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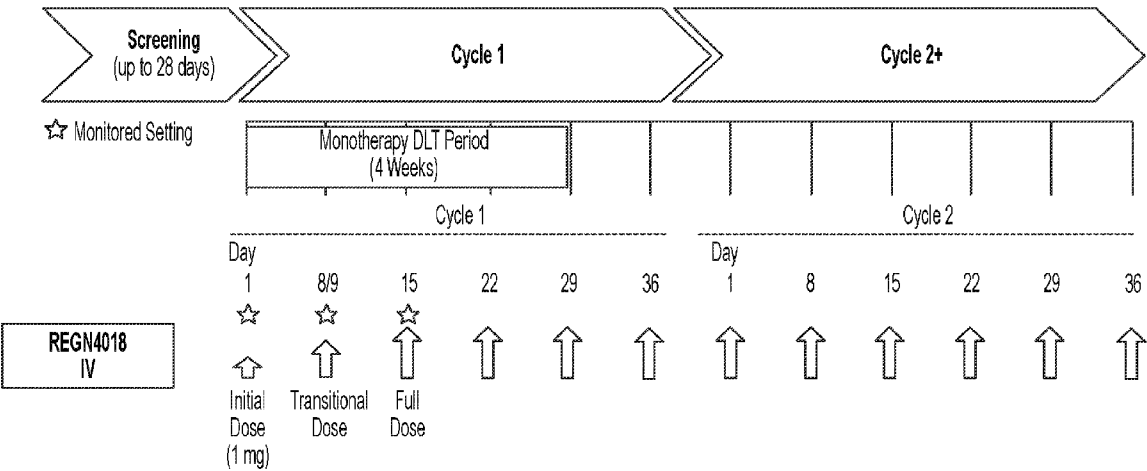


FIG. 1

(57) Abstract: The present disclosure provides methods for treating, reducing the severity, or inhibiting the growth of endometrial cancer. The methods of the present disclosure comprise administering to a subject in need thereof a therapeutically effective amount of a bispecific antibody that specifically binds Mucin 16 (MUC16) and CD3 alone, or in combination with a therapeutically effective amount of an antibody or antigen-binding fragment thereof that specifically binds to programmed death 1 (PD-1) receptor.

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**METHODS OF TREATING ENDOMETRIAL CANCER WITH BISPECIFIC
ANTI-MUC16 x ANTI-CD3 ANTIBODIES ALONE OR IN COMBINATION WITH
ANTI-PD-1 ANTIBODIES**

REFERENCE TO A SEQUENCE LISTING

[0001] This application incorporates by reference a computer readable Sequence Listing in ST.26 XML format, titled 11640WO01_Sequence, created on December 4, 2024, and containing 54,668 bytes.

FIELD OF THE INVENTION

[0002] The present disclosure relates to methods for treating endometrial cancer with a bispecific antibody that binds to mucin 16 (MUC16) and CD3, alone or in combination with an anti-PD-1 antibody.

BACKGROUND

[0003] Mucin 16 (MUC16), also known as cancer antigen 125, carcinoma antigen 125, carbohydrate antigen 125, or CA-125, is a single transmembrane domain highly glycosylated integral membrane glycoprotein that is expressed in many cancer types. MUC16 consists of three major domains: an extracellular N-terminal domain, a large tandem repeat domain interspersed with sea urchin sperm, enterokinase, and agrin (SEA) domains, and a carboxyl terminal domain that comprises a segment of the transmembrane region and a short cytoplasmic tail. Proteolytic cleavage results in shedding of the extracellular portion of MUC16 into the bloodstream. MUC16 is overexpressed in cancers including endometrial cancer, ovarian cancer, breast cancer, pancreatic cancer, non-small-cell lung cancer, intrahepatic cholangiocarcinoma-mass forming type, adenocarcinoma of the uterine cervix, and adenocarcinoma of the gastric tract, and in diseases and conditions including inflammatory bowel disease, liver cirrhosis, cardiac failure, peritoneal infection, and abdominal surgery. (Haridas, D. *et al.*, 2014, *FASEB J.*, 28:4183-4199).

