treatment with a conventional anti-cancer agent, including anti-androgen therapy). For example, the expression includes subjects who have been treated with chemotherapy, or anti-androgen therapy such as, for example, abiraterone, enzalutamide, apalutamide, or darolutamide. The expression also includes subjects with a prostate tumor for which conventional anti-cancer therapy is inadvisable, for example, due to toxic side effects. For example, the expression includes patients who have received one or more cycles of chemotherapy or other anti-cancer therapy with toxic side

effects. In certain embodiments, the expression "a subject in need thereof" includes patients with a prostate tumor which has been treated but which has subsequently relapsed or metastasized. For example, patients with a prostate tumor that may have received treatment with one or more anti-cancer agents leading to tumor regression; however, subsequently have relapsed with cancer resistant to the one or more anti-cancer agents (*e.g.*, castration-resistant prostate cancer) are treated with the methods of the present disclosure.

[0065] In certain embodiments, the methods of the present disclosure may be used to treat patients that have histologically or cytologically confirmed adenocarcinoma of the prostate without pure small cell carcinoma. In certain embodiments, the methods of the present disclosure may be used to treat patients that have metastatic castration-resistant prostate cancer with a prostate specific antigen (PSA) value of ≥ 4 ng/ml (*e.g.*, 4 ng/ml, 4.5 ng/ml, 5 ng/ml, 5.5 ng/ml, 6 ng/ml, 6.5 ng/ml, 7 ng/ml, 7.5 ng/ml, 8 ng/ml, 8.5 ng/ml, 9 ng/ml, 9.5 ng/ml, or 10 ng/ml or more) prior to treatment with the bispecific antibody (PSMA x CD3, or PSMA x CD3 and PSMA x CD28). In certain embodiments, the methods of the present disclosure may be used to treat patients with prostate cancer that has progressed within a period (*e.g.*, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 7 months, 8 months, 9 months, or more) prior to treatment with the bispecific antibody (PSMA x CD3, or PSMA x CD3 and PSMA x CD28), wherein cancer progression is determined by, for example,: (a) a rising PSA level confirmed with an interval of ≥ 1 week (*e.g.*, 1 week, 2 weeks, 3 weeks, 4 weeks, or more) between each assessment; (b) radiographic disease progression in soft tissue with or without a rise in PSA; and/or (c) radiographic disease progression in bone with an appearance of two or more bone lesions on bone scan with or without a rise in PSA. In certain embodiments, the methods of the present disclosure may be used to treat patients that have had an orchiectomy. In certain embodiments, the methods of the present disclosure may be used to treat patients that have or are receiving luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy, and have a serum testosterone level of < 50 ng/ml (*e.g.*, from 1 ng/ml to 49 ng/ml, about 45 ng/ml, about 40 ng/ml, about 35 ng/ml, about 30 ng/ml, about 25 ng/ml, about 20 ng/ml, about 15 ng/ml, about 10 ng/ml, or about 5 ng/ml) prior to treatment with the bispecific antibody (PSMA x CD3, or PSMA x CD3 and PSMA x CD28).

[0066] In certain embodiments, the methods of the present disclosure are used in a subject with prostate cancer. The terms "tumor", "cancer" and "malignancy" are interchangeably used herein. The term "prostate cancer", as used herein, refers to tumors of the prostate, including metastatic tumors originating in the prostate.

[0067] According to certain embodiments, the present disclosure includes methods for treating, or delaying or inhibiting the growth of a tumor. In certain embodiments, the present disclosure includes methods to promote tumor regression. In certain embodiments, the present disclosure includes

methods to reduce tumor cell load or to reduce tumor burden. In certain embodiments, the present disclosure includes methods to prevent tumor recurrence. The methods, according to this aspect of the disclosure, comprise administering a bispecific anti-PSMA/anti-CD3 antibody alone, or in combination with an anti-PD-1 antibody, or administering a bispecific anti-PSMA x CD3 antibody in combination with a bispecific anti-PSMA x CD28 antibody to a subject in need thereof, wherein each antibody is administered to the subject in multiple doses, *e.g.*, as part of a specific therapeutic dosing regimen. For example, the therapeutic dosing regimen may comprise administering one or more doses of an anti-PSMA x CD3 antibody to the subject at a frequency of about once a day, once every two days, once every three days, once every four days, once every five days, once every six days, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, once every two months, once every three months, once every four months, or less frequently. In certain embodiments, the anti-PSMA x anti-CD3 antibody is administered once a week. In certain embodiments, the anti-PSMA x anti-CD3 antibody is administered once every three weeks. In certain embodiments, the one or more doses of anti-PD-1 antibody are administered in combination with the one or more doses of a bispecific anti-PSMA/anti-CD3 antibody, wherein the one or more doses of the anti-PD-1 antibody are administered to the subject at a frequency of about once a day, once every two days, once every three days, once every four days, once every five days, once every six days, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, once every two months, once every three months, once every four months, or less frequently. In certain embodiments, the anti-PD-1 antibody is administered to the subject once every three weeks. In certain embodiments, the one or more doses of anti-PSMA x anti-CD28 antibody are administered in combination with the one or more doses of a bispecific anti-PSMA/anti-CD3 antibody, wherein the one or more doses of the anti-PSMA x anti-CD28 antibody are administered to the subject at a frequency of about once a day, once every two days, once every three days, once every four days, once every five days, once every six days, once a week, once every two weeks, once every three weeks, once every four weeks, once a month, once every two months, once every three months, once every four months, or less frequently. In certain embodiments, the anti-PSMA x anti-CD28 antibody is administered to the subject once per week.

[0068] In certain embodiments, doses of the anti-PSMA/anti-CD3 antibody and/or the anti-PSMA/anti-CD28 antibody are administered in two or more fractions, *e.g.*, in 2-5 fractions ("split dosing") within the given dosing period. In certain embodiments, a dose of the bispecific antibody (anti-PSMAxCD3 or anti-PSMAxCD28) is split into 2 or more fractions, wherein each fraction comprises an amount of the antibody equal to the other fractions. In certain embodiments, a dose of the bispecific antibody (anti-PSMAxCD3 or anti-PSMAxCD28) is administered split into 2 or more

fractions, wherein the fractions comprise unequal amounts of the antibody, *e.g.*, more than or less than the first fraction.

[0069] In certain embodiments, the present disclosure includes methods to inhibit, retard or stop tumor metastasis or tumor infiltration into peripheral organs. The methods, according to this aspect, comprise administering a bispecific anti-PSMA/anti-CD3 antibody alone, or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody to a subject in need thereof.

[0070] In specific embodiments, the present disclosure provides methods for increased anti-tumor efficacy or increased tumor inhibition. The methods, according to this aspect of the disclosure, comprise administering to a subject with prostate cancer one or more doses of a bispecific anti-PSMA/anti-CD3 antibody prior to administering an anti-PD-1 antibody, wherein the bispecific anti-PSMA/anti-CD3 antibody may be administered about 1 day, more than 1 day, more than 2 days, more than 3 days, more than 4 days, more than 5 days, more than 6 days, or more than 7 days prior to the anti-PD-1 antibody. In some embodiments, the two antibodies (anti-PSMAxCD3 and anti-PD-1) are administered within 7 days of one another, within 6 days of one another, within 5 days of one another, within 4 days of one another, within 3 days of one another, within 2 days of one another, within 24 hours of one another, within 12 hours of one another, or within 6 hours of one another. In certain embodiments, the methods provide for increased tumor inhibition, *e.g.*, by about 20%, more than 20%, more than 30%, more than 40%, more than 50%, more than 60%, more than 70% or more than 80% as compared to a subject administered the bispecific antibody alone.

[0071] In specific embodiments, the present disclosure provides methods for anti-tumor efficacy or tumor inhibition. but with reduced risk of adverse events (*e.g.*, CRS). The methods, according to this aspect of the disclosure, comprise administering to a subject with prostate cancer one or more doses of a bispecific anti-PSMA/anti-CD3 antibody prior to administering a bispecific anti-PSMA/anti-CD28 antibody, wherein the one or more doses may be a subtherapeutic dose and wherein the bispecific anti-PSMA/anti-CD3 antibody may be administered about 1 day, more than 1 day, more than 2 days, more than 3 days, more than 4 days, more than 5 days, more than 6 days, or more than 7 days prior to the bispecific anti-PSMA/anti-CD28 antibody. In some embodiments, the two antibodies (anti-PSMAxCD3 and anti-PSMAxCD28) are administered within 7 days of one another, within 6 days of one another, within 5 days of one another, within 4 days of one another, within 3 days of one another, within 2 days of one another, within 24 hours of one another, within 12 hours of one another, or within 6 hours of one another.

[0072] In certain embodiments, the methods of the present disclosure are used to treat a patient with a MRD-positive disease. Minimum residual disease (MRD) refers to small numbers of cancer cells that remain in the patient during or after treatment, wherein the patient may or may not show

symptoms or signs of the disease. Such residual cancer cells, if not eliminated, frequently lead to relapse of the disease. The present disclosure includes methods to inhibit and/or eliminate residual cancer cells in a patient upon MRD testing. MRD may be assayed according to methods known in the art (*e.g.*, MRD flow cytometry). The methods, according to this aspect of the disclosure, comprise administering a bispecific anti-PSMA/anti-CD3 antibody alone, or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody to a subject in need thereof.

[0073] The methods of the present disclosure, according to certain embodiments, comprise administering to a subject a bispecific anti-PSMA/anti-CD3 antibody alone, or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody and, optionally, an additional therapeutic agent or therapeutic regimen. The additional therapeutic agent or therapeutic regimen may be selected from the group consisting of, *e.g.*, radiation, chemotherapy, surgery, a cancer vaccine, an oncolytic virus, a PD-L1 inhibitor (*e.g.*, an anti-PD-L1 antibody), a LAG3 inhibitor (*e.g.*, an anti-LAG3 antibody), a CTLA-4 inhibitor (*e.g.*, an anti-CTLA-4 antibody), a TIM3 inhibitor, a BTLA inhibitor, a TIGIT inhibitor, a CD47 inhibitor, an indoleamine-2,3-dioxygenase (IDO) inhibitor, a vascular endothelial growth factor (VEGF) antagonist, an Ang2 inhibitor, a transforming growth factor beta (TGF.β) inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an antibody to a tumor-specific antigen, a cytotoxin, a chemotherapeutic agent, anti-androgen therapy, an IL-6R inhibitor, an IL-4R inhibitor, an IL-10 inhibitor, a cytokine such as IL-2, IL-7, IL-21, and IL-15, an anti-inflammatory drug such as corticosteroids, and non-steroidal anti-inflammatory drugs, and a dietary supplement such as anti-oxidants. In certain embodiments, the antibodies may be administered in combination with therapy including a chemotherapeutic agent, radiation and surgery. As used herein, the phrase "in combination with" includes administration of the antibodies to the subject at the same time as, just before, or just after administration of the additional therapeutic agent or therapeutic regimen (*e.g.*, within one week, within 96 hours, within 72 hours, within 48 hours, within 36 hours, or within 24 hours). In certain embodiments, the antibody or antibodies, and the additional therapeutic agent are administered in separate formulations.

[0074] In any of the various embodiments discussed herein, the methods of the present disclosure may further comprise administration of a steroid (*e.g.*, dexamethasone or an equivalent steroid), or an anti-IL-6 receptor antibody. In some cases, the anti-IL-6 receptor antibody is tocilizumab or sarilumab. In some cases, the steroid (*e.g.*, dexamethasone) may be administered at a dose of from 1 mg to 20 mg (*e.g.*, from 5 mg to 10 mg) IV or PO. In some cases, these agents may be administered as premedications prior to (*e.g.*, within 12-36 hours) administration of the bispecific anti-PSMA/anti-CD3 antibody (*e.g.*, REGN4336) and/or the bispecific anti-PSMA/anti-

CD28 antibody (e.g., REGN5678).

[0075] In certain embodiments, the methods of the present disclosure comprise administering to a subject in need thereof a bispecific anti-PSMA/anti-CD3 antibody alone, or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody. Where the bispecific anti-PSMA/anti-CD3 antibody or the combination is administered, the administration of the antibodies leads to increased inhibition of tumor growth. In certain embodiments, tumor growth is inhibited by at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70% or about 80% as compared to an untreated subject or a subject administered with either antibody as monotherapy, respectively. In certain embodiments, the administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination leads to increased tumor regression, tumor shrinkage and/or disappearance. In certain embodiments, the administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination leads to delay in tumor growth and development, e.g., tumor growth may be delayed by about 3 days, more than 3 days, about 7 days, more than 7 days, more than 15 days, more than 1 month, more than 3 months, more than 6 months, more than 1 year, more than 2 years, or more than 3 years as compared to an untreated subject or a subject treated with either antibody as monotherapy, respectively. In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination prevents tumor recurrence and/or increases duration of survival of the subject, e.g., increases duration of survival by more than 15 days, more than 1 month, more than 3 months, more than 6 months, more than 12 months, more than 18 months, more than 24 months, more than 36 months, or more than 48 months relative to an untreated subject or a subject which is administered either antibody as monotherapy, respectively. In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination increases progression-free survival or overall survival. In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination increases response and duration of response in a subject, e.g., by more than 2%, more than 3%, more than 4%, more than 5%, more than 6%, more than 7%, more than 8%, more than 9%, more than 10%, more than 20%, more than 30%, more than 40% or more than 50% over an untreated subject or a subject which has received either antibody as monotherapy, respectively. In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination to a subject with prostate cancer leads to complete disappearance of all evidence of tumor cells ("complete response"). In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination to a subject with prostate cancer leads to at least 30% or more decrease in tumor cells or tumor size ("partial response"). In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody or the combination to a subject with prostate cancer leads to complete or partial disappearance of tumor cells/lesions including new measurable lesions.

Tumor reduction can be measured by any of the methods known in the art, e.g., X-rays, positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), cytology, histology, or molecular genetic analyses. In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody and the anti-PD-1 antibody produces a synergistic anti-tumor effect that exceeds the combined effects of the two agents when administered alone. In certain embodiments, administration of the bispecific anti-PSMA/anti-CD3 antibody and the bispecific anti-PSMA/anti-CD28 antibody produces a therapeutic effect as discussed above or herein, but with a reduced incidence or risk of adverse events (e.g., CRS) relative to administration of a higher dose of the bispecific anti-PSMA/anti-CD3 antibody alone.

[0076] In certain cases, the response of a subject to therapy is categorized as a complete response (CR), a partial response (PR), progressive disease (PD), or as stable disease (SD). A CR is defined as disappearance of all target lesions, and a reduction in short axis of any pathological lymph nodes (whether target or non-target) to <10 mm (<1 cm). A PR is defined as an at least 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. PD is defined as an at least 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered a progression). SD is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

[0077] In certain cases, immune-based therapy response criteria may be used to evaluate responses. Immune-based therapy response criteria differ from RECIST (Version 1.1) in that progressive disease is slightly more challenging to confirm, as it must occur in the scan immediately following an unconfirmed progressive disease scan. This difference is based upon understanding that immune therapies may cause pseudoprogression based on inflammation up to and including development of new lesions. Hence, two scans no less than 4 weeks apart must agree that disease is progressing for confirmed progressive disease. The criteria used to evaluate target lesions and non-target lesions are discussed below.

[0078] Evaluation of Target Lesions

Immune Complete Response (iCR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm)

Immune Partial Response (iPR): At least a 30% decrease in the sum of the diameters of target lesions taking as reference the baseline sum diameters

Immune Unconfirmed Progressive Disease (iUPD): At least a 20% increase in the sum of the diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) that are new since the last imaging done. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm)

Immune Confirmed Progressive Disease (iCPD): Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4 to 8 weeks later) confirms a further increase in sum or measures of target disease from iUPD, with an increase of at least 5mm.

Immune Stable Disease (iSD): Neither sufficient shrinkage to qualify for iPR nor sufficient increase to qualify for iUPD or iCPD, taking as reference the smallest sum diameters while on study and including the measurements of new lesions

[0079] Evaluation of Non-Target Lesions

Immune Complete Response (iCR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis). If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response

Non-iCR/Non-iUPD or -iCPD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Immune Unconfirmed Progressive Disease (iUPD): Unequivocal progression of existing non-target lesions without an iUPD on immediate prior scan. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Immune Confirmed Progressive Disease (iCPD): Unequivocal progression of existing non-target lesions with an iUPD on immediate prior scan. Progressive disease in the non-target lesion category is confirmed if subsequent imaging, done 4 to 8 weeks after iUPD, shows a further increase from iUPD. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

[0080] In certain cases, imaging may be used to evaluate a subject's response to therapy (alone or in combination with evaluation of PSA levels), and/or to select patients for treatment with the antibodies or combination of antibodies discussed herein. PSMA PET/CT has been shown to provide a sensitive measure of both PSMA expression and tumor burden in prostate cancer patients. With improved sensitivity and specificity over current conventional imaging modalities for

tumor lesion detection, PSMA PET/CT has been shown to improve the effectiveness of tumor response assessment and treatment strategy.