[0004] In a small series of 12 cases of endometrial cancers detailed in the Human Protein Atlas, 75% of cases expressed MUC16 in 25% of cells (The Human Protein Atlas). A similar MUC16 prevalence was observed in a 485-person evaluation of endometrial cancer at time of resection of the uterus (Kakimoto, 2021). Another evaluation showed an estimated 73% of cases having ≥25% of tumor cells that stain positive for MUC16 by immunohistochemistry. Cleaved MUC16 detected as serum CA125 is elevated in 70% of women with Stage 4 endometrial cancer and circulating levels may be high in women with serous histology

endometrial cancer (LyBarger, 2022), (Schmidt, 2018). Expression on cancer cells is shown to protect tumor cells from the immune system. Felder, M. et al., 2014, *Molecular Cancer*, 13:129. Oregovomab and abgovomab are anti-MUC16 antibodies which have had limited success. Felder, *supra*, Das, S. and Batra, S.K. 2015, *Cancer Res.* 75:4660-4674.

[0005] 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.

[0006] Programmed death receptor-1 (PD-1) 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] Endometrial cancer has an annual incidence of 66,000 cases and causes 13,000 deaths per year in the US (SEER, 2022). In the National Cancer Database, 34.1% of Black women and 19.1% of White women present with advanced disease (Kucera, 2023). Until recently, the standard of care for the 1st line therapy for women with advanced endometrial cancer, including cancer that has progressed after surgery and/or radiation, has been carboplatin and paclitaxel. This line of therapy is based on a study that showed non-inferior overall survival with this regimen compared to the more toxic regimen of doxorubicin, cisplatin and paclitaxel (Miller, 2020). There are two FDA approved anti-PD1 antibodies, pembrolizumab (O'Malley, 2022) and dostarlimab (Oaknin, 2022), for second line treatment in patients with dMMR endometrial cancer, which comprises about 25% of endometrial cancer cases (Lorenzi, 2020). The overall response rate with anti-PD-1 in this setting is approximately 45% with

responses being durable in a majority of patients. For patients with pMMR dMMR advanced endometrial cancer, the combination of pembrolizumab and lenvatinib was FDA approved in 2022 based on demonstration of improved PFS compared to chemotherapy in the KEYNOTE - 775 study (Makker, 2022). Recently, results of two randomized phase 3 studies were published that demonstrated in the first-line setting for advanced or recurrent endometrial cancer, anti-PD-1 therapy with pembrolizumab or dostarlimab added to carboplatin and paclitaxel lead to significant improvement in PFS especially in women with dMMR endometrial cancer (Eskander, 2023), (Mirza, 2023). In spite of these successes, there remains a high unmet need, and additional therapies for targeting endometrial cancer are needed.

BRIEF SUMMARY OF THE INVENTION

[0008] In one aspect, the present disclosure includes a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject a bispecific antibody or antigen-binding fragment thereof comprising a first antigen-binding domain that specifically binds mucin 16 (MUC16), and a second antigen-binding domain that specifically binds human CD3. In some embodiments, the bispecific antibody or antigen-binding fragment thereof is administered to the subject at a dose of at least 1 mg (*e.g.*, weekly).

[0009] In some embodiments, the subject has previously been treated with a platinum-based chemotherapy. In some embodiments, the subject has previously been treated with an antibody that binds human programmed death receptor-1 (PD-1). In some embodiments, the subject has previously been treated with a platinum-based chemotherapy, and an antibody that binds human PD-1. In some embodiments, the subject has received at least two prior lines of therapy to treat the endometrial cancer. In some embodiments, the endometrial cancer is advanced or recurrent endometrial cancer. In some embodiments, the endometrial cancer is MUC16-expressing cancer.

[0010] In some embodiments, the present disclosure provides methods, as discussed herein, wherein the bispecific antibody or antigen-binding fragment thereof comprises a first antigen-binding domain comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1; and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.

[0011] In some embodiments, the first antigen-binding domain comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 8, a HCDR2 comprising the amino acid

sequence of SEQ ID NO: 9, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 10. In some embodiments, the first antigen-binding domain comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 11, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 12, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 13. In some embodiments of the methods disclosed herein, the first antigen-binding domain 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: 2.

[0012] In some embodiments, including those in which the first antigen-binding domain is as discussed above, the bispecific antibody or antigen-binding fragment thereof comprises a second antigen-binding domain comprising three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 3; and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2. In some embodiments, the second antigen-binding domain comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 14, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 15, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 16. In some embodiments, the second antigen-binding domain comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 11, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 12, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 13. In some embodiments, the second antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 3, and a LCVR comprising the amino acid sequence of SEQ ID NO: 2.

[0013] In some embodiments of the methods of the present disclosure, the bispecific antibody comprises a human IgG heavy chain constant region. In some embodiments, the human IgG heavy chain constant region is isotype IgG1. In some embodiments, the human IgG heavy chain constant region is isotype IgG4. In some embodiments, the bispecific antibody comprises a chimeric hinge that reduces Fcγ receptor binding relative to a wild-type hinge of the same isotype. In some embodiments, 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.