[0081] Two major PSMA PET tracers, Fluorine F 18 DCFPyL (^{18}F -DCFPyL) and Gallium Ga 68 PSMA-11 (^{68}Ga -PSMA-11), are radiolabeled small molecules that bind to the extracellular domain of PSMA with high affinity. They have been tested in multiple phase 1 to 3 studies and found to be well tolerated in patients with different stages of prostate cancer. Both PSMA PET tracers received FDA and EU approvals for detecting PSMA positive lesions in men with prostate cancer with suspected metastasis who are candidates for initial definitive therapy or with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. 18-FDCFPyL is also approved in EU for PSMA positive lesion detection in patients who are at high risk of metastasis and have received previous treatment for prostate cancer and in whom the cancer is suspected to have returned. In addition to the approved patient populations, 18F-DCFPyL and ^{68}Ga -PSMA-11 have both been studied in several other cancer populations. These PSMA PET/CT imaging tracers may be used for assessing whole body tumor burden and the anti-tumor activity of REGN4336 alone and in combination with REGN5678 or cemiplimab in mCRPC patients.

[0082] The dose for the PSMA PET/CT imaging tracers used in connection with the therapies discussed herein will be same as those authorized in the label for each respective tracer. Radiation dose from the PSMA PET tracers used herein is about 7.5 mSv per scan. By comparison, a typical CT scan dose of the chest, abdomen and pelvis is estimated to be approximately 25 mSv, one bone scan is approximately 4.4 mSv and annual natural background radiation dose in the United States is approximately 3.1 mSv. Three PSMA PET scans within a year would result in an approximate dose of approximately 22.5 mSv, which is approximately 45% of the recommended maximum allowed dose of 50 mSv for an adult research patient in a single year. For subjects receiving potentially 4 PSMA PET scans (3 on schedule plus 1 unscheduled), the total radiation dose from those scans would be approximately 30mSv, which is approximately 60% of the recommended maximum allowed annual dose for an adult research patient. Taken together, utilization of PSMA PET/CT and FDG PET as a component of patients' clinical care will assist in evaluating the mechanism of anti-activity of REGN4336 monotherapy or in combination with cemiplimab or REGN5678 in patients with mCRPC. No significantly increased risk in these patient populations is therefore anticipated compared to the ones listed on the labels for the tracers and the ones reported in clinical trials across cancer types.

[0083] Optional FDG PET/CT is also included to help assess metabolically active tumor burden in patients. PSMA expressing and non-expressing tumors have been detected by FDG PET/CT in prostate cancer patients. Complementary FDG and PSMA PET/CT data is expected to provide insight on tumor responses to REGN4336. The use of both modalities will help delineate intra-

patient discrepancies in PSMA expression amongst tumor lesions and help assess if the loss of tumor PSMA positivity may be a mechanism of tumor resistance to therapy (e.g., REGN4336, or combinations of REGN4336 and cemiplimab, or combinations of REGN4336 and REGN5678).

Bispecific Anti-PSMA x Anti-CD3 Antibodies and Bispecific Anti-PSMA x Anti-CD28 Antibodies, and Antigen-Binding Fragments Thereof

[0084] According to certain exemplary embodiments of the present disclosure, the methods comprise administering a bispecific antibody that specifically binds CD3 and PSMA, or combinations of bispecific antibodies that bind CD3 and PSMA, and CD28 and PSMA. Such antibodies may be referred to, respectively, herein as, e.g., "anti-PSMA/anti-CD3," or "anti-PSMA x CD3" or "PSMA x CD3" bispecific antibodies, and e.g., "anti-PSMA/anti-CD28," or "anti-PSMA x CD28" or "PSMA x CD28" bispecific antibodies, or other similar terminology.

[0085] As used herein, the expression "bispecific antibody" refers to an immunoglobulin protein comprising at least a first antigen-binding domain and a second antigen-binding domain. In the context of the present disclosure, the first antigen-binding domain specifically binds a first antigen (e.g., PSMA), and the second antigen-binding domain specifically binds a second, distinct antigen (e.g., CD3 or CD28). Each antigen-binding domain of a bispecific antibody comprises a heavy chain variable region (HCVR) and a light chain variable region (LCVR), each comprising three complementarity determining regions (CDRs). In the context of a bispecific antibody, the CDRs of the first antigen-binding domain may be designated with the prefix "A" and the CDRs of the second antigen-binding domain may be designated with the prefix "B". Thus, the CDRs of the first antigen-binding domain may be referred to herein as A-HCDR1, A-HCDR2, and A-HCDR3; and the CDRs of the second antigen-binding domain may be referred to herein as B-HCDR1, B-HCDR2, and B-HCDR3. In some embodiments, the bispecific antibody comprises a first heavy chain paired with a light chain, and a second heavy chain paired with a light chain (the light chain may be common to both heavy chains, i.e., two separate, but identical light chains, each separately paired with one of the heavy chains). The two heavy chains each comprise a HCVR comprising HCDR1, HCDR2 and HCDR3 in framework regions, a CH1 domain, a hinge, a CH2 domain, and a CH3 domain. The two light chain each comprise a LCVR comprising LCDR1, LCDR2 and LCDR3 in framework regions, and a light chain constant (CL) domain.

[0086] The first antigen-binding domain and the second antigen-binding domain are each connected to a separate multimerizing domain. As used herein, a "multimerizing domain" is any macromolecule, protein, polypeptide, peptide, or amino acid that has the ability to associate with a second multimerizing domain of the same or similar structure or constitution. In the context of the present disclosure, the multimerizing component is an Fc portion of an immunoglobulin (comprising

a C_{H2}-C_{H3} domain), *e.g.*, an Fc domain of an IgG selected from the isotypes IgG1, IgG2, IgG3, and IgG4, as well as any allotype within each isotype group.

[0087] Bispecific antibodies of the present disclosure typically comprise two multimerizing domains, *e.g.*, two Fc domains that are each individually part of a separate antibody heavy chain. The first and second multimerizing domains may be of the same IgG isotype such as, *e.g.*, IgG1/IgG1, IgG2/IgG2, IgG4/IgG4. Alternatively, the first and second multimerizing domains may be of different IgG isotypes such as, *e.g.*, IgG1/IgG2, IgG1/IgG4, IgG2/IgG4, etc.

[0088] Any bispecific antibody format or technology may be used to make the bispecific antibodies of the present disclosure. For example, an antibody or fragment thereof having a first antigen binding specificity can be functionally linked (*e.g.*, by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment having a second antigen-binding specificity to produce a bispecific antibody. Specific exemplary bispecific formats that can be used in the context of the present disclosure include, without limitation, *e.g.*, scFv-based or diabody bispecific formats, IgG-scFv fusions, dual variable domain (DVD)-Ig, Quadroma, knobs-into-holes, common light chain (*e.g.*, common light chain with knobs-into-holes, etc.), CrossMab, CrossFab, (SEED)body, leucine zipper, Duobody, IgG1/IgG2, dual acting Fab (DAF)-IgG, and Mab₂ bispecific formats (see, *e.g.*, Klein et al. 2012, mAbs 4:6, 1-11, and references cited therein, for a review of the foregoing formats).

[0089] In the context of bispecific antibodies of the present disclosure, Fc domains may comprise one or more amino acid changes (*e.g.*, insertions, deletions or substitutions) as compared to the wild-type, naturally occurring version of the Fc domain. For example, the disclosure includes bispecific antibodies comprising one or more modifications in the Fc domain that results in a modified Fc domain having a modified binding interaction (*e.g.*, enhanced or diminished) between Fc and FcRn. In one embodiment, the bispecific antibody comprises a modification in a C_{H2} or a C_{H3} region, wherein the modification increases the affinity of the Fc domain to FcRn in an acidic environment (*e.g.*, in an endosome where pH ranges from about 5.5 to about 6.0). Non-limiting examples of such Fc modifications are disclosed in US Patent Publication No. 20150266966, incorporated herein in its entirety.

[0090] The present disclosure also includes bispecific antibodies comprising a first C_{H3} domain and a second Ig C_{H3} domain, wherein the first and second Ig C_{H3} domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bispecific antibody to Protein A as compared to a bispecific antibody lacking the amino acid difference. In one embodiment, the first Ig C_{H3} domain binds Protein A and the second Ig C_{H3} domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_{H3} may further

comprise a Y96F modification (by IMGT; Y436F by EU). See, for example, US Patent No. 8,586,713. Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies.

[0091] In certain embodiments, the heavy chain constant region may be chimeric, combining sequences derived from more than one immunoglobulin isotype. For example, a chimeric heavy chain constant region can comprise part or all of a C_H2 sequence derived from a human IgG1, human IgG2 or human IgG4 C_H2 region, and part or all of a C_H3 sequence derived from a human IgG1, human IgG2 or human IgG4. A chimeric heavy chain constant region can also contain a chimeric hinge region. For example, a chimeric hinge may comprise an "upper hinge" sequence, derived from a human IgG1, a human IgG2 or a human IgG4 hinge region, combined with a "lower hinge" sequence, derived from a human IgG1, a human IgG2 or a human IgG4 hinge region. A particular example of a chimeric heavy chain constant region that can be included in any of the antibodies set forth herein comprises, from N- to C-terminus: [IgG4 C_H1]-[IgG4 upper hinge]-[IgG2 lower hinge]-[IgG4 CH2]-[IgG4 CH3]. Another example of a chimeric heavy chain constant region that can be included in any of the antibodies set forth herein comprises, from N- to C-terminus: [IgG1 C_H1]-[IgG1 upper hinge]-[IgG2 lower hinge]-[IgG4 CH2]-[IgG1 CH3]. These and other examples of chimeric heavy chain constant regions that can be included in any of the antibodies of the present disclosure are described in WO 2014/121087, which is herein incorporated in its entirety. Chimeric heavy chain constant regions having these general structural arrangements, and variants thereof, can have altered Fc receptor binding, which in turn affects Fc effector function.

[0092] In various embodiments in which the multimerizing domain comprises a heavy chain constant region including a hinge domain, positions 233-236 within the hinge domain may be G, G, G and unoccupied; G, G, unoccupied, and unoccupied; G, unoccupied, unoccupied, and unoccupied; or all unoccupied, with positions numbered by EU numbering. Optionally, the heavy chain constant region comprises from N-terminal to C-terminal the hinge domain, a CH2 domain and a CH3 domain. Optionally, the heavy chain constant region comprises from N-terminal to C-terminal a CH1 domain, the hinge domain, a CH2 domain and a CH3 domain. Optionally, the CH1 region, if present, remainder of the hinge region, if any, CH2 region and CH3 region are the same human isotype. Optionally, the CH1 region, if present, remainder of the hinge region, if any, CH2 region and CH3 region are human IgG1. Optionally, the CH1 region, if present, remainder of the hinge region, if any, CH2 region and CH3 region are human IgG2. Optionally, the CH1 region if

present, remainder of the hinge region, if any, CH2 region and CH3 region are human IgG4.

Optionally, the constant region has a CH3 domain modified to reduce binding to protein A. These and other examples of multimerizing heavy chain constant regions that can be included in any of the antigen-binding molecules of the present invention are described in WO 2016/161010.

[0093] According to certain embodiments, the bispecific antibodies used in the methods of the present disclosure specifically bind PSMA, CD3 and/or CD28. The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" PSMA, CD3 or CD28, as used in the context of the present disclosure, includes antibodies that bind PSMA, CD3, or CD28, or a portion thereof with a K_D of less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or less than about 0.5 nM, as measured in a surface plasmon resonance assay. An isolated antibody that specifically binds human PSMA, CD3 or CD28 may, however, have cross-reactivity to other antigens, such as PSMA, CD3 or CD28 molecules from other (non-human) species.

[0094] According to certain exemplary embodiments of the present disclosure, the bispecific anti-PSMA/anti-CD3 antibody or antigen-binding fragment thereof that can be used in the context of the methods of the present disclosure comprises: (a) a first antigen-binding arm that binds human PSMA and comprises the heavy chain complementarity determining regions (A-HCDR1, A-HCDR2 and A-HCDR3) of a heavy chain variable region (A-HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and the light chain complementarity determining regions (A-LCDR1, A-LCDR2 and A-LCDR3) of a light chain variable region (A-LCVR) comprising the amino acid sequence of SEQ ID NO: 9; and (b) a second antigen-binding arm that binds human CD3 and comprises the heavy chain CDRs (B-HCDR1, B-HCDR2 and B-HCDR3) of a HCVR (B-HCVR) comprising an amino acid sequence of SEQ ID NO: 5, and the light chain CDRs (B-LCDR1, B-LCDR2 and B-LCDR3) of a LCVR (B-LCVR) comprising the amino acid sequence of SEQ ID NO: 9. According to certain embodiments, the A-HCDR1 comprises the amino acid sequence of SEQ ID NO: 2; the A-HCDR2 comprises the amino acid sequence of SEQ ID NO: 3; the A-HCDR3 comprises the amino acid sequence of SEQ ID NO: 4; the A-LCDR1 comprises the amino acid sequence of SEQ ID NO: 10; the A-LCDR2 comprises the amino acid sequence of SEQ ID NO: 11; the A-LCDR3 comprises the amino acid sequence of SEQ ID NO: 12; the B-HCDR1 comprises the amino acid sequence of SEQ

ID NO: 6; the B-HCDR2 comprises the amino acid sequence of SEQ ID NO: 7; and the B-HCDR3 comprises the amino acid sequence of SEQ ID NO: 8; and the B-LCDR1 comprises the amino acid sequence of SEQ ID NO: 10; the B-LCDR2 comprises the amino acid sequence of SEQ ID NO: 11; the B-LCDR3 comprises the amino acid sequence of SEQ ID NO: 12. In yet other embodiments, the bispecific anti-PSMA/anti-CD3 antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding arm that binds human PSMA and comprises a HCVR (A-HCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a LCVR (A-LCVR) comprising the amino acid sequence of SEQ ID NO: 9; and (b) a second antigen-binding arm that binds human CD3 and comprises a HCVR (B-HCVR) comprising the amino acid sequence of SEQ ID NO: 5, and a LCVR (B-LCVR) comprising the amino acid sequence of SEQ ID NO: 9. In certain exemplary embodiments, the bispecific anti-PSMA x CD3 antibody comprises a PSMA-binding arm comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 13 and a light chain comprising the amino acid sequence of SEQ ID NO: 15, and a CD3-binding arm comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 14 and a light chain comprising the amino acid sequence of SEQ ID NO: 15.

[0095] According to certain exemplary embodiments of the present disclosure, the bispecific anti-PSMA/anti-CD28 antibody or antigen-binding fragment thereof that can be used in the context of the methods of the present disclosure comprises: (a) a first antigen-binding arm that binds human PSMA and comprises the heavy chain complementarity determining regions (A-HCDR1, A-HCDR2 and A-HCDR3) of a heavy chain variable region (A-HCVR) comprising the amino acid sequence of SEQ ID NO: 16 and the light chain complementarity determining regions (A-LCDR1, A-LCDR2 and A-LCDR3) of a light chain variable region (A-LCVR) comprising the amino acid sequence of SEQ ID NO: 24; and (b) a second antigen-binding arm that binds human CD28 and comprises the heavy chain CDRs (B-HCDR1, B-HCDR2 and B-HCDR3) of a HCVR (B-HCVR) comprising an amino acid sequence of SEQ ID NO: 20, and the light chain CDRs (B-LCDR1, B-LCDR2 and B-LCDR3) of a LCVR (B-LCVR) comprising the amino acid sequence of SEQ ID NO: 24. According to certain embodiments, the A-HCDR1 comprises the amino acid sequence of SEQ ID NO: 17; the A-HCDR2 comprises the amino acid sequence of SEQ ID NO: 18; the A-HCDR3 comprises the amino acid sequence of SEQ ID NO: 19; the A-LCDR1 comprises the amino acid sequence of SEQ ID NO: 25; the A-LCDR2 comprises the amino acid sequence of SEQ ID NO: 26; the A-LCDR3 comprises the amino acid sequence of SEQ ID NO: 27; the B-HCDR1 comprises the amino acid sequence of SEQ ID NO: 21; the B-HCDR2 comprises the amino acid sequence of SEQ ID NO: 22; and the B-HCDR3 comprises the amino acid sequence of SEQ ID NO: 23; and the B-LCDR1 comprises the amino acid sequence of SEQ ID NO: 25; the B-LCDR2 comprises the amino acid sequence of SEQ ID NO: 26; the B-LCDR3 comprises the amino acid sequence of SEQ ID NO: 27. In yet other

embodiments, the bispecific anti-PSMA/anti-CD28 antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding arm that binds human PSMA and comprises a HCVR (A-HCVR) comprising the amino acid sequence of SEQ ID NO: 16 and a LCVR (A-LCVR) comprising the amino acid sequence of SEQ ID NO: 24; and (b) a second antigen-binding arm that binds human CD28 and comprises a HCVR (B-HCVR) comprising the amino acid sequence of SEQ ID NO: 20, and a LCVR (B-LCVR) comprising the amino acid sequence of SEQ ID NO: 24. In certain exemplary embodiments, the bispecific anti-PSMA x CD28 antibody comprises a PSMA-binding arm comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 28 and a light chain comprising the amino acid sequence of SEQ ID NO: 30, and a CD28-binding arm comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 29 and a light chain comprising the amino acid sequence of SEQ ID NO: 30.