[0014] In some embodiments of the methods of the present disclosure, the bispecific antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 29. In some embodiments, the bispecific antibody comprises a second heavy chain comprising the amino

acid sequence of SEQ ID NO: 31. In some embodiments, the bispecific antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 29, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 31, and a common light chain comprising the amino acid sequence of SEQ ID NO: 30. In some embodiments, the bispecific antibody is REGN4018 (ubamatamab).

[0015] In one aspect, the present disclosure provides the methods disclosed herein where the subject has a serum CA-125 level equal to or greater than 60 U/ml. In some cases, the subject's serum CA-125 level is greater than 65 U/ml, 70 U/ml, 75 U/ml, 80 U/ml, 85 U/ml, 90 U/ml, or 95 U/ml.

[0016] In some embodiments, the methods further comprise administering a second therapeutic agent or therapeutic regimen. In some embodiments, the second therapeutic agent or therapeutic regimen comprises an anti-PD-1 antibody or antigen-binding fragment thereof. In some embodiments, the anti-PD-1 antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 33; and three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 34.

[0017] In some embodiments, the anti-PD-1 antibody or antigen-binding fragment comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 35, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 37. In some embodiments, the anti-PD-1 antibody or antigen-binding fragment comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 38, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 39, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 40. In some embodiments, the anti-PD-1 antibody or antigen-binding fragment comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 33, and a LCVR comprising the amino acid sequence of SEQ ID NO: 34. In some embodiments, the anti-PD-1 antibody or antigen-binding fragment is an anti-PD-1 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 and a light chain comprising the amino acid sequence of SEQ ID NO: 42. In some embodiments, the anti-PD-1 antibody is cemiplimab,

[0018] In one aspect, the present disclosure provides methods wherein the bispecific antibody (or fragment thereof) is administered in a dosing regimen comprising a split initial dose. In some embodiments, the bispecific antibody (or fragment thereof) is administered to the subject

at a dose of from 10 mg to 1000 mg weekly. In some embodiments, the bispecific antibody (or fragment thereof) is administered to the subject at a dose of about 250 mg weekly, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg. In some embodiments, the bispecific antibody (or fragment thereof) is administered to the subject at a dose of about 800 mg weekly, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 750 mg. In some embodiments, the bispecific antibody (or fragment thereof) is administered to the subject at a dose of from 10 mg to 1000 mg once every three weeks. In some embodiments, the bispecific antibody (or fragment thereof) is administered to the subject at a dose of about 250 mg once every three weeks, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg. In some embodiments, the bispecific antibody (or fragment thereof) is administered to the subject at a dose of about 800 mg once every three weeks, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 750 mg.

[0019] In one aspect, the present disclosure provides methods wherein the bispecific antibody or antigen-binding fragment thereof is administered in a dosing regimen comprising: (i) administering 1 mg of the bispecific antibody (or fragment thereof) in week 1, optionally wherein the dose is split into a first fraction of about 0.5 mg and a second fraction of about 0.5 mg; (ii) administering 20 mg of the bispecific antibody (or fragment thereof) in week 2, optionally wherein the dose is split into a first fraction of about 10 mg and a second fraction of about 10 mg; and (iii) administering 250 mg of the bispecific antibody (or fragment thereof) in week 3, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg. In some embodiments, the methods further comprises administration of the bispecific antibody (or fragment thereof) at a dose of about 250 mg once every week from week 4 onwards. In some embodiments, the methods further comprise administration of the bispecific antibody (or fragment thereof) at a dose of about 250 mg once every three weeks from week 4 onwards. In some embodiments, the methods further comprises administration of the bispecific antibody (or fragment thereof) at a dose of about 800 mg once every three weeks from week 4 onwards.

[0020] In one aspect, the present disclosure provides methods wherein an anti-PD-1 antibody is administered to the subject at a dose of from 300 to 400 mg once every three weeks. In some embodiments, the anti-PD-1 antibody is administered to the subject at a dose of 350 mg once every three weeks.

[0021] In one aspect, the present disclosure provides methods wherein the subject has stable disease, a partial response, or a complete response following administration of the bispecific antibody (or fragment thereof) for at least one week at a dose of 1–800 mg. In some embodiments, the subject has stable disease, a partial response, or a complete response following administration of the bispecific antibody (or fragment thereof) for at least one week at a dose of 20–800 mg.

[0022] In one aspect, the present disclosure provides methods where the bispecific antibody (or fragment thereof) is administered to the subject at a dose sufficient to achieve a serum concentration of at least 4 mg/L.

[0023] In one aspect, the present disclosure provides methods wherein MUC16 is expressed on $\geq 25\%$ of tumor cells in the subject, as determined by immunohistochemical staining. In some embodiments, the subject has a baseline MUC16 immunohistochemical staining score of 2 in a MUC16-expressing tumor; or a baseline MUC16 immunohistochemical staining score of 2+ in a MUC16-expressing tumor; or a baseline MUC16 immunohistochemical staining score of 3 in a MUC16-expressing tumor; or a baseline MUC16 immunohistochemical staining score of 3+ in a MUC16-expressing tumor; or a baseline MUC16 immunohistochemical staining score of 4 in a MUC16-expressing tumor; or a baseline MUC16 immunohistochemical staining score of 4+ in a MUC16-expressing tumor; or a baseline MUC16 immunohistochemical staining score of 5 in a MUC16-expressing tumor; or a tumor with MUC16-expression in $\geq 25\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 30\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 35\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 40\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 45\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 50\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 55\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 60\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 65\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 70\%$ of tumor cells; or a tumor with MUC16-expression in $\geq 75\%$ of tumor cells.

[0024] In one aspect, the present disclosure provides methods wherein MUC16 is expressed on tumor cells in the subject, as determined by immunohistochemical staining. In some embodiments, the subject has: an H-score ≥ 100 ; an H-score ≥ 105 ; an H-score ≥ 110 ; an H-score ≥ 115 ; an H-score ≥ 120 ; an H-score ≥ 125 ; an H-score ≥ 130 ; an H-score ≥ 135 ; an H-score ≥ 140 ; an H-score ≥ 145 ; an H-score ≥ 150 ; an H-score ≥ 155 ; an H-score ≥ 160 ; an H-score ≥ 165 ; an H-score ≥ 170 ; an H-score ≥ 175 ; an H-score ≥ 180 ; an H-score ≥ 185 ; an H-score ≥ 190 ; an H-score ≥ 195 ; or an H-score ≥ 200 , as determined by immunohistochemical staining discussed in Example 6. In some cases, the subject has a serous subtype of endometrial cancer. In some

cases, the subject has a carcinosarcoma subtype of endometrial cancer. In some cases, the subject has a grade 3 endometrial cancer. In some cases, the subject has a mixed serous and endometrioid subtype of endometrial cancer. In some cases, the subject has a mixed serous and clear cell subtype of endometrial cancer. In some cases, the subject has a mixed clear cell and grade 3 endometrial cancer.

[0025] In one aspect, the present disclosure provides methods wherein the bispecific antibody (or fragment thereof) is administered intravenously. In some embodiments, the bispecific antibody (or fragment thereof) is administered subcutaneously. In some embodiments, the anti-PD-1 antibody or antigen-binding fragment is administered intravenously.

BRIEF DESCRIPTION OF THE FIGURES

[0026] **Figure 1** shows a schema of a monotherapy study design with intravenous dosing of REGN4018.

[0027] **Figure 2** shows a schema of a combination therapy study design with intravenous dosing of REGN4018 and cemiplimab.

[0028] **Figure 3** shows a schema of a monotherapy study design with subcutaneous initial and transitional dosing of REGN4018, followed by second transitional IV dosing and subsequent full IV dosing of REGN4018. Where CRS is not observed in initial patients, the second transitional IV dosing may be omitted for additional patients.

[0029] **Figure 4** shows the variability of MUC16 expression by histology, with H-scores across pathology diagnosis categories, as determined in Example 6.

DETAILED DESCRIPTION

[0030] Before the present disclosure is described, it is to be understood that this disclosure 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 disclosure 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 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.

[0031] 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 disclosure

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.).

[0032] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, 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.

Methods for Treating or Inhibiting the Growth of Cancers

[0033] 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 cancer (*e.g.*, endometrial cancer) in a subject. The methods according to this aspect of the disclosure comprise administering a therapeutically effective amount of a bispecific antibody or antigen-binding fragment thereof against MUC16 and CD3 as monotherapy, or in combination with a therapeutically effective amount of an antibody or antigen-binding fragment thereof that specifically binds PD-1 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.