[0096] According to certain exemplary embodiments, the methods of the present disclosure comprise the use of REGN4336, REGN5678, or a bioequivalent thereof. The term "bioequivalent", as used herein, refers to anti-PSMA/anti-CD3 antibodies or anti-PSMA/anti-CD28 antibodies that are pharmaceutical equivalents or pharmaceutical alternatives whose rate and/or extent of absorption do not show a significant difference with that of REGN4336 or REGN5678, respectively, when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose. In the context of the disclosure, the term refers to antigen-binding proteins that bind to PSMA/CD3 or PSMA/CD28, which do not have clinically meaningful differences with REGN4336 or REGN5678, respectively, in their safety, purity and/or potency.

Anti-PD-1 Antibodies and Antigen-Binding Fragments Thereof

[0097] According to certain exemplary embodiments of the present disclosure, the methods comprise administering an anti-PD-1 antibody or antigen-binding fragment thereof. The term "antibody," as used herein, includes immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). In a typical antibody, each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain constant region. The heavy chain constant region comprises three domains, C_{H1} , C_{H2} and C_{H3} . Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_{L1}). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the

disclosure, the FRs of the anti-PD-1 antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0098] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0099] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')₂ fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0100] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0101] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary

configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present disclosure include: (i) V_H - C_H1 ; (ii) V_H - C_H2 ; (iii) V_H - C_H3 ; (iv) V_H - C_H1 - C_H2 ; (v) V_H - C_H1 - C_H2 - C_H3 ; (vi) V_H - C_H2 - C_H3 ; (vii) V_H - C_L ; (viii) V_L - C_H1 ; (ix) V_L - C_H2 ; (x) V_L - C_H3 ; (xi) V_L - C_H1 - C_H2 ; (xii) V_L - C_H1 - C_H2 - C_H3 ; (xiii) V_L - C_H2 - C_H3 ; and (xiv) V_L - C_L . In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present disclosure may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[0102] The antibodies used in the methods of the present disclosure (including the bispecific antibodies discussed in the preceding section) may be human antibodies. The term "human antibody," as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the disclosure may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (*e.g.*, mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in particular CDR3. However, the term "human antibody," as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0103] The antibodies used in the methods of the present disclosure (including the bispecific antibodies discussed in the preceding section) may be recombinant human antibodies. The term "recombinant human antibody," as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (*e.g.*, a mouse) that is transgenic for human immunoglobulin genes (see *e.g.*, Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig

sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0104] According to certain embodiments, the antibodies used in the methods of the present disclosure specifically bind PD-1. The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" PD-1, as used in the context of the present disclosure, includes antibodies that bind PD-1 or portion thereof with a K_D of less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or less than about 0.5 nM, as measured in a surface plasmon resonance assay. An isolated antibody that specifically binds human PD-1 may, however, have cross-reactivity to other antigens, such as PD-1 molecules from other (non-human) species.

[0105] According to certain exemplary embodiments of the present disclosure, the anti-PD-1 antibody or antigen-binding fragment thereof that can be used in the context of the methods of the present disclosure comprises the heavy chain complementarity determining regions (HCDRs) of a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 31 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 35. According to certain embodiments, the anti-PD-1 antibody or antigen-binding fragment thereof comprises three HCDRs (HCDR1, HCDR2 and HCDR3) and three LCDRs (LCDR1, LCDR2 and LCDR3), wherein the HCDR1 comprises the amino acid sequence of SEQ ID NO: 32; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 33; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 34; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 36; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 37; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 38. In yet other embodiments, the anti-PD-1 antibody or antigen-binding fragment thereof comprises an HCVR comprising the amino acid sequence of SEQ ID NO: 31 and an LCVR comprising the amino acid sequence of SEQ ID NO: 35. In certain embodiments, the methods of the present disclosure comprise the use of an anti-PD-1 antibody, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 39. In some embodiments, the

anti-PD-1 antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 40. An exemplary antibody comprising a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 31 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 35 is the fully human anti-PD-1 antibody known as REGN2810 (also known as cemiplimab; LIBTAYO®). According to certain exemplary embodiments, the methods of the present disclosure comprise the use of REGN2810, or a bioequivalent thereof. The term "bioequivalent", as used herein, refers to anti-PD-1 antibodies or PD-1-binding proteins or fragments thereof that are pharmaceutical equivalents or pharmaceutical alternatives whose rate and/or extent of absorption do not show a significant difference with that of REGN2810 when administered at the same molar dose under similar experimental conditions, either single dose or multiple dose. In the context of the disclosure, the term refers to antigen-binding proteins that bind to PD-1 which do not have clinically meaningful differences with REGN2810 in their safety, purity and/or potency.

Combination Therapies

[0106] The methods of the present disclosure, according to certain embodiments, comprise administering to the subject an anti-PSMA/anti-CD3 bispecific antibody in combination with an anti-PD-1 antibody, or in combination with an anti-PSMA/anti-CD28 antibody. In certain embodiments, the methods of the present disclosure comprise administering the antibodies for additive or synergistic activity to treat a PSMA-expressing cancer, preferably prostate cancer, or to treat a PSMA-expressing cancer (*e.g.*, prostate cancer) with a reduced risk or incidence of CRS. As used herein, the expression "in combination with" means that the anti-PSMA/anti-CD3 bispecific antibody is administered before, after, or concurrent with the anti-PD-1 antibody or anti-PSMA/anti-CD28 antibody. The term "in combination with" also includes sequential or concomitant administration of an anti-PD-1 antibody and a bispecific anti-PSMA/anti-CD3 antibody, or a bispecific anti-PSMA/anti-CD28 antibody and a bispecific anti-PSMA/anti-CD3 antibody. For example, one antibody in a combination may be administered "before" the other antibody, such that the one antibody may be administered more than 150 hours, about 150 hours, about 100 hours, about 72 hours, about 60 hours, about 48 hours, about 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes or about 10 minutes prior to the administration of the other antibody. Administration of one antibody in a combination "concurrent" with the other antibody means that the one antibody is administered to the subject in a separate dosage form within less than 1 hour (before, after, or at the same time) of administration of the other antibody, or the antibodies are administered to the subject as a single combined dosage formulation.

[0107] In certain embodiments, the methods of the present disclosure comprise administration of

an additional therapeutic agent wherein the additional therapeutic agent is an anti-cancer drug. In certain embodiments, the methods of the disclosure comprise administering the antibody or antibodies in combination with radiation therapy, surgery or other anti-cancer therapy to generate long-term durable anti-tumor responses and/or enhance survival of patients with a PSMA-expressing cancer.

[0108] In some embodiments, the methods of the disclosure comprise administering radiation therapy prior to, concomitantly or after administering the antibody or antibodies discussed herein to a cancer patient. For example, radiation therapy may be administered in one or more doses to tumor lesions after administration of one or more doses of the antibody or antibodies. In some embodiments, radiation therapy may be administered locally to a tumor lesion to enhance the local immunogenicity of a patient's tumor (adjuvating radiation) and/or to kill tumor cells (ablative radiation) after systemic administration of the antibody or antibodies. In certain embodiments, the methods comprise administering surgery prior to or after administration of the antibody (neo-adjuvant or adjuvant use).

Pharmaceutical Compositions and Administration

[0109] The present disclosure includes methods which comprise administering a bispecific anti-PSMA/anti-CD3 antibody alone, or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody to a subject wherein the antibody or antibodies are contained within separate or a combined (single) pharmaceutical composition. The pharmaceutical compositions of the disclosure may be formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like.

[0110] Various delivery systems are known and can be used to administer the pharmaceutical composition(s) of the disclosure, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, *e.g.*, Wu *et al.*, 1987, *J. Biol. Chem.* 262: 4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, or by injection, and may be administered together with other biologically active agents.

[0111] A pharmaceutical composition of the present disclosure can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present disclosure. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical

composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0112] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present disclosure. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present disclosure include, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL), to name only a few.

[0113] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Fla. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0114] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by known methods. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and

other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent. The injection thus prepared is preferably filled in an appropriate ampoule.

[0115] Advantageously, the pharmaceutical compositions for use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, a vial or a prefilled syringe.

Administration Regimens

[0116] The present disclosure includes methods comprising administering to a subject a bispecific anti-PSMA x CD3 antibody as monotherapy or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody at a dosing frequency of about four times a week, twice a week, once a week, once every two weeks, once every three weeks, once every four weeks, once every five weeks, once every six weeks, once every eight weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved.

[0117] According to certain embodiments of the present disclosure, multiple doses of a bispecific anti-PSMA/anti-CD3 antibody as monotherapy, or in combination with an anti-PD-1 antibody, or in combination with a bispecific anti-PSMA/anti-CD28 antibody may be administered to a subject over a defined time course. The methods according to this aspect of the disclosure comprise sequentially administering to a subject one or more doses of a bispecific anti-PSMA/anti-CD3 antibody as monotherapy, or in combination with one or more doses of an anti-PD-1 antibody, or in combination with one or more doses of a bispecific anti-PSMA/anti-CD28 antibody. As used herein, "sequentially administering" means that each dose of the antibody is administered to the subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present disclosure includes methods which comprise sequentially administering to the patient a single initial dose of an antibody, followed by one or more secondary doses of the antibody, and optionally followed by one or more tertiary doses of the antibody.

[0118] The terms "initial dose," "secondary dose," and "tertiary dose," refer to the temporal sequence of administration. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary dose" is the dose which are administered after the initial dose (may be referred to herein as a "transitional dose"); and the "tertiary dose" is the dose which is administered after the secondary dose. The tertiary dose may be a "transitional dose," or a "target dose" depending on the dosing regimen. The initial, secondary, and tertiary doses may all contain the same amount of the antibody (anti-PD-1 antibody or bispecific antibody/antibodies). In certain embodiments, however, the amount contained in the initial, secondary and/or tertiary doses varies from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, one or more (*e.g.*, 1, 2, 3, 4, or

5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (*e.g.*, "maintenance doses").

[0119] In one exemplary embodiment of the present disclosure, each secondary and/or tertiary dose is administered 0.5 to 14 (*e.g.*, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 12.5, 13, 13.5, 14) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of an antibody that is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0120] The methods according to this aspect of the disclosure may comprise administering to a patient any number of secondary and/or tertiary doses of an antibody or antibodies discussed herein. For example, in certain embodiments, only a single secondary (transitional) dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses (*e.g.*, transitional doses) are administered to the patient. Likewise, in certain embodiments, only a single tertiary (target) dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0121] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1, 2 or 3 weeks (*e.g.*, 1 week or 3 weeks) after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 1 to 4 weeks (*e.g.*, 1 week or 3 weeks) after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

[0122] In certain embodiments, one or more doses of the antibody or antibodies discussed herein are administered at the beginning of a treatment regimen as "induction doses" on a more frequent basis (twice a week, once a week, once in 2 weeks, or once in 3 weeks) followed by subsequent doses ("consolidation doses" or "maintenance doses") that are administered on the same or a less frequent basis (*e.g.*, once in 4-12 weeks).

Dosage

[0123] In certain embodiments, the methods of the present disclosure comprise administering a bispecific anti-PSMA/anti-CD3 antibody as monotherapy in a dosing regimen comprising an initial

dose, a transitional dose and a target dose. In certain embodiments, the target dose results in a therapeutic response. A therapeutic response includes, for example, (a) a reduction in the severity or duration of a symptom of a cancer (*e.g.*, prostate cancer); (b) inhibition of tumor growth, or an increase in tumor necrosis, tumor shrinkage and/or tumor disappearance; (c) delay in tumor growth and development; (d) inhibition or retardation or elimination of tumor metastasis; (e) prevention of recurrence of tumor growth; (f) increase in survival of a subject with cancer (*e.g.*, prostate cancer); (g) a reduction in the use or need for conventional anti-cancer therapy (*e.g.*, reduced or eliminated use of chemotherapeutic or cytotoxic agents); and/or (h) reduced cytokine release syndrome in the patient. Therapeutic response can be measured, for example, as complete response, or partial response, or as increased survival, or as reduction in PSA levels or a modification of any other parameter as disclosed elsewhere herein. In certain other embodiments, the methods of the present disclosure comprise administering a bispecific anti-PSMA/anti-CD3 antibody in a dosing regimen comprising an initial dose, a transitional dose and a target dose wherein the bispecific anti-PSMA/anti-CD3 antibody is administered in combination with an anti-PD-1 antibody or a bispecific anti-PSMA/anti-CD28 antibody, and wherein the target dose is less than the target dose of the bispecific anti-PSMA/anti-CD3 antibody administered as monotherapy. In such embodiments, the target dose of the bispecific anti-PSMA/anti-CD3 antibody is a “sub-therapeutic” dose, *i.e.*, it is lower than the target dose administered as monotherapy. For example, if the bispecific anti-PSMA/anti-CD3 antibody is administered as monotherapy at a target dose of 9 mg and it leads to a therapeutic response in the patient, a “subtherapeutic dose” of the antibody would comprise less than 9 mg, *e.g.*, 8 mg, 7 mg, 6 mg, 5 mg, 4 mg, 3 mg, or less. In some embodiments, the subtherapeutic dose is 50% or less than the target dose administered as monotherapy. For example, if the target dose as monotherapy is 9 mg, a subtherapeutic dose may be 4.5 mg or less. A subtherapeutic dose may not lead to a therapeutic response if administered as monotherapy. In the context of the present methods, a subtherapeutic dose of the bispecific anti-PSMA/anti-CD3 antibody administered in combination with an anti-PD-1 antibody or with a bispecific anti-PSMA/anti-CD28 antibody results in a therapeutic response. In certain embodiments, a subtherapeutic dose is also referred to as “low dose” (see, *e.g.*, Example 1 herein).

[0124] In general, the bispecific anti-PSMA/anti-CD3 antibody is administered at a dose from about 0.01 milligrams (mg) to about 2000 mg, *e.g.*, about 0.01 mg, about 0.03 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about

600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of the bispecific anti-PSMA/anti-CD3 antibody. In certain embodiments, 0.03 mg, 0.09 mg, 0.1 mg, 0.3 mg, 0.9 mg, 1 mg, 3 mg, 9 mg, 10 mg, 30 mg, 90 mg, 100 mg, 300 mg, or 900 mg of the bispecific anti-PSMA x anti-CD3 antibody is administered (*e.g.*, once weekly or once every three weeks) to the subject to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer).

[0125] In certain embodiments, the anti-PD-1 antibody is administered at a dose from about 0.05 mg to about 600 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-PD-1 antibody. In certain embodiments, 300 mg to 400 mg of the anti-PD-1 antibody is administered (*e.g.*, once every three weeks) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 350 mg of an anti-PD-1 antibody is administered (*e.g.*, once every three weeks) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer).

[0126] In certain embodiments, the bispecific anti-PSMA/anti-CD28 antibody is administered at a dose from about 0.01 milligrams (mg) to about 500 mg, *e.g.*, about 0.01 mg, about 0.05 mg, about 0.1 mg, about 0.5 mg, about 1 mg, about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, about 40 mg, about 41 mg, about 42 mg, about 43 mg, about 44 mg, about 45 mg, about 46 mg, about 47 mg, about 48 mg, about 49 mg, about 50 mg, about 51 mg, about 52 mg, about 53 mg, about 54 mg, about 55 mg, about 56 mg, about 57 mg, about 58 mg, about 59 mg, about 60 mg, about 65 mg, about 70 mg, about 75

mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, or about 500 mg of the bispecific anti-PSMA x anti-CD28 antibody is administered (*e.g.*, once weekly or once every three weeks) to the subject to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 20 mg to 40 mg of the anti-PSMA/anti-CD28 antibody is administered (*e.g.*, once weekly) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 30 mg of an anti-PSMA/anti-CD28 antibody is administered (*e.g.*, once weekly) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 50 mg to 150 mg of the anti-PSMA/anti-CD28 antibody is administered (*e.g.*, once every three weeks) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 100 mg of an anti-PSMA/anti-CD28 antibody is administered (*e.g.*, once every three weeks) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 250 mg to 350 mg of the anti-PSMA/anti-CD28 antibody is administered (*e.g.*, once every three weeks) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer). In certain embodiments, 300 mg of an anti-PSMA/anti-CD28 antibody is administered (*e.g.*, once every three weeks) to the subject in combination with the bispecific anti-PSMA/anti-CD3 antibody to treat a PSMA-expressing cancer or prostate cancer (*e.g.*, metastatic and/or castration-resistant prostate cancer).

[0127] The amount of the antibody or antibodies may be expressed in terms of milligrams of antibody per kilogram of subject body weight (*i.e.*, mg/kg). In an adult human subject, the body weight may be regarded as an average of about 60-80 kg (*e.g.*, 70 kg).

[0128] A summary of the sequences and the corresponding SEQ ID NOs referenced herein is shown in Table 1, below.

Table 1: Summary of Sequences

Antibody	SEQ ID NO:	Description
REGN4336 (anti-PSMA x CD3)	1	Anti-PSMA Heavy Chain Variable Region
	2	Anti-PSMA HCDR1
	3	Anti-PSMA HCDR2
	4	Anti-PSMA HCDR3
	5	Anti-CD3 Heavy Chain Variable Region
	6	Anti-CD3 HCDR1
	7	Anti-CD3 HCDR2
	8	Anti-CD3 HCDR3
	9	Anti-PSMA and Anti-CD3 Light Chain Variable Region
	10	Anti-PSMA and Anti-CD3 LCDR1
	11	Anti-PSMA and Anti-CD3 LCDR2
	12	Anti-PSMA and Anti-CD3 LCDR3
	13	Anti-PSMA Heavy Chain
	14	Anti-CD3 Heavy Chain
	15	Anti-PSMA and Anti-CD3 Light Chain
REGN5678 (anti-PSMA x CD28)	16	Anti-PSMA Heavy Chain Variable Region
	17	Anti-PSMA HCDR1
	18	Anti-PSMA HCDR2
	19	Anti-PSMA HCDR3
	20	Anti-CD28 Heavy Chain Variable Region
	21	Anti-CD28 HCDR1
	22	Anti-CD28 HCDR2
	23	Anti-CD28 HCDR3
	24	Anti-PSMA and Anti-CD28 Light Chain Variable Region
	25	Anti-PSMA and Anti-CD28 LCDR1
	26	Anti-PSMA and Anti-CD28 LCDR2
	27	Anti-PSMA and Anti-CD28 LCDR3
	28	Anti-PSMA Heavy Chain
	29	Anti-CD28 Heavy Chain
	30	Anti-PSMA and Anti-CD28 Light Chain
Cemipli mab (anti- PD-1)	31	Anti-PD-1 Heavy Chain Variable Region
	32	Anti-PD-1 HCDR1
	33	Anti-PD-1 HCDR2

	34	Anti-PD-1 HCDR3
	35	Anti-PD-1 Light Chain Variable Region
	36	Anti-PD-1 LCDR1
	37	Anti-PD-1 LCDR2
	38	Anti-PD-1 LCDR3
	39	Anti-PD-1 Heavy Chain
	40	Anti-PD-1 Light Chain

EXAMPLES

[0129] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0130] The antibodies used in the following examples include: an anti-PSMA x CD3 bispecific antibody (REGN4336), which comprises the CDRs, variable regions, and heavy and light chains shown in Table 1; an anti-PSMA x CD28 bispecific antibody (REGN5678), which comprises the CDRs, variable regions, and heavy and light chains shown in Table 1; and an anti-PD-1 antibody (cemiplimab), which comprises the CDRs, variable regions, and heavy and light chains shown in Table 1.

Example 1: Anti-Tumor Efficacy of Low Dose REGN4336 in Combination with Varying Doses of REGN5678 in PSMA/CD3/CD28-Humanized Tumor-Bearing Mice

[0131] In this experiment, anti-tumor efficacy and cytokine release was compared between groups of mice administered a low (0.02 mg/kg) or high (5 mg/kg) dose of REGN4336 in combination with IgG4^{P-PVA} isotype control (*i.e.*, REGN4336 monotherapy), or groups of mice administered low dose REGN4336 in combination with REGN5678 at varying doses (0.005, 0.05, 0.5, or 5 mg/kg). Mice were genetically engineered using VelociGene® technology to express the human, rather than mouse, PSMA, CD3, and CD28. On Day 0, mice were SC implanted in the right hind flank with mouse prostate carcinoma cells which were engineered to express human PSMA (TRAMPC2/hPSMA cells). On Days 0, 3, and 7 post tumor implantation, mice were dosed IP with either REGN4336 (0.02 or 5 mg/kg) or non-TAAxCD3, a CD3-binding bispecific antibody which

does not bind to tumor antigens in this model (5 mg/kg), in combination with REGN5678 (0.005, 0.05, 0.5, or 5 mg/kg) or IgG4^{P-PVA} isotype control (5 mg/kg).

[0132] Tumor burden was monitored by caliper measurement beginning on Day 7 post tumor implantation and measured twice weekly until Day 25. The administration of low dose REGN4336 monotherapy resulted in minimal tumor reduction. The addition of REGN5678 (all tested doses) to low dose REGN4336 resulted in dose-dependent, enhanced anti-tumor efficacy compared with low dose REGN4336 monotherapy. A statistically significant (hereinafter referred to as significant) reduction in tumor volume was observed for mice administered low dose REGN4336 + REGN5678 (5 mg/kg) by Day 18 compared with mice administered low dose REGN4336 monotherapy. There was not a significant difference in tumor volume between the group administered high dose REGN4336 monotherapy and the group administered low dose REGN4336 + REGN5678 (5 mg/kg). These results are shown in Fig. 1.

[0133] Blood was taken from mice 4 hours post-dosing on Day 0. Serum samples were analyzed to measure cytokine production. Levels of all cytokines examined (IFNG, IL1B, IL2, IL4, IL5, IL6, IL10, IL12, KC-GRO, and TNFA) trended higher in the group administered high dose REGN4336 monotherapy compared with the group dosed with non-TAAxCD3 + IgG4^{P-PVA} isotype control (hereinafter referred to as the "control group"). For all cytokines examined, the addition of REGN5678 (all tested doses) to low dose REGN4336 did not induce cytokine release relative to administration of high dose REGN4336 monotherapy. These results are shown in Figs. 2A and 2B.

Example 2: Effect of Low Dose REGN4336 in Combination with REGN5678 on Mouse Survival and IFNG Release in PSMA/CD3/CD28-Humanized Tumor-Bearing Mice

[0134] In this experiment, mouse survival and cytokine release were evaluated in groups of mice administered low (0.02 mg/kg) or high (5 mg/kg) dose REGN4336 monotherapy and a group administered low dose REGN4336 in combination with REGN5678 (5 mg/kg). Mice were genetically engineered using VelociGene[®] technology to express the human, rather than mouse, PSMA, CD3, and CD28. On Day 0, mice were SC implanted in the right hind flank with mouse prostate carcinoma cells which were engineered to express human PSMA (TRAMPC2/hPSMA cells). On Days 0, 3, and 7 post tumor implantation, mice were dosed IP with either REGN4336 (0.02 or 5 mg/kg) or non-TAAxCD3, a CD3-binding bispecific antibody which does not bind to tumor antigens in this model (5 mg/kg), in combination with REGN5678 (5 mg/kg) or IgG4^{P-PVA} isotype control (5 mg/kg). Mice were monitored through Day 110 PTI to assess survival. Administration of low dose REGN4336 in combination with REGN5678 resulted in similar survival as administration of high

dose REGN4336 monotherapy, and both dosing groups had significantly increased survival compared with the control group. These results are shown in Fig. 3.

[0135] Blood was collected from mice 4 hours post-dosing on Day 0 and IFNG levels in serum were measured. Administration of REGN4336 as a monotherapy resulted in increased IFNG levels relative to dosing with the control group, with the high dose monotherapy resulting in significantly higher levels. Conversely, administration of low dose REGN4336 in combination with REGN5678 resulted in near-negligible release of IFNG, similar to IFNG levels from the control group. These results are shown in Fig. 4.

[0136] In summary, the studies discussed in Examples 1A and 1B demonstrate that combining low dose REGN4336 with REGN5678 reduces tumor burden and allows for increased survival while minimizing cytokine release in PSMA/CD3/CD28-humanized mice bearing TRAMPC2/hPSMA tumors.

Example 3: Combinations of REGN4336 and REGN5678 Produce Formation of an Artificial Immune Synapse *In Vitro* and Increase Anti-Tumor Efficacy and Durability *In Vivo*

[0137] This experiment was designed to evaluate whether a PSMA x CD28 bispecific antibody (REGN5678) potentiates T cell activation enhanced by a PSMA x CD3 bispecific antibody (REGN4336) *in vitro* and safely enhances anti-tumor efficacy *in vivo*. The dynamics of CD3 and CD28 interaction *in vitro* was demonstrated by identifying the bispecific antibodies localized at the immunological synapse of T cell and target cell conjugates. *In vivo* anti-tumor efficacy was evaluated in a PSMA x CD3 sensitive syngeneic tumor model. Tumor growth over time, and phenotypic changes in tumor infiltrating T cells were profiled by high-dimensional computational flow cytometry and serum cytokine was monitored to show response to PSMA x CD28 and PSMA x CD3 combination treatment. Sample sizes were chosen empirically to ensure adequate statistical power and were in line with field standards for the techniques used in the study.

Synapse Formation

[0138] Efficient T cell activation depends on co-clustering of TCR/CD3 and CD28 complexes at the immune synapse. To determine the relative localization of PSMA x CD3 and PSMA x CD28 at the immune synapse, we developed an *in vitro* model system using Jurkat T cells and Raji cells engineered to overexpress PSMA. Jurkat/hPD-1 T cells and Raji/CD80-/CD86-/hPSMA target cells were incubated with PSMAxCD3-Alexa488 (0.3 or 0.03 µg/ml) alone or together with PD-1-Alexa647 (PD-1 blocker or PD-1 non blocker, 1 µg/ml) for 1 hour at 37 °C. Cells were gently washed with flow cytometry (FACS) buffer consisting of 3 % FBS, 2 mM ethylenediaminetetraacetic acid (EDTA) in Dulbecco's Phosphate-Buffered Saline Solution (D-PBS, Irvine Scientific) twice and stained with CD28-PE (BD, 2 µg/ml) and Hoechst 33342 (Thermo Fisher H3570, 1 µM) for 15 min

at 4 °C. Cells were washed with FACS buffer and stored in BD stabilizing fixative (BD 338036). Images of cells were collected on Amnis Imaging Flow Cytometer and analyzed by IDEAS software. Cells were gated on doublet bright-field, doublet nucleus, nucleus focus, single spot count, singlet CD28. Synapse area was defined by valley mask based on nucleus staining. The ratio of PD-1 or CD28 in/out of synapse was calculated by the following formula: $\text{intensity in synapse} / (\text{total intensity} - \text{intensity in synapse}) * 100\%$.

[0139] Fluorescently labeled PSMA x CD3 and PSMA x CD28 bispecific antibodies were used to simulate peptide MHC / TCR and B7 / CD28 binding and to identify T cell interactions with the target cells forming an immune synapse. As might be expected, PSMA expression on target cells promoted accumulation of PSMA x CD3 and PSMA x CD28 on T cells at the immune synapse in contrast to the PSMA antibody control. The distribution of PSMA x CD3 and PSMA x CD28 was quantified by calculating the ratio of antibody staining inside versus outside of the immune synapse. The quantitative data analysis confirmed that expression of PSMA on target cells enhanced PSMA x CD3 and PSMA x CD28 localization at the immune synapse simultaneously, and in contrast, reduced the relative amount of PSMA x CD28 alone and thereby increased the relative ratio of CD3 and CD28 at the synapse. These data support a “immune synapse localization model” explaining how PSMA x CD3 and PSMA x CD28 can potentiate CD3 and CD28 activation at the immune synapse and thus synergize to enhance T cell activation, thus allowing more efficient promotion of T cell activation when encountering its ligand on the target cell.

[0140] When Jurkat T cells alone were bound to a fluorescently labeled PSMA x CD3 bispecific (PSMA x CD3⁴⁸⁸) or to a fluorescently labeled PSMA x CD28 bispecific (PSMA x CD28⁶⁴⁷), immunofluorescent analyses demonstrated that the bispecifics remain uniformly distributed around the surface of the T cell. Similarly, when isolated target cells were bound to PSMA x CD3⁴⁸⁸ or PSMA x CD28⁶⁴⁷, PSMA tumor antigen remained uniformly distributed around the surface of the target cell. However, when T cells and target cells were brought together by the PSMA x CD3 and PSMA x CD28 bispecific antibodies, both bispecific antibodies clustered at an artificial synapse that formed between the two cells, mimicking a natural immune synapse. Quantification of the fluorescent signal inside versus outside of the synapse confirmed that the combination of PSMA x CD3 with PSMA x CD28 significantly ($p < 0.0001$) increased the accumulation of both bispecific antibodies within the artificial synapse.

Increased Anti-Tumor Immunity

[0141] Mice expressing human CD28, human CD3 and human PSMA in place of the corresponding mouse genes were generated using VelociGene® technology (referred to as hCD3/hCD28/hPSMA humanized mice). hCD3/hCD28/hPSMA mice (8-16 weeks old) were injected

with 5×10^6 Trampc2/hPSMA tumor cells subcutaneously on the flank. Bispecific antibodies were administered as a monotherapy or in combination by intraperitoneal injection on day 0, 3 and 7 at 5 mg/kg REGN4336 + 5 mg/kg isotype control, or 0.02 mg/kg REGN4336 + 5 mg/kg REGN5678. Tumor inhibition of primary tumor implants and cytokine production from bispecific antibody administration were consistent with those of Examples 1 and 2. Mice that completely rejected primary tumor implants were re-challenged with a secondary subcutaneous tumor implant with 5×10^6 Trampc2/hPSMA cells per mouse at 100+ days after primary tumor implant, and the frequency of tumor-free mice 21 days after re-challenge was evaluated. In addition, spleens of re-challenged mice were harvested over 100 days after implant. Splenocytes were cultured overnight in T cell media with 10 mg/ml peptide. After overnight incubation, IFN γ ELISPOT assay was performed following standard procedures (R&D Systems, Catalog # EL485).

[0142] Combining CD3 activation with PSMA x CD28 generated long-term anti-tumor memory and immunity: that is, after the initial tumor response due to treatment with the PSMA x CD28 bispecific and a low dose of PSMA x CD3, these mice were able to reject a second tumor challenge with TRAMPC2/hPSMA tumor cells without any additional therapy, demonstrating the generation of endogenous immune memory. Mice that rejected TRAMPC2/hPSMA tumors with either the high dose of PSMA x CD3 (5 mg/kg) or the low dose PSMA x CD3 (0.02 mg/kg) and PSMA x CD28 combination were implanted more than 100 days after primary tumor implant and treatment start. The frequency of mice that rejected the second tumor implant was significantly higher in mice treated with the low dose PSMA x CD3 (0.02 mg/kg) and PSMA x CD28 combination compared to the high dose of PSMA x CD3 (5 mg/kg) (Fig. 5A). In addition, the spleens of mice treated with the low dose PSMA x CD3 (0.02 mg/kg) and PSMA x CD28 combination contained a higher number of TRAMPC2 specific T cells recognizing the SPAS1 neoantigen compared to the high dose of PSMA x CD3 (5 mg/kg) (Fig. 5B).

Example 4: A Phase 1/2 Study of a Bispecific Anti-PSMA x Anti-CD3 Antibody Administered Alone or in Combination with an Anti-PD-1 Antibody or a Bispecific Anti-PSMA x Anti-CD28 Antibody in Patients with Metastatic Castration-Resistant Prostate Cancer

[0143] This is an open-label, Phase 1/2, first-in-human, multicenter dose-escalation study with cohort expansion evaluating safety, tolerability, pharmacokinetics (PK), and antitumor activity of REGN4336 administered subcutaneously or intravenously (i) as monotherapy, (ii) in combination with cemiplimab, and (iii) in combination with REGN5678 in patients with metastatic castration-resistant prostate cancer (mCRPC). Patients must have received at least two prior lines of systemic therapy approved for metastatic and/or castration-resistant disease including a second-generation anti-androgen therapy. REGN4336 as monotherapy is administered weekly. REGN4336 will be

administered weekly in combination with cemiplimab (350 mg; Q3W) following a 3-week REGN4336 monotherapy lead-in cycle. REGN4336 will be administered weekly in combination with REGN5678 (30 mg; QW) following a 3-week REGN4336 monotherapy lead-in cycle.

[0144] The primary objectives in dose escalation are to evaluate the safety, tolerability, PK, and recommended phase 2 dosing regimen (RP2DR) of REGN4336 as monotherapy and in combinations with cemiplimab or REGN5678. During the expansion phase, the primary objective is to assess anti-tumor activity of REGN4336 as monotherapy and in combinations with cemiplimab and REGN5678, as measured by objective response rate (ORR) per modified Prostate Cancer Working Group 3 criteria. At selected sites, PSMA positron emission tomography/computed tomography scans will be performed at predefined timepoints on study. Additional details are provided below.

[0145] The secondary objectives of the study are to assess preliminary anti-tumor activity as measured by ORR per modified PCWG3 criteria or as measured by prostate-specific antigen (PSA) decline, to characterize the safety profile, to characterize PK, and to evaluate immunogenicity of REGN4336 as monotherapy and in combinations with cemiplimab or REGN5678.

[0146] The exploratory objectives of the study are (for REGN4336 as monotherapy, in combination with cemiplimab, and in combination with REGN5678, separately by cohort and for each combination):

- To assess preliminary anti-tumor activity, as measured by percent change in PSA, disease control rate (DCR), duration of response (DOR), radiographic progression-free survival (rPFS), PSA progression-free survival, overall survival (OS), time to response, and time to progression
- To evaluate exploratory molecular biomarkers for the assessment of anti-tumor effects, to understand REGN4336 mechanism of action, observed toxicity, the disease/target, and genomic factors underlying disease and responsiveness in the patient population
- To characterize the relationship between serum cytokine levels and clinical tolerability
- To identify features of the tumor and its microenvironment in lesional tissue which are predictive of anti-tumor activity, or which respond pharmacodynamically to study treatment
- To identify features of the peripheral immune cell population which are predictive of anti-tumor activity or toxicity, or which respond pharmacodynamically to study treatment
- To evaluate the impact of study treatment on PSMA-positive and fluorodeoxyglucose (FDG)-positive tumors as assessed by PET/CT

- To evaluate the impact of study treatment on patient reported health-related quality of life (HRQoL), functioning, and general cancer and prostate cancer specific symptom measures (EORTC, QLQ-C30, EORTC QLQ-PR25, PGIC, PGIS).
- To evaluate the impact of study treatment on patient reported pain using the BPI-SF and a daily diary for tracking opioid analgesic usage and BPI-SF Item 3 “pain at its worst in the last 24 hours”.