[0034] 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 an endometrial 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, chest pain/pressure, unexplained weight loss, fever, night sweats, persistent fatigue, loss of appetite, enlargement of spleen, itching. The expression includes subjects with primary or established endometrial tumors. In specific embodiments, the expression includes human subjects that have and need treatment for endometrial cancer or another tumor expressing MUC16, for example, endometrial cancer. In other specific embodiments, the expression includes subjects with MUC16+ tumors (*e.g.*, a tumor with MUC16

expression as determined by flow cytometry or immunohistochemistry). In certain embodiments, the expression includes human subjects with a tumor that shows high expression of MUC16 in >50%, >55%, >60%, >65%, >70% or >75% of tumor cells. The expression of MUC16 may be determined and evaluated by any method known in the art (see *e.g.*, Shimizu et al 2012, Cancer Sci. 103: 739-746). In certain embodiments, the expression includes human subjects with a baseline MUC16 immunohistochemical staining score of 2+ (*e.g.*, 2, 3, 4 or 5) in a MUC16-expressing tumor. In certain embodiments, the expression includes human subjects with a baseline MUC16 immunohistochemical staining score of 2, 2+, 3, 3+, 4, 4+, or 5 in a MUC16-expressing tumor. Immunohistochemical staining scores, in this context, incorporate the percentage of cells, and the intensity and pattern of the staining according to the following standards: score 1 (<5% strong or weak); score 2 (5-50% strong or weak); score 3 (51-75% strong or 51-100% weak); score 4 (76-99% strong); and score 5 (100% strong staining). In certain embodiments, the expression "a subject in need thereof" includes patients with an endometrial cancer that is resistant to or refractory to or is inadequately controlled by prior therapy (*e.g.*, treatment with an anti-cancer agent). For example, the expression includes subjects who have been treated with chemotherapy, such as a platinum-based chemotherapeutic agent (*e.g.*, cisplatin) or a taxol compound (*e.g.*, docetaxel). The expression also includes subjects with an endometrial 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 with toxic side effects. In certain embodiments, the expression "a subject in need thereof" includes patients with an endometrial tumor which has been treated but which has subsequently relapsed or metastasized. For example, patients with an endometrial 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.*, chemotherapy-resistant cancer) are treated with the methods of the present disclosure.

[0035] The expression "a subject in need thereof" also includes subjects who are at risk of developing endometrial cancer, *e.g.*, persons with a family history of endometrial cancer, persons with a past history of infections associated with endometrial cancer, persons with mutations in the BRCA1/2 genes, or persons with an immune system compromised due to HIV infection or due to immunosuppressive medications.

[0036] In certain embodiments, the methods of the present disclosure may be used to treat patients that show elevated levels of one or more cancer-associated biomarkers (*e.g.*, programmed death ligand 1 (PD-L1), MUC16, CA125, human epididymis protein 4 (HE4),

and/or carcinoembryonic antigen (CEA)). For example, the methods of the present disclosure comprise administering a therapeutically effective amount of an anti-PD-1 antibody or antigen-binding fragment thereof in combination with a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a patient with an elevated level of MUC16 and/or CA125. Methods to determine MUC16 and/or CA125 expression are well-known in the art. In certain embodiments, the expression of MUC16 in tumor tissue is determined by an immunohistochemistry (IHC) assay (see *e.g.*, Bast et al 1981, J. Clin. Invest. 68: 1331-1337). MUC16 expression may be evaluated by any method known in the art (*e.g.*, Shimizu et al 2012, Cancer Sci. 103: 739-746). In certain embodiments, the expression of MUC16 is determined by imaging with a labeled anti-MUC16 antibody, for example, by immuno-positron emission tomography or iPET (described elsewhere herein).

[0037] In certain embodiments, the methods of the present disclosure are used in a subject with an endometrial cancer. The terms "tumor", "cancer" and "malignancy" are interchangeably used herein. The term "endometrial cancer", as used herein, refers to tumors of the uterus and includes adenocarcinoma (*e.g.*, endometrioid), uterine carcinosarcoma, squamous cell carcinoma, small cell carcinoma, transitional carcinoma, and serous carcinoma. Endometrioid cancers include adenocarcinoma, adenoacanthoma, adenosquamous, secretory carcinoma, ciliated carcinoma, and villoglandular adenocarcinoma. Advanced or recurrent endometrial cancer refers to those tumors, respectively, that cannot be treated with surgery or radiation alone, or that have recurred following prior therapy.

[0038] 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 therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof as monotherapy, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof 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-MUC16 x CD3 antibody or antigen-binding fragment thereof 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 one or more doses of anti-PD-1 antibody or antigen-binding fragment thereof are administered in combination with one or more doses