[0147] Study Design

[0148] This is a phase 1/2, first-in-human (FIH), open-label, multicenter study evaluating safety, tolerability, efficacy, and PK of REGN4336, an anti-PSMA x anti-CD3 bispecific antibody (bsAb), administered subcutaneously (SC) or intravenously (IV) as monotherapy (Module 1), in combination with cemiplimab (Module 2), and in combination with REGN5678 (Module 3), in patients with treatment-experienced metastatic castration-resistant prostate cancer (mCRPC).

[0149] There are two parts of the study, dose escalation and dose expansion. All patients in the study will be treated with at least 2 successive “step-up” doses (initial dose and transitional dose) of REGN4336 before reaching the target dose. The RP2DR, including the step-up dosing regimen and the target dose of REGN4336, determined in dose escalation, will be further evaluated in dose expansion.

[0150] Dose Escalation: Dose levels are defined by the target dose of REGN4336. Dose levels are designed in which the target dose of REGN4336 will be escalated in ½ (half)-log increments. Dose increments of <100% may be implemented based on observed toxicities at any given dose level.

[0151] Module 1 - Determination of the step-up dosing regimen and dose escalation of monotherapy REGN4336: Module 1 dose escalation began by evaluating REGN4336 administered SC QW. The initial dose of the step-up dosing regimen starts at the minimum anticipated biological effect level (MABEL) based dose of 0.03 mg SC. All 3 doses (initial, transitional, target) will be escalated in ½-log increments per dose level until the occurrence of specified adverse events (AEs) result in a modification to the dosing regimen (for initial and transitional doses) or the maximum tolerated dose (MTD)/RP2DR is defined (for the target dose). A separate dose escalation cohort evaluating monotherapy REGN4336 by IV QW administration was added to Module 1. The starting dose of REGN4336 administered IV will be 0.01 mg IV supported by a MABEL-based assessment. A single dose of sarilumab 350 mg IV will be administered prior to the initial dose of REGN4336 when administered IV for mitigation of cytokine release syndrome (CRS). All 3 doses (initial, transitional, target) may then be escalated in ½-log increments until the occurrence of specified adverse events (AEs) result in a modification to the dosing regimen (for initial and transitional

doses) or the maximum tolerated dose (MTD)/RP2DR is defined (for the target dose). Dose increments of $\leq 100\%$ may be implemented based on observed toxicities at a given dose level.

[0152] Module 2 – Dose escalation of REGN4336 in combination with cemiplimab: Patients enrolling in Module 2 will receive a 3-week REGN4336 QW monotherapy lead-in cycle consisting of initial, transitional and target doses (Cycle 1). Following the monotherapy lead-in cycle and once the REGN4336 target dose is tolerated with Grade ≤ 1 CRS, REGN4336 will be administered QW in combination with cemiplimab 350 mg Q3W IV (Cycles 2+). Dose escalation of REGN4336 in Module 2 will begin at least 1 dose level below the minimum pharmacologically active dose level of REGN4336 determined in Module 1. REGN4336 will be administered SC or IV depending on the experience in Module 1. A single dose of sarilumab 350 mg IV will be administered prior to the initial dose of REGN4336 when administered IV for mitigation of CRS.

[0153] Module 3 – Dose escalation of REGN4336 in combination with REGN5678: Patients enrolling in Module 3 will receive a 3-week REGN4336 QW monotherapy lead-in cycle consisting of initial, transitional and target doses (Cycle 1). Following the monotherapy lead-in cycle and once the REGN4336 target dose is tolerated with Grade ≤ 1 CRS, REGN5678 at a fixed dose of 30 mg QW will be administered in combination with REGN4336 QW (Cycles 2+). The starting dose level of REGN4336 in Module 3 will begin at least 1 dose level below the dose shown tolerable in Module 1 at the time Module 3 opens. Module 3 will begin with REGN4336 administered SC but may subsequently evaluate REGN4336 administered IV in separate dose escalation cohorts depending on the experience in Module 1. A single dose of sarilumab 350 mg IV will be administered prior to the initial dose of REGN4336 when administered IV for mitigation of CRS.

[0154] Assessment of Dose-Limiting Toxicities in Dose Escalation: A dose limiting toxicity (DLT) is any adverse event (AE) that could preclude advancing to higher dose levels. The DLT criteria incorporate AEs reported with other bsAbs and checkpoint inhibitors. Toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0, except for CRS, which will be graded according to current American Society for Transplantation and Cellular Therapy (ASTCT) criteria.

[0155] In all modules, dose level escalation (*i.e.*, target dose escalation) will follow Bayesian optimal interval (BOIN) design rules applied with the following conditions: 1) DLTs associated with previously untested doses of REGN4336 will be considered, 2) dose levels will be escalated until a MTD with a toxicity rate of 30% is observed for the target dose of REGN4336, and 3) the maximum number of patients treated at a dose level is 12.

[0156] In Module 1, because the step-up dosing regimen consists of doses that have been tested and deemed tolerable as a target dose in prior escalation cohorts (after dose level 1 in Module 1),

separate rules will be applied to modify the step-up dosing regimen based on the occurrence and severity of CRS and other DLTs.

[0157] DLT Observation Periods:

[0158] Module 1: The DLT observation period (minimum duration of 28 days) in Module 1 begins when the first dose of study drug is administered. Monitoring for DLTs continues for at least 2 weeks following the first administration of the REGN4336 target dose at the given dose level. Due to the allowance of up to 2 weeks of dose delays during step-up dosing prior to the first administration of the target dose, the maximum duration of the DLT period is 42 days. DLTs observed during step-up dosing will be considered separately from DLTs observed at the target dose and be considered for modification of the step-up dosing regimen. DLTs observed at the target dose will determine tolerability of the target dose and considered for dose level escalation.

[0159] Module 2: The DLT observation period is defined as 21 days from the first dose of combination therapy (REGN4336 and cemiplimab) beginning on cycle 2 day 1.

[0160] Module 3: The DLT observation period is defined as 21 days from the first dose of combination therapy (REGN4336 and REGN5678) beginning on cycle 2 day 1.

[0161] Dose Expansion: During dose expansion, patients will receive either monotherapy REGN4336 (Module 1), a combination therapy with cemiplimab 350 mg IV Q3W (Module 2), or combination therapy with REGN5678 QW (Module 3) at the assigned DL (*e.g.*, RP2DR). If multiple DLs reveal pharmacodynamic activity and are well tolerated, up to 2 expansion cohorts in total may be opened. In both dose escalation and dose expansion, safety evaluations will be conducted at each study drug dosing visit. Radiographic response assessment will be performed every 9 weeks (Q9W) throughout the study.

[0162] Study Population

[0163] Up to 370 patients will be enrolled for the study, as follows: Anticipated enrollment is approximately up to 208 patients in the dose escalation phase across modules. Approximately 162 patients in the dose expansion phase. Sample size estimation is based on up to 2 expansion cohorts for each module with up to 27 patients per cohort.

[0164] The study population includes men with treatment-experienced mCRPC. For inclusion in this study, patients must have received at least 2 approved therapies for metastatic and/or castration-resistant disease, including a second-generation anti-androgen therapy (*e.g.*, abiraterone, enzalutamide, apalutamide, or darolutamide).

[0165] Inclusion Criteria: A patient must meet the following criteria to be eligible for inclusion in the study:

1. Males ≥ 18 years of age

2. Histologically or cytologically confirmed adenocarcinoma of the prostate without pure small cell carcinoma
3. Metastatic, castration-resistant prostate cancer (mCRPC) with PSA value at screening ≥ 4 ng/mL that has progressed within 6 months prior to screening according to 1 of the following:
 - a. PSA progression as defined by a rising PSA level confirmed with an interval of ≥ 1 week between each assessment.
 - b. Radiographic disease progression in soft tissue based on RECIST version 1.1 criteria with or without PSA progression
 - c. Radiographic disease progression in bone defined as the appearance of 2 or more new bone lesions on bone scan with or without PSA progression. NOTE: Measurable disease per RECIST version 1.1 per local reading at screening is not an eligibility criterion for enrollment
4. Has progressed upon or is intolerant to ≥ 2 lines prior systemic therapy approved in the metastatic and/or castration resistant setting (in addition to androgen deprivation therapy [ADT]) including at least 1 second-generation anti-androgen therapy (eg, abiraterone, enzalutamide, apalutamide, or darolutamide)

NOTE: a non-taxane based chemotherapy regimen given for metastatic prostate cancer with mixed histology is permissible and will be included when evaluating line of therapy
5. Able and willing to provide tumor tissue, either archival or newly obtained. NOTE: If archival or fresh tissue is not available, a pathology report that confirms diagnosis of prostate cancer may be submitted
6. Have had either orchiectomy OR be on luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy with serum testosterone < 50 ng/dL AND agree to stay on LHRH agonist or antagonist therapy during the study
7. Has an ECOG performance status of 0 or 1
8. Has adequate organ and bone marrow function documented by:
 - a. Hemoglobin ≥ 8.5 g/dL
 - b. Absolute neutrophil count $\geq 1.5 \times 10^9/L$
 - c. Platelet count $\geq 100 \times 10^9/L$
9. Serum creatinine $\leq 1.5 \times$ ULN or estimated glomerular filtration rate > 50 mL/min/1.73 m². A 24-hour urine creatinine collection may substitute for the calculated creatinine clearance to meet eligibility criteria.
10. Adequate hepatic function:

Total bilirubin $\leq 1.5 \times$ ULN; for patients with known Gilbert's syndrome, $\leq 3 \times$ the institutional ULN is permitted

AST $\leq 2.5 \times$ ULN

ALT $\leq 2.5 \times$ ULN

ALP $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN if evidence of bone involvement by prostate cancer)

11. Is willing and able to comply with clinic visits and study-related procedures and requirements

12. Is willing and able to provide informed consent as specified by health authorities and institutional guidelines

13. Is able to understand and complete study-related questionnaires

[0166] Exclusion Criteria: A patient who meets any of the following criteria will be excluded from the study:

1. Currently receiving treatment in another study
2. Has participated in a study of an investigational agent or an investigational device within 4 weeks of first dose of study therapy
3. Has received treatment with an approved systemic therapy (including Sipuleucel-T) within 3 weeks of dosing or has not yet recovered (*i.e.*, grade ≤ 1 or baseline) from any acute toxicities except for laboratory changes as described in inclusion criteria and as below:
 - a. Patients with grade ≤ 2 neuropathy
4. Has received radiation therapy or major surgery within 14 days of first administration of study drug or has not recovered (*ie*, grade ≤ 1 or baseline) from AEs, except for laboratory changes as described in inclusion criteria and as below:
 - a. Patients with grade ≤ 2 neuropathy
5. Has received any previous systemic biologic or immune-modulating therapy (except for Sipuleucel-T) within 5 half-lives of first dose of study therapy. Examples of immune-modulating agents including blockers of PD-1/PD-L1, CTLA-4, 4-1BB (CD137) or OX-40, therapeutic vaccines, phosphoinositide 3-kinase (PI3K) delta inhibitors or cytokine anti-cancer treatments. Note: Patients previously treated with cetuximab, rituximab, or other non-immunomodulatory antibodies with half-lives longer than 7 days are permitted after a discussion with the sponsor if at least 30 days have elapsed since last treatment. NOTE: Patients who have received prior investigational cell-based therapies (CAR-T cells) are excluded. NOTE: In Module 2 Dose Expansion, no prior anti-cancer immunotherapy is permitted, except Sipuleucel-T
6. Has received prior PSMA-targeting therapy. Exception: prior therapy with approved PSMA-targeted radioligand(s) is permitted

7. Patients who have not recovered (*i.e.*, grade ≤ 1 or baseline) from immune-mediated AEs 3 months prior to initiation of study drug therapy except for endocrinopathies adequately managed with hormone replacement
8. Patients who have permanently discontinued anti-cancer immune modulating therapies due to immune-related AEs
9. Has any condition requiring ongoing/continuous corticosteroid therapy (>10 mg prednisone/day or anti-inflammatory equivalent) within 1 week prior to the first dose of study drug. Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder. Note: Patients who require a brief course of steroids (up to 2 days in the week before enrollment) or physiologic replacement may be enrolled into the study
10. Has ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments. The following are not exclusionary: vitiligo, childhood asthma that has resolved, endocrinopathies (such as hypothyroidism or type 1 diabetes) that require only hormone replacement, or psoriasis that does not require systemic treatment.
11. Has liver metastases
12. Has another malignancy that is progressing or requires active treatment, except:
 - a. Non-melanoma skin cancer that has undergone potentially curative therapy
 - b. Any tumor that has been deemed to be effectively treated with definitive local control (with or without continued adjuvant hormonal therapy)
13. Dose Escalation: History of CNS metastases, including previously treated metastases
Dose Expansion: Untreated or active primary brain tumor, CNS metastases, leptomeningeal disease, or spinal cord compression
Exception: Patients with previously treated central nervous system metastases or spinal cord compression may participate provided there is:
 - a. No evidence of progression for at least 6 weeks prior to the first dose of study drug, and any neurologic symptoms have returned to baseline
 - b. No evidence of new or enlarging central nervous system metastases
 - c. No requirement for systemic corticosteroids for management of central nervous system metastases or spinal cord compression within 2 weeks prior to the first dose of study drug
14. Has encephalitis, meningitis, neurodegenerative disease (with the exception of mild dementia that does not interfere with activities of daily living [ADLs]) or uncontrolled seizures in the year prior to first dose of study therapy

15. Has a known history of, or any evidence of, interstitial lung disease or active, noninfectious pneumonitis within 5 years prior to the first dose of study drug. A history of radiation pneumonitis in the radiation field is permitted
16. Has uncontrolled infection with human immunodeficiency virus, hepatitis B, or hepatitis C infection; or has a diagnosis of immunodeficiency
 - a. Participants will be tested for hepatitis C virus (HCV) and hepatitis B virus (HBV) at screening
 - b. Participants with known HIV infection who have controlled infection (undetectable viral load (HIV RNA PCR) and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards
 - c. Participants with HBV surface antigen positive (HBsAg+) who have controlled infection (serum HBV DNA PCR that is below the limit of detection AND receiving antiviral therapy for HBV) are permitted.
 - d. Participants with HBsAg negative but total HBV core antibody positive (HBcAb+) are permitted with the following requirements: If serum HBV DNA PCR is above the limit of detection at screening, antiviral therapy for HBV must be initiated prior to study entry. If serum HBV DNA PCR is below the limit of detection, periodic monitoring of HBsAg must be performed.
 - e. Participants who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted
17. Has any infection requiring hospitalization or treatment with intravenous anti-infectives within 2 weeks of first dose of study drug
18. Has received a live vaccine within 28 days of planned start of study drug
19. Has had prior allogeneic stem cell transplantation or received organ transplants at any time, or autologous stem cell transplantation within 12 weeks of the start of study drug
20. Has known allergy or hypersensitivity to study drugs or to any of their components/excipients
21. Has known psychiatric or substance abuse disorders that would interfere with participation with the requirements of the study
22. Has any medical condition, co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical study due to high safety risks and/or potential to affect interpretation of results of the study including, but not limited to, significant

cardiovascular disease (eg, New York Heart Association Class III or IV cardiac disease, myocardial infarction within the previous 6 months, unstable arrhythmias or unstable angina) and/or significant pulmonary disease (eg, obstructive pulmonary disease and history of symptomatic bronchospasm)

23. Has a cardiac ejection fraction <40% by echocardiogram or multi-gated acquisition scan (MUGA)
24. Exclusion criteria related to tuberculosis and opportunistic infections:
 - a. Known active tuberculosis or history of incompletely treated active or latent tuberculosis. Acceptable treatments for latent tuberculosis would be 9 months of isoniazid 300 mg by mouth daily or equivalent proven regimen per local guidelines. Note: For patients who are to receive sarilumab, exclusion of tuberculosis with an interferon gamma release assay is required unless there is a prior history of treated tuberculosis.
 - b. History of invasive opportunistic infections including but not limited to histoplasmosis, coccidioidomycosis, Pneumocystis jirovecii, or aspergillosis, or John Cunningham virus (progressive multifocal leukoencephalopathy)
25. History of bowel perforation, severe diverticulitis, or inflammatory bowel disease.

[0167] Study Treatments

[0168] Module 1: REGN4336 at the assigned DL will be administered by SC or IV injection QW. Doses are detailed in the tables below. Doses of 1 mg to 900 mg will be administered. If sarilumab prophylaxis is required, then sarilumab should be administered prior to REGN4336. Sarilumab will be administered by IV infusion over 60 minutes and will be given once prior to the initial dose of REGN4336.

[0169] Module 2: REGN4336 will be administered as above. Cemiplimab 350 mg will be administered by IV infusion over 30 minutes every 3 weeks (Q3W). Doses are detailed in the tables below. When both drugs are administered on the same day, REGN4336 will be administered first and cemiplimab administration should follow no sooner than 30 minutes following completion of REGN4336 administration. If sarilumab prophylaxis is required, then sarilumab should be administered prior to both REGN4336 and cemiplimab. Sarilumab will be administered by IV infusion over 60 minutes.

[0170] Module 3: REGN4336 will be administered as above. REGN5678, 30 mg, at the assigned DL will be administered by IV infusion over 30 minutes to 2 hours QW. Doses are detailed in the tables below. When both drugs are administered on the same day, REGN4336 will be administered first and REGN5678 should follow no sooner than 30 minutes following completion of REGN4336

administration. If sarilumab prophylaxis is required, then sarilumab should be administered prior to REGN4336. Sarilumab will be administered by IV infusion over 60 minutes.

[0171] All Modules: In patients at select sites, ^{18}F -DCFPyL or ^{68}Ga -PSMA-11 will be administered for experimental PSMA PET/CT imaging procedures.

[0172] Intravenous REGN4336: For cohorts using intravenous dosing of REGN4336 in Modules 1-3, a single dose of sarilumab 350 mg IV will be administered prior to the initial dose of REGN4336.

[0173] Routine premedication with steroids will be required for all enrolled patients, as follows: 10 mg dexamethasone IV/PO on the day of and day after dosing from the first (initial) dose of REGN4336 through the 2nd full (target) dose; Initiate taper after second full (target) dose: 10 mg IV/PO on day of 3rd full dose; 6 mg IV/PO on day of 4th full dose.

Table 2: Dose Escalation Scheme for Module 1 (Monotherapy REGN4336 [SC])

DL ^{1,2,3}	Initial dose	Transitional dose	Target dose
DL1-SC	0.03 mg	0.1 mg	0.3 mg
DL2-SC	0.09 mg	0.3 mg	0.9 mg
DL3-SC	0.3 mg	0.9 mg	3 mg
DL4-SC	0.9 mg	3 mg	9 mg
DL5-SC	3 mg	9 mg	30 mg
DL6-SC	10 mg	30 mg	100 mg
DL7-SC	30 mg	100 mg	300 mg
DL8-SC	100 mg	300 mg	900 mg

¹Cohorts that administer REGN4336 SC will be denoted with "SC" (e.g. M1-DL2-SC).

²Dose levels are determined by the target dose, independent of the step-up regimen. For example, if the step-up regimen is fixed at 0.3 mg (initial) and 0.9 mg (transitional) while the target dose escalates to 30 mg, the dose level will be referred to as DL5-SC.

³Intermediate dose levels for REGN4336 administered SC may be evaluated and are detailed in Tables 8 and 9 below.

Table 3: Dose Escalation Scheme for Module 1 (Monotherapy REGN4336 [IV])

DL ^{1,2,3}	Initial dose	Transitional dose	Target dose
DL1-IV	0.01 mg	0.05 mg	1 mg ⁴
DL2-IV	0.03 mg	0.15 mg	3 mg
DL3-IV	0.09 mg	0.45 mg	9 mg
DL4-IV	0.3 mg	1.35 mg	30 mg

DL5-IV	0.9 mg	4 mg	100 mg
DL6-IV	3 mg	12 mg	300 mg
DL7-IV	10 mg	36 mg	900 mg

¹Cohorts that administer REGN4336 IV will be denoted with “IV” (e.g. M1-DL2-IV).

²Dose levels are determined by the target dose, independent of the step-up regimen. For example, if the step-up regimen is fixed at 0.3 mg (initial) and 0.9 mg (transitional) while the target dose escalates to 30 mg, the dose level will be referred to as DL4-IV.

³Intermediate dose levels for REGN4336 administered IV may be evaluated and are detailed in Tables 10 and 11 below.

⁴Target dose levels for M1-IV represent the maximum permitted target dose. The first target dose level in M1-IV will be no greater than one log lower than the target dose shown tolerable for REGN4336 administered SC and no greater than 1 mg. REGN4336 target dose levels lower than 1 mg are provided in Tables 10 and 11 below.

Table 4: Dose Escalation Scheme for Module 2 (REGN4336 QW [SC] in Combination with Cemiplimab Q3W [IV])

	REGN4336			Cemiplimab
DL^{1,2,3}	Initial dose	Transitional dose	Target dose	
DL1-SC	0.03 mg	0.1 mg	0.3 mg	350 mg
DL2-SC	derived from M1	derived from M1	0.9 mg	350 mg
DL3-SC	derived from M1	derived from M1	3 mg	350 mg
DL4-SC	derived from M1	derived from M1	9 mg	350 mg
DL5-SC	derived from M1	derived from M1	30 mg	350 mg
DL6-SC	derived from M1	derived from M1	100 mg	350 mg
DL7-SC	derived from M1	derived from M1	300 mg	350 mg
DL8-SC	derived from M1	derived from M1	900 mg	350 mg

¹Cohorts that administer REGN4336 SC will be denoted with “SC” (e.g. M2-DL2-SC). Dose levels are determined by the REGN4336 target dose, independent of the step-up regimen.

²If Module 2 begins at a dose level in which the initial and transitional doses are defined in Module 1, those defined doses will be implemented in Module 2. If Module 2 begins prior to the definition of initial and transitional doses, then the same doses of REGN4336 as specified in Table 2 will be used for initial and transitional doses in Module 2.

³Intermediate dose levels for REGN4336 administered SC may be evaluated and are detailed in Tables 8 and 9 below.

Table 5: Dose Escalation Scheme for Module 2 (REGN4336 QW [IV] in Combination with Cemiplimab Q3W [IV])

DL ^{1,2,3}	REGN4336			Cemiplimab
	Initial dose	Transitional dose	Target dose	
DL1-IV	0.01 mg	0.05 mg	1 mg ³	350 mg
DL2-IV	derived from M1	derived from M1	3 mg	350 mg
DL3-IV	derived from M1	derived from M1	9 mg	350 mg
DL4-IV	derived from M1	derived from M1	30 mg	350 mg
DL5-IV	derived from M1	derived from M1	100 mg	350 mg
DL6-IV	derived from M1	derived from M1	300 mg	350 mg
DL7-IV	derived from M1	derived from M1	900 mg	350 mg

¹Cohorts that administer REGN4336 IV will be denoted with "IV" (e.g. M2-DL2-IV). Dose levels are determined by the REGN4336 target dose, independent of the step-up regimen.

²If Module 2 begins at a dose level in which the initial and transitional doses are defined in Module 1, those defined doses will be implemented in Module 2. If Module 2 begins prior to the definition of initial and transitional doses, then the same doses of REGN4336 as specified in Table 3 will be used for initial and transitional doses in Module 2.

³REGN4336 target dose levels lower than 1 mg are shown in Tables 10 and 11 below. Intermediate dose levels for REGN4336 administered IV may be evaluated and are detailed in Tables 10 and 11 below.

Table 6: Dose Escalation Scheme for Module 3 (REGN4336 QW [SC] in Combination with REGN5678 QW [IV])

DL ^{1,2,3,4}	REGN4336			REGN5678
	Initial dose	Transitional dose	Target dose	
DL1-SC	0.03 mg	0.1 mg	0.3 mg	30 mg
DL2-SC	derived from M1	derived from M1	0.9 mg	30 mg
DL3-SC	derived from M1	derived from M1	3 mg	30 mg
DL4-SC	derived from M1	derived from M1	9 mg	30 mg
DL5-SC	derived from M1	derived from M1	30 mg	30 mg
DL6-SC	derived from M1	derived from M1	100 mg	30 mg
DL7-SC	derived from M1	derived from M1	300 mg	30 mg
DL8-SC	derived from M1	derived from M1	900 mg	30 mg

¹Cohorts that administer REGN4336 SC will be denoted with "SC" (e.g. M3-DL2-SC). Dose levels are determined by the REGN4336 target dose, independent of the step-up regimen.

²If Module 2 begins at a dose level in which the initial and transitional doses are defined in Module 1, those defined doses will be implemented in Module 2. If Module 2 begins prior to the definition of initial and

transitional doses, then the same doses of REGN4336 as specified in Table 2 will be used for initial and transitional doses in Module 3.

³Intermediate dose levels for REGN4336 administered SC may be evaluated and are detailed in Tables 8 and 9 below.

⁴See also Figure 8 (schematic describing Module 3).

Table 7: Dose Escalation Scheme for Module 3 (REGN4336 QW [IV] in Combination with REGN5678 [IV])

DL ^{1,2,3}	REGN4336			REGN5678
	Initial dose	Transitional dose	Target dose	
DL1-IV	0.01 mg	0.05 mg	1 mg ³	30 mg
DL2-IV	derived from M1	derived from M1	3 mg	30 mg
DL3-IV	derived from M1	derived from M1	9 mg	30 mg
DL4-IV	derived from M1	derived from M1	30 mg	30 mg
DL5-IV	derived from M1	derived from M1	100 mg	30 mg
DL6-IV	derived from M1	derived from M1	300 mg	30 mg
DL7-IV	derived from M1	derived from M1	900 mg	30 mg

¹Cohorts that administer REGN4336 IV will be denoted with "IV" (e.g. M3-DL2-IV). Dose levels are determined by the REGN4336 target dose, independent of the step-up regimen.

²If Module 2 begins at a dose level in which the initial and transitional doses are defined in Module 1, those defined doses will be implemented in Module 2. If Module 2 begins prior to the definition of initial and transitional doses, then the same doses of REGN4336 as specified in Table 3 will be used for initial and transitional doses in Module 3.

³REGN4336 target dose levels lower than 1 mg are shown in Tables 10 and 11 below. Intermediate dose levels for REGN4336 administered IV may be evaluated and are detailed in Tables 10 and 11 below. See also Figure 8 (schematic describing Module 3).

Table 8: Dose Levels with Increments Limited to 50% and/or 100%

Dose Level	Initial	Transition	Target	Dose Increment Percentage
DL-1-SC	0.03 mg	0.03 mg	0.03 mg	N/A
DL1-SC	0.03 mg	0.1 mg	0.3 mg	N/A
DL1-INT1-SC	0.05 mg ¹	0.15 mg	0.45 mg	DL1 +≤50%
DL1-INT2-SC	0.06 mg	0.2 mg	0.6 mg	DL1-INT1 +≤50% and DL1 +≤100%
DL2-SC	0.09 mg	0.3 mg	0.9 mg	DL1-INT2 +≤50%
DL2-INT1-SC	0.14 mg ²	0.45 mg	1.35 mg	DL2 +≤50%

DL2-100-SC	0.18 mg	0.6 mg	1.8 mg	DL2 $\pm$ 100%
DL2-INT2-SC	0.2 mg	0.65 mg	2 mg	DL2-INT1 $\pm$ 50%
DL3-SC	0.3 mg	0.9 mg	3 mg	DL2-INT2 $\pm$ 50%
DL3-INT1-SC	0.45 mg	1.35 mg	4.5 mg	DL3 $\pm$ 50%
DL3-100-SC	0.6 mg	1.8 mg	6 mg	DL3 $\pm$ 100%
DL3-INT2-SC	0.65 mg	2 mg	6.5 mg	DL3-INT1 $\pm$ 50%
DL4-SC	0.9 mg	3 mg	9 mg	DL3-INT2 $\pm$ 50%
DL4-INT1-SC	1.35 mg	4.5 mg	13.5 mg	DL4 $\pm$ 50%
DL4-100-SC	1.8 mg	6 mg	18 mg	DL4 $\pm$ 100%
DL4-INT2-SC	2 mg	6.5 mg	20 mg	DL4-INT1 $\pm$ 50%
DL5-SC	3 mg	9 mg	30 mg	DL4-INT2 $\pm$ 50%
DL5-INT1-SC	4.5 mg	13.5 mg	45 mg	DL5 $\pm$ 50%
DL5-100-SC	6 mg	18 mg	60 mg	DL5 $\pm$ 100%
DL5-INT2-SC	6.75 mg	20.25 mg	67.5 mg	DL5-INT1 $\pm$ 50%
DL6-SC	10 mg	30 mg	100 mg	DL5-INT2 $\pm$ 50%
DL6-INT1-SC	15 mg	45 mg	150 mg	DL6 $\pm$ 50%
DL6-100-SC	20 mg	60 mg	200 mg	DL6 $\pm$ 100%
DL6-INT2-SC	22.5 mg	67.5 mg	225 mg	DL6-INT1 $\pm$ 50%
DL7-SC	30 mg	100 mg	300 mg	DL6-INT2 $\pm$ 50%
DL7-INT1-SC	45 mg	150 mg	450 mg	DL7 $\pm$ 50%
DL7-100-SC	60 mg	200 mg	600 mg	DL7 $\pm$ 100%
DL7-INT2-SC	67.5 mg	225 mg	675 mg	DL7-INT1 $\pm$ 50%
DL8-SC	100 mg	300 mg	900 mg	DL7-INT2 $\pm$ 50%

DL=dose level; INT=intermediate, SC=subcutaneous

¹This value was rounded up from 0.045 mg for operational feasibility and results in DL1+66%.

²This value was rounded up from 0.135 mg for operational feasibility and results in DL2+56%.

Table 9: Dose Escalation of REGN4336 (SC) with Intermediate Dose Levels with Increment Limits of 30%

Dose Level	Initial	Transitional	Target
DL1-SC	0.03mg	0.1 mg	0.3 mg
DL1-30.1-SC	0.04 mg	0.13 mg	0.4 mg
DL1-30.2-SC	0.05 mg	0.16 mg	0.5 mg
DL1-30.3-SC	0.06 mg	0.21 mg	0.6 mg
DL1-30.4-SC	0.07 mg	0.25 mg	0.7 mg
DL2-SC	0.09 mg	0.3 mg	0.9 mg
DL2-30.1-SC	0.11 mg	0.4 mg	1.1 mg
DL2-30.2-SC	0.15 mg	0.5 mg	1.5 mg
DL2-30.3-SC	0.19 mg	0.65 mg	1.9 mg
DL2-30.4-SC	0.24 mg	0.8 mg	2.4 mg
DL3-SC	0.3 mg	0.9 mg	3 mg
DL3-30.1-SC	0.4 mg	1.1 mg	4 mg
DL3-30.2-SC	0.5 mg	1.5 mg	5 mg
DL3-30.3-SC	0.65 mg	1.9 mg	6.5 mg
DL3-30.4-SC	0.84 mg	2.4 mg	8.4 mg
DL4-SC	0.9 mg	3 mg	9 mg
DL4-30.1-SC	1.1 mg	4 mg	11 mg
DL4-30.2-SC	1.5 mg	5 mg	15 mg
DL4-30.3-SC	1.9 mg	6.5 mg	19 mg
DL4-30.4-SC	2.4 mg	8.4 mg	24 mg
DL5-SC	3 mg	9 mg	30 mg
DL5-30.1-SC	3.9 mg	11.7 mg	39 mg
DL5-30.2-SC	5.1 mg	15.2 mg	51 mg
DL5-30.3-SC	6.6 mg	19.8 mg	66 mg
DL5-30.4-SC	8.6 mg	25.7 mg	86 mg
DL6-SC	10 mg	30 mg	100 mg
DL6-30.1-SC	13 mg	39 mg	130 mg
DL6-30.2-SC	17 mg	50.7 mg	169 mg
DL6-30.3-SC	22 mg	66 mg	220 mg
DL6-30.4-SC	28.6 mg	85.7 mg	286 mg
DL7-SC	30 mg	100 mg	300 mg
DL7-30.1-SC	39 mg	130 mg	390 mg
DL7-30.2-SC	50.7 mg	169 mg	507 mg

DL7-30.3-SC	66 mg	222 mg	659 mg
DL7-30.4-SC	85.7 mg	286 mg	857 mg
DL8-SC	100 mg	300 mg	900 mg

DL=dose level; SC=subcutaneous

Dose level escalation increments are limited to $\leq 30\%$.

Some doses are rounded for operational feasibility.

Table 10: Dose Escalation of REGN4336 (IV) with Intermediate Dose Levels with Increments Limited to 50% and/or 100%

Dose Level	Initial	Transition	Target	Dose Increment Percentage
DL-1-IV	0.01 mg	0.03 mg	0.3 mg	N/A
DL-1-INT1-IV	0.01 mg	0.03 mg	0.45 mg	DL-1 $\pm \leq 50\%$
DL-1-INT2-IV	0.01 mg	0.04 mg	0.6 mg	DL-1-INT1 $\pm \leq 50\%$ and DL-1 $\pm \leq 100\%$
DL1-IV	0.01 mg	0.05 mg	1 mg	N/A
DL1-INT1-IV	0.02 mg	0.08 mg	1.5 mg	DL1 $\pm \leq 50\%$
DL1-INT2-IV	0.02 mg	0.11 mg	2.3 mg	DL1-INT1 $\pm \leq 50\%$ and DL1 $\pm \leq 100\%$
DL2-IV	0.03 mg	0.15 mg	3 mg	DL1-INT2 $\pm \leq 50\%$
DL2-INT1-IV	0.05 mg	0.23 mg	4.5 mg	DL2 $\pm \leq 50\%$
DL2-100-IV	0.06 mg	0.3 mg	6 mg	DL2 $\pm \leq 100\%$
DL2-INT2-IV	0.07 mg	0.34 mg	6.8 mg	DL2-INT1 $\pm \leq 50\%$
DL3-IV	0.09 mg	0.45 mg	9 mg	DL2-INT2 $\pm \leq 50\%$
DL3-INT1-IV	0.14 mg	0.6 mg	13.5 mg	DL3 $\pm \leq 50\%$
DL3-100-IV	0.18 mg	0.8 mg	18 mg	DL3 $\pm \leq 100\%$
DL3-INT2-IV	0.20 mg	0.9 mg	20.3 mg	DL3-INT1 $\pm \leq 50\%$
DL4-IV	0.30 mg	1.35 mg	30 mg	DL3-INT2 $\pm \leq 50\%$
DL4-INT1-IV	0.45 mg	2 mg	45 mg	DL4 $\pm \leq 50\%$
DL4-100-IV	0.60 mg	2.7 mg	60 mg	DL4 $\pm \leq 100\%$

DL4-INT2-IV	0.68 mg	3 mg	67.5 mg	DL4-INT1 + $\leq$ 50%
DL5-IV	0.90 mg	4 mg	100 mg	DL4-INT2 + $\leq$ 50%
DL5-INT1-IV	1.4 mg	6 mg	150 mg	DL5 + $\leq$ 50%
DL5-100-IV	1.8 mg	8 mg	200 mg	DL5 + $\leq$ 100%
DL5-INT2-IV	2 mg	9 mg	225 mg	DL5-INT1+ $\leq$ 50%
DL6-IV	3 mg	12 mg	300 mg	DL5-INT2 + $\leq$ 50%
DL6-INT1-IV	4.5 mg	18 mg	450 mg	DL6 + $\leq$ 50%
DL6-100-IV	6 mg	24 mg	600 mg	DL6 + $\leq$ 100%
DL6-INT2-IV	6.8 mg	27 mg	675 mg	DL6-INT1+ $\leq$ 50%
DL7-IV	10 mg	36 mg	900 mg	DL6-INT2 + $\leq$ 50%

DL=dose level; INT=intermediate, IV=intravenous
Some doses are rounded for operational feasibility.

Table 11: Dose Escalation of REGN4336 (IV) with Intermediate Dose Levels with Increment Limits of 30%

Dose Level	Initial	Transitional	Target
DL-1-IV	0.01 mg	0.03 mg	0.3 mg
DL-1-30.1-IV	0.01 mg	0.03 mg	0.39 mg
DL-1-30.2-IV	0.01 mg	0.03 mg	0.51 mg
DL-1-30.3-IV	0.01 mg	0.04 mg	0.66 mg
DL-1-30.4-IV	0.01 mg	0.04 mg	0.86 mg
DL1-IV	0.01 mg	0.05 mg	1 mg
DL1-30.1-IV	0.013 mg	0.07 mg	1.3 mg
DL1-30.2-IV	0.017 mg	0.08 mg	1.7 mg
DL1-30.3-IV	0.022 mg	0.11 mg	2.2 mg
DL1-30.4-IV	0.029 mg	0.14 mg	2.9 mg
DL2-IV	0.03 mg	0.15 mg	3 mg
DL2.30.1-IV	0.04 mg	0.20 mg	3.9 mg
DL2-30.2-IV	0.05 mg	0.25 mg	5.1 mg
DL2-30.3-IV	0.07 mg	0.33 mg	6.6 mg
DL2-30.4-IV	0.09 mg	0.43 mg	8.6 mg

DL3-IV	0.09 mg	0.45 mg	9 mg
DL3-30.1-IV	0.12 mg	0.59 mg	11.7 mg
DL3-30.2-IV	0.15 mg	0.76 mg	15.2 mg
DL3-30.3-IV	0.20 mg	0.99 mg	19.8 mg
DL3-30.4-IV	0.26 mg	1.3 mg	25.7 mg
DL4-IV	0.3 mg	1.35 mg	30 mg
DL4-30.1-IV	0.39 mg	1.8 mg	39 mg
DL4-30.2-IV	0.51 mg	2.3 mg	50.7 mg
DL4-30.3-IV	0.66 mg	3.0 mg	65.9 mg
DL4-30.4-IV	0.86 mg	3.9 mg	85.7 mg
DL5-IV	0.9 mg	4 mg	100 mg
DL5-30.1-IV	1.2 mg	5.2 mg	130 mg
DL5-30.2-IV	1.5 mg	6.8 mg	169 mg
DL5-30.3-IV	2.0 mg	8.8 mg	220 mg
DL5-30.4-IV	2.6 mg	11.4 mg	286 mg
DL6-IV	3 mg	12 mg	300 mg
DL6-30.1-IV	3.9 mg	15.5 mg	390 mg
DL6-30.2-IV	5.1 mg	20.3 mg	507 mg
DL6-30.3-IV	6.6 mg	26.4 mg	659 mg
DL6-30.4-IV	8.6 mg	34.3 mg	857 mg
DL7-IV	10 mg	36 mg	900 mg

DL=dose level; INT=intermediate, IV=intravenous
Dose level escalation increments are limited to $\leq 30\%$.
Some doses are rounded for operational feasibility.

[0174] Based on review of emerging CRS events during dose escalation, an additional transitional dose may be added to the step-up regimen to evaluate whether an extended step-up will allow patients to achieve higher target doses while minimizing the incidence and severity of CRS. The decision to introduce an additional transitional dose will be informed by the timepoints at which CRS occurs, the severity of the CRS events, and an assessment of whether further escalation of the target dose might improve efficacy and overall risk:benefit.

[0175] It is anticipated that the additional transitional dose will be added to mitigate CRS observed at the target dose. The next target dose level to be evaluated after the decision to incorporate an additional transitional dose will be determined by the usual dose escalation rules based on toxicity observed in patients treated with that target dose. For example, if patients are being treated with a target dose of REGN4336 (SC) 9 mg (DL4) with an initial and transitional dose that have been previously fixed at 0.3 mg and 0.9 mg respectively, and unacceptable CRS is observed with

administration of the 9 mg target dose, an additional transitional dose may be added between 0.9 and 9 mg. This new transitional dose will be based upon the previously highest tolerable target dose (e.g. from DL3). The following considerations apply to the additional transitional dose: (i) If it is determined that the additional transitional dose has had a favorable effect on mitigating CRS, then subsequent dose levels will continue to include the additional transitional dose; and (ii) the additional transitional dose may be fixed using the same approach for the initial and first transitional doses with continued escalation of the target dose as tolerated according to protocol-specified BOIN criteria.

[0176] Study Endpoints

[0177] The primary endpoints of the study are: Dose-limiting toxicities, other treatment-emergent adverse events (TEAEs; including irAEs), serious AEs (SAEs), adverse events of special interest (AESIs), and laboratory abnormalities (in dose escalation); REGN4336 concentrations in serum as monotherapy, in combination with cemiplimab (in dose escalation), and in combination with REGN5678 (in dose escalation); and Objective Response Rate (ORR) per modified Prostate Cancer Working Group 3 (PCWG3) criteria, (in dose expansion) defined as the percentage of patients who have achieved response based on:

- $\geq 50\%$ decline of PSA from baseline, confirmed by a second PSA test ≥ 3 weeks later, AND/OR
- Confirmed radiographic response of complete response (CR) or partial response (PR)

[0178] The key secondary endpoints are: ORR per modified PCWG3 criteria (in dose escalation), defined as the percentage of patients who have achieved response based on $\geq 50\%$ decline of PSA from baseline, confirmed by a second PSA test ≥ 3 weeks later, and/or confirmed radiographic response of complete response (CR) or partial response (PR); dose-limiting toxicities, other TEAEs (including irAEs), SAEs, AESIs, and laboratory abnormalities (in dose expansion); REGN4336 concentrations in serum as monotherapy, in combination with cemiplimab (in dose expansion), and in combination with REGN5678 (in dose expansion); percentage of patients with $\geq 50\%$ reduction in PSA from baseline, confirmed by a second PSA test ≥ 3 weeks later (in dose escalation and expansion); percentage of patients with $\geq 90\%$ reduction in PSA from baseline, confirmed by a second PSA test ≥ 3 weeks later (in dose escalation and expansion); and immunogenicity, as measured by anti-drug antibodies (ADA) to REGN4336 in Module 1, ADA to REGN4336 and/or cemiplimab in Module 2, and ADA to REGN4336 and/or REGN5678 in Module 3 (in dose escalation and expansion).

[0179] The exploratory endpoints are:

- Percent change in PSA
- Disease Control Rate (DCR) (via modified PCWG3 and iRECIST)
- Duration of Response (DOR), based upon radiographic response (rDOR) (via modified PCWG3 and iRECIST)
- DOR based upon PSA response
- Radiographic Progression-free Survival (rPFS) (via modified PCWG3 and iRECIST)
- Progression free survival (based on PSA)
- Overall survival (OS)
- Time to response based upon radiographic response (via modified PCWG3 and iRECIST)
- Time to response based upon PSA response
- Time to progression based upon radiographic progression
- Time to progression based upon PSA progression
- Abundance and distribution of therapeutic targets (*e.g.*, PD-1/PD-L1, PSMA, and CD3+ T cells) in tumor tissue samples at baseline and over time on therapy
- Association of CTC abundance and molecular features with clinical efficacy
- Tumor mutational profiling of ctDNA, CTCs, and/or tumor tissue at baseline and on treatment, including assessment of individual somatic variants, tumor mutational burden (TMB), alterations of the DNA repair pathway genes, and evaluation of the relationship between these features and drug response
- Abundance and phenotype of circulating T-cell subsets at baseline and on treatment, and the association of their pharmacodynamic responsiveness with clinical efficacy or toxicity
- Concentrations of systemic inflammatory markers (*e.g.*, serum cytokines) and immune activity and clinical toxicity
- Changes from baseline in tumor PSMA and FDG PET signal after therapy initiation
- Association of baseline PSMA PET tumor positivity with clinical activity
- Time to Pain Progression (TTPP) as Assessed by Brief Pain Inventory-Short Form (BPI-SF) Item 3 ("Worst Pain in 24 Hours") and Opiate Analgesic Use
- Change from baseline in pain severity and pain interference as measured by the BPI-SF
- Change from baseline in GHS/QoL as measured by the EORTC QLQ-C30 GHS/QoL scale score

- Change from baseline in Physical functioning as measured by the EORTC QLQ-C30 physical functioning scale score
- Change from baseline in urinary symptoms as measured by the EORTC QLQ-PR25 urinary symptom scale score

[0180] Results: Among six patients treated with the combination of anti-PSMA x CD3 (3 mg) and anti-PSMA x CD28 (30 mg), to date, five showed absolute reductions in absolute PSA levels of from 6% to 91% relative to baseline. Two of the six patients had previously been treated by PLUVICTO® (lutetium Lu 177 vipivotide tetraxetan), a radioligand therapeutic agent. No more than grade 1 or grade 2 CRS was observed in any of the patients.

[0181] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Sequences

SEQ ID NO: 1

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYAGNNKYYADSVKGRFTVSRD
NSKKTLYLQMNSLRSEDVAVYYCAKDSYYDFLTDPDVLDIWGQGTMTVTVSS

SEQ ID NO: 2

GFTFSSYG

SEQ ID NO: 3

ISYAGNNK

SEQ ID NO: 4

AKDSYYDFLTDPDVLDI

SEQ ID NO: 5

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIQYADSVKGRFTISR
NAKNSLYLQMNSLRAEDTALYYCAKYGSYGKFFYYGMDVWGQGTITVTVSS

SEQ ID NO: 6

GFTFDDYS

SEQ ID NO: 7

ISWNSGSI

SEQ ID NO: 8

AKYGSYGKFFYYGMDV

SEQ ID NO: 9

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQSYSTPPITFGQGRLEIK

SEQ ID NO: 10

QSISSY

SEQ ID NO: 11

AAS

SEQ ID NO: 12

QQSYSTPPIT

SEQ ID NO: 13

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVISYAGNNKYYADSVKGRFTVSRD
NSKKTLYLQMNSLRSEDYAVYYCAKDSYYDFLTDPDVLDIWGQGTMTVTVSSASTKGPSVFPLAPCSRSTSEST
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVD
KRVESKYGPPCPAPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNNH
YTQKSLSLSLGK

SEQ ID NO: 14

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWRQAPGKGLEWVSGISWNSGSIYADSVKGRFTISR
NAKNSLYLQMNSLRAEDTALYYCAKYGSGYGFYYGMDVWGQGTITVTVSSASTKGPSVFPLAPCSRSTSEST
AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVD
KRVESKYGPPCPAPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNR
FTQKSLSLSPGK

SEQ ID NO: 15

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDFTL
TISSLQPEDFATYYCQQSYSTPPITFGQGRLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 16

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFMSYDGSNKFYSDSVKGRFTISR
NSRKMLFLQMNNLRAEDTAVYYCARDQYYDFLTDHGVFDYWGQGTILVTVSS

SEQ ID NO: 17

GFTFSSYG

SEQ ID NO: 18

MSYDGSNK

SEQ ID NO: 19

ARDQYYDFLTDHGVFDY

SEQ ID NO: 20

QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGITHYNPSLKSRVTISVDT
SKIQFSLKLSSVTAADTAVYYCARWGVRRDYYYYGMDVWGQGTTTVTVSS

SEQ ID NO: 21

GGSISSYY

SEQ ID NO: 22

IYYSGIT

SEQ ID NO: 23

ARWGVRRDYYYYGMDV

SEQ ID NO: 24

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFT
LTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIK

SEQ ID NO: 25

RASQSVSSSYLA

SEQ ID NO: 26

GASSRAT

SEQ ID NO: 27

QQYGSSPWT

SEQ ID NO: 28

QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAFMSYDGSNKFYSDSVKGRFTISRDN
NSRKMLFLQMNNLRAEDTAVYYCARDQYYDFLTDHGVFDYWGQGTTLTVTVSSASTKGPSVFPLAPCSRSTSEST
AALGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVD
KRVESKYGPCCPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKT
KPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQ
VSLTCLVKGFIYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNH
YTQKSLSLSLGK

SEQ ID NO: 29

QVQLQESGPGLVKPSSETLSLTCTVSGGSISSYYWSWIRQPPGKGLEWIGYIYYSGITHYNPSLKSRVTISVDT
SKIQFSLKLSSVTAADTAVYYCARWGVRRDYYYYGMDVWGQGTTTVTVSSASTKGPSVFPLAPCSRSTSESTAA
LGCLVKDYFPEPTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGKTYTCNVDHKPSNTKVDKR
VESKYGPCCPPCAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDGVEVHNAKT
REEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVS
LTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNH
QKSLSLSPGK

SEQ ID NO: 30

EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGIPDRFSGSGSGTDFT
LTISRLEPEDFAVYYCQQYGSSPWTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAK
VQWKVDNALQSGNSQESVTEQDSKDSSTLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO: 31

EVQLLESQGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFADSVKGRFTISRDN
NSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGLVTVSS

SEQ ID NO: 32

GFTFSNFG

SEQ ID NO: 33

ISGGGRDT

SEQ ID NO: 34

VKWGNIYFDY

SEQ ID NO: 35

DIQMTQSPSSLSASVGDSTITITCRASLSINTFLNHWYQQKPGKAPNLLIYAASSLHGGVPSRFSGSGSGTDFTL
TIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR

SEQ ID NO: 36

LSINTF

SEQ ID NO: 37

AAS

SEQ ID NO: 38

QQSSNTPFT

SEQ ID NO: 39

EVQLLESQGGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDTYFADSVKGRFTISRDN
NSKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGQGLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLV
KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVTPSSSLGKTYTCNVDPKPSNTKVDKRVESKY
GPPCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDPEVQFNWYVDGVEVHNAKTKPREEQ
FNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL
VKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRWQEGNVFSCSVMEALHNHYTQKSL
SLSLGK

SEQ ID NO: 40

DIQMTQSPSSLSASVGDSTITITCRASLSINTFLNHWYQQKPGKAPNLLIYAASSLHGGVPSRFSGSGSGTDFTL
TIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFRRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKV
QWKVDNALQSGNSQESVTEQDSKDSSTLSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

What is claimed is:

1. A method of treating a prostate-specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, comprising administering to the subject a bispecific anti-PSMA x anti-CD3 antibody in a dosing regimen, wherein the dosing regimen comprises:

administering an initial dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during week 1 of the dosing regimen;

administering at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject, wherein one transitional dose is administered during week 2 of the dosing regimen; and

administering a target dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during a subsequent week of the dosing regimen,

wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 2, 3 and 4, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 6, 7 and 8, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively.

2. A method of treating a prostate-specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, comprising administering to the subject a bispecific anti-PSMA x anti-CD3 antibody in combination with an anti-PD-1 antibody that binds human programmed cell death-1 (PD-1) in a dosing regimen, wherein the dosing regimen comprises:

administering an initial dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during week 1 of the dosing regimen;

administering at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject, wherein one transitional dose is administered during week 2 of the dosing regimen;

administering a target dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during a first subsequent week of the dosing regimen; and

administering the target dose of the bispecific anti-PSMA x anti-CD3 antibody, and a dose of the anti-PD-1 antibody during a second subsequent week of the dosing regimen,

wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 2, 3 and 4, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 6, 7 and 8, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and

wherein the anti-PD-1 antibody comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 32, 33 and 34, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 36, 37 and 38.

3. A method of treating a prostate-specific membrane antigen (PSMA)-expressing cancer in a subject in need thereof, comprising administering to the subject a bispecific anti-PSMA x anti-CD3 antibody in combination with a bispecific anti-PSMA x anti-CD28 antibody in a dosing regimen, wherein the dosing regimen comprises:

administering an initial dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during week 1 of the dosing regimen;

administering at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject, wherein one transitional dose is administered during week 2 of the dosing regimen;

administering a target dose of the bispecific anti-PSMA x anti-CD3 antibody to the subject during a first subsequent week of the dosing regimen; and

administering the target dose of the bispecific anti-PSMA x anti-CD3 antibody, and a dose of the anti-PSMA x anti-CD28 antibody during a second subsequent week of the dosing regimen,

wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 2, 3 and 4, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 6, 7 and 8, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 10, 11 and 12, respectively, and

wherein the bispecific anti-PSMA x anti-CD28 antibody comprises a first antigen-binding domain that binds human PSMA and a second antigen-binding domain that binds human CD3, wherein the first antigen-binding domain comprises a heavy chain variable region (HCVR) comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 17, 18 and 19, respectively, and a light chain variable region (LCVR) comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 25, 26 and 27, respectively, and wherein the second antigen-binding domain comprises a HCVR comprising three heavy chain complementarity determining regions, HCDR1, HCDR2 and HCDR3 comprising the amino acid sequences of SEQ ID NO: 21, 22 and 23, respectively, and a LCVR comprising three light chain complementarity determining regions LCDR1, LCDR2 and LCDR3 comprising the amino acid sequences of SEQ ID NO: 25, 26 and 27, respectively.

4. The method of any one of claims 1-3, wherein the first antigen-binding domain of the bispecific anti-PSMA x anti-CD3 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 1 and a LCVR comprising the amino acid sequence of SEQ ID NO: 9, and the second antigen-binding domain of the bispecific anti-PSMA x anti-CD3 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 5 and a LCVR comprising the amino acid sequence of SEQ ID NO: 9.

5. The method of claim 2 or 4, wherein the anti-PD-1 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 31 and a LCVR comprising the amino acid sequence of SEQ ID NO: 35.

6. The method of claim 3 or 4, wherein the first antigen-binding domain of the bispecific anti-PSMA x anti-CD28 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 16 and a LCVR comprising the amino acid sequence of SEQ ID NO: 24, and the second antigen-binding domain of the bispecific anti-PSMA x anti-CD28 antibody comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 20 and a LCVR comprising the amino acid sequence of SEQ ID NO: 24.

7. The method of any one of claims 1-6, wherein the bispecific anti-PSMA x anti-CD3 antibody, the bispecific anti-PSMA x CD28 antibody, and/or the anti-PD-1 antibody comprises a human IgG heavy chain constant region.

8. The method of claim 7, wherein the human IgG heavy chain constant region is isotype IgG1.

9. The method of claim 7, wherein the human IgG heavy chain constant region is isotype IgG4.

10. The method of claim 8 or 9, wherein the bispecific anti-PSMA x anti-CD3 antibody, the bispecific anti-PSMA x CD28 antibody, and/or the anti-PD-1 antibody comprises a chimeric hinge that reduces Fcγ receptor binding relative to a wild-type hinge of the same isotype.

11. The method of any one of claims 7-10, wherein the bispecific anti-PSMA x anti-CD3 antibody and/or the bispecific anti-PSMA x CD28 antibody comprises a first heavy chain paired with a light chain, and a second heavy chain paired with a light chain, and wherein the first heavy chain or the second heavy chain, but not both, comprises a CH3 domain comprising a H435R (EU numbering) modification and a Y436F (EU numbering) modification.

12. The method of any one of claims 1-6, wherein the bispecific anti-PSMA x anti-CD3 antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 13, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 14, and a common light chain comprising the amino acid sequence of SEQ ID NO: 15.

13. The method of any one of claims 2, 4, 5 or 12, wherein the anti-PD-1 antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 39, and a light chain comprising the amino acid sequence of SEQ ID NO: 40.

14. The method of any one of claims 3, 4, 6 or 12, wherein the bispecific anti-PSMA x anti-CD28 antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 28, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 29, and a common light chain comprising the amino acid sequence of SEQ ID NO: 30.

15. The method of any one of claims 1-14, wherein the PSMA-expressing cancer is prostate cancer.

16. The method of claim 15, wherein the prostate cancer is metastatic prostate cancer, castration-resistant prostate cancer, or metastatic castration-resistant prostate cancer.

17. The method of any one of claims 1-14, wherein the PSMA-expressing cancer is prostate cancer, breast cancer, lung cancer, colorectal cancer, bladder cancer, renal cell carcinoma (RCC), a primary brain tumor, pancreatic cancer, breast adenocarcinoma, non-small-cell lung cancer, colorectal adenocarcinoma, transitional cell carcinoma, glioblastoma multiforme, pancreatic ductal adenocarcinoma, gastric adenocarcinoma, clear cell RCC, papillary RCC, chromophobe RCC, oncocytoma, angiomyolipoma, squamous cell carcinoma osteosarcoma, adenoid cystic carcinoma, cervical cancer, endometrial cancer, primary ovarian cancer, or metastatic ovarian cancer.

18. The method of claim 16, wherein the subject has received at least two prior therapies for metastatic and/or castration-resistant prostate cancer.

19. The method of claim 15 or 16, wherein the subject has received at least one anti-androgen therapy.

20. The method of claim 19, wherein the anti-androgen therapy is selected from abiraterone, enzalutamide, apalutamide, or darolutamide.

21. The method of any one of claims 1-20, wherein the subject has histologically or cytologically confirmed adenocarcinoma of the prostate without pure small cell carcinoma.

22. The method of any one of claims 1-21, wherein the subject has metastatic castration-resistant prostate cancer with a prostate specific antigen (PSA) value of ≥ 4 ng/ml prior to treatment with the dosing regimen.

23. The method of claim 22, wherein the subject's cancer has progressed within a six month period prior to treatment with the dosing regimen, wherein cancer progression is determined by: (a) a rising PSA level confirmed with an interval of ≥ 1 week between each assessment; (b) radiographic disease progression in soft tissue with or without a rise in PSA; and/or (c) radiographic disease progression in bone with an appearance of two or more bone lesions on bone scan with or without a rise in PSA.

24. The method of any one of claims 1-23, wherein the subject has had an orchiectomy.

25. The method of any one of claims 1-23, wherein the subject is receiving luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy, and has a serum testosterone level of < 50 ng/ml prior to treatment with the dosing regimen.

26. The method of any one of claims 1-25, wherein the dosing regimen further comprises administering an additional therapeutic agent, therapy or therapeutic regimen.

27. The method of claim 26, wherein the additional therapeutic agent, therapy or therapeutic regimen comprises surgery, radiation, chemotherapy or anti-androgen therapy.

28. The method of any one of claims 1-27, wherein the subject is administered a steroid or an anti-IL-6R antibody concomitantly with a dose of the bispecific anti-PSMA x anti-CD3 antibody and/or the bispecific anti-PSMA x CD28 antibody.

29. The method of any one of claims 2-28, wherein the target dose of the bispecific anti-PSMA x anti-CD3 antibody is a subtherapeutic dose.

30. The method of any one of claims 1-29, wherein the subsequent week or the first subsequent week is week 3 of the dosing regimen.

31. The method of any one of claims 2-30, wherein the second subsequent week is week 4 of the dosing regimen.

32. The method of any one of claims 1-29, wherein the at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody comprises the one transitional dose administered during week 2 of the dosing regimen and a second transitional dose administered during week 3 of the dosing regimen, wherein the second transitional dose is greater than the one transitional dose, but less than the target dose.

33. The method of claim 32, wherein the subsequent week or the first subsequent week is week 4 of the dosing regimen.

34. The method of any one of claims 2-29, 32 and 33, wherein the second subsequent week is week 5 of the dosing regimen.

35. The method of any one of claims 1-29, wherein the at least one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody comprises the one transitional dose administered during week 2 of the dosing regimen, a second transitional dose administered during week 3 of the dosing regimen, and a third transitional dose administered during week 4 of the dosing regimen, wherein the second transitional dose is greater than the one transitional dose, and the third transitional dose is greater than the second transitional dose, but less than the target dose.

36. The method of claim 35, wherein the subsequent week or the first subsequent week is week 5 of the dosing regimen.

37. The method of any one of claims 2-29, 35 and 36, wherein the second subsequent week is week 6 of the dosing regimen.

38. The method of any one of claims 1-37, wherein the initial dose of the bispecific anti-PSMA x anti-CD3 antibody is 0.01 mg to 100 mg, and the one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody is greater than the initial dose and is 0.03 mg to 300 mg.

39. The method of claim 38, wherein the target dose of the bispecific anti-PSMA x anti-CD3 antibody is 0.03 mg to 900 mg.

40. The method of any one of claims 1-37, wherein the initial dose of the bispecific anti-PSMA x anti-CD3 antibody administered during week 1 of the dosing regimen, and the one transitional dose of the bispecific anti-PSMA x anti-CD3 antibody administered during week 2 of the dosing regimen comprise, respectively:

0.01 mg and 0.03 mg;

0.01 mg and 0.04 mg;

0.01 mg and 0.05 mg;
0.013 mg and 0.07 mg;
0.017 mg and 0.08 mg;
0.02 mg and 0.08 mg;
0.02 mg and 0.11 mg;
0.022 mg and 0.11 mg;
0.029 mg and 0.14 mg;
0.03 mg and 0.15 mg;
0.03 mg and 0.03 mg;
0.03 mg and 0.1 mg;
0.04 mg and 0.13 mg;
0.04 mg and 0.2 mg;
0.045 mg and 0.1 mg;
0.05 mg and 0.15 mg;
0.05 mg and 0.16 mg;
0.05 mg and 0.23 mg;
0.05 mg and 0.25 mg;
0.06 mg and 0.2 mg;
0.06 mg and 0.21 mg;
0.06 mg and 0.3 mg;
0.07 mg and 0.25 mg;
0.07 mg and 0.33 mg;
0.07 mg and 0.34 mg;
0.09 mg and 0.3 mg;
0.09 mg and 0.43 mg;
0.09 mg and 0.45 mg;
0.11 mg and 0.4 mg;
0.12 mg and 0.59 mg;
0.135 mg and 0.45 mg;
0.14 mg and 0.45 mg;
0.14 mg and 0.6 mg;
0.14 mg and 0.9 mg;
0.14 mg and 1 mg;
0.14 mg and 1.1 mg;
0.14 mg and 1.2 mg;

0.14 mg and 1.25 mg;
0.15 mg and 0.5 mg;
0.15 mg and 0.76 mg;
0.18 mg and 0.6 mg;
0.18 mg and 0.8 mg;
0.19 mg and 0.65 mg;
0.2 mg and 0.65 mg;
0.2 mg and 0.9 mg;
0.2 mg and 0.99 mg;
0.24 mg and 0.8 mg;
0.26 mg and 1.3 mg;
0.3 mg and 0.9 mg;
0.3 mg and 1.35 mg;
0.39 mg and 1.8 mg;
0.4 mg and 1.1 mg;
0.45 mg and 1.35 mg;
0.45 mg and 2 mg;
0.5 mg and 1.5 mg;
0.51 mg and 2.3 mg;
0.6 mg and 1.8 mg;
0.6 mg and 2.7 mg;
0.65 mg and 1.9 mg;
0.65 mg and 2 mg;
0.66 mg and 3 mg;
0.68 mg and 3 mg;
0.84 mg and 2.4 mg;
0.86 mg and 3.9 mg;
0.9 mg and 3 mg;
0.9 mg and 4 mg;
1.1 mg and 4 mg;
1.2 mg and 5.2 mg;
1.35 mg and 4.5 mg;
1.4 mg and 6 mg;
1.5 mg and 5 mg;
1.5 mg and 6.8 mg;

1.8 mg and 6 mg;
1.8 mg and 8 mg;
1.9 mg and 6.5 mg;
2 mg and 6.5 mg;
2 mg and 8.8 mg;
2 mg and 9 mg;
2.4 mg and 8.4 mg;
2.6 mg and 11.4 mg;
3 mg and 9 mg;
3 mg and 12 mg;
3.9 mg and 11.7 mg;
3.9 mg and 15.5 mg;
4.5 mg and 13.5 mg;
4.5 mg and 18 mg;
5.1 mg and 15.2 mg;
5.1 mg and 20.3 mg;
6 mg and 18 mg;
6 mg and 24 mg;
6.6 mg and 19.8 mg;
6.6 mg and 26.4 mg;
6.75 mg and 20.25 mg;
6.8 mg and 27 mg;
8.6 mg and 25.7 mg;
8.6 mg and 34.3 mg;
10 mg and 30 mg;
10 mg and 36 mg;
13 mg and 39 mg;
15 mg and 45 mg;
17 mg and 50.7 mg;
20 mg and 60 mg;
22 mg and 66 mg;
22.5 mg and 67.5 mg;
28.6 mg and 85.7 mg;
30 mg and 100 mg;
39 mg and 130 mg;

45 mg and 150 mg;
50.7 mg and 169 mg;
60 mg and 200 mg;
66 mg and 222 mg;
67.5 mg and 225 mg;
85.7 mg and 286 mg; or
100 mg and 300 mg.

41. The method of any one of claims 1-40, wherein the target dose of the bispecific anti-PSMA x anti-CD3 antibody is 0.03 mg, 0.3 mg, 0.39 mg, 0.4 mg, 0.45 mg, 0.5 mg, 0.51 mg, 0.6 mg, 0.66 mg, 0.7 mg, 0.86 mg, 0.9 mg, 1 mg, 1.1 mg, 1.3 mg, 1.35 mg, 1.5 mg, 1.7 mg, 1.8 mg, 1.9 mg, 2 mg, 2.2 mg, 2.3 mg, 2.4 mg, 2.9 mg, 3 mg, 3.9 mg, 4 mg, 4.5 mg, 5 mg, 5.1 mg, 6 mg, 6.5 mg, 6.6 mg, 6.8 mg, 8.4 mg, 8.6 mg, 9 mg, 11 mg, 11.7 mg, 13.5 mg, 15 mg, 15.2 mg, 18 mg, 19 mg, 19.8 mg, 20 mg, 20.3 mg, 24 mg, 25.7 mg, 30 mg, 39 mg, 45 mg, 50.7 mg, 51 mg, 60 mg, 65.9 mg, 66 mg, 67.5 mg, 85.7 mg, 86 mg, 100 mg, 130 mg, 150 mg, 169 mg, 200 mg, 220 mg, 225 mg, 286 mg, 300 mg, 390 mg, 450 mg, 507 mg, 600 mg, 659 mg, 675 mg, 857 mg or 900 mg.

42. The method of any one of claims 2-41, wherein the target dose of the bispecific anti-PSMA x anti-CD3 antibody is 5 mg, 5.1 mg, 6 mg, 6.5 mg, 6.6 mg, 6.8 mg, 8.4 mg, 8.6 mg, 9 mg, 11 mg, 11.7 mg, 13.5 mg, 15 mg, 15.2 mg, 18 mg, 19 mg, 19.8 mg, 20 mg, 20.3 mg, 24 mg, 25.7 mg, 30 mg, 39 mg, 45 mg, 50.7 mg, 51 mg, 60 mg, 65.9 mg, 66 mg, 67.5 mg, 85.7 mg, 86 mg or 100 mg.

43. The method of any one of claims 1-42, wherein the target dose of the bispecific anti-PSMA x anti-CD3 antibody is administered to the subject weekly, or once every three weeks, thereafter in the dosing regimen.

44. The method of any one of claims 2 and 4-43, wherein the anti-PD-1 antibody is administered to the subject at a dose of 300 to 400 mg.

45. The method of claim 44, wherein the anti-PD-1 antibody is administered to the subject at a dose of 350 mg.

46. The method of claim 44 or 45, wherein the anti-PD-1 antibody is administered to the subject once every three weeks thereafter in the dosing regimen.

47. The method of any one of claims 3-43, wherein the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 20 mg to 40 mg, or 50 mg to 150 mg, or 250 mg to 350 mg.

48. The method of claim 47, wherein the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject at a dose of 30 mg, or 100 mg, or 300 mg.

49. The method of claim 47 or 48, wherein the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject weekly, or once every three weeks, thereafter in the dosing regimen.

50. The method of any one of claims 1-49, wherein the bispecific anti-PSMA x anti-CD3 antibody, the anti-PD-1 antibody and/or the bispecific anti-PSMA x anti-CD28 antibody is administered to the subject subcutaneously or intravenously.

51. The method of any one of claims 1-50, wherein the subject has stable disease, a partial response, or a complete response following administration of the dosing regimen.

52. The method of any one of claims 1-51, wherein the subject is subjected to radiographic imaging following administration of one or more doses of the bispecific antibody.

53. The method of claim 52, wherein the radiographic imaging comprises a Fluorine F18 DCFPyL PET/CT scan.

54. The method of claim 52, wherein the radiographic imaging comprises a Gallium Ga PSMA-11 PET/CT scan.

55. The method of any one of claims 1-54, wherein the subject has previously received an androgen deprivation therapy and a taxane chemotherapy, optionally wherein the androgen deprivation therapy comprises abiraterone, enzalutamide, apalutamide, and/or darolutamide, and optionally wherein the taxane chemotherapy comprises docetaxel.

56. The method of any one of claims 1-55, wherein the subject has previously received a radioligand therapeutic agent, optionally wherein the radioligand therapeutic agent is lutetium Lu 177 vipivotide tetraxetan.

57. The method of any one of claims 1-17 and 28-54, wherein the subject has not previously received a therapy for treatment of the PSMA-expressing cancer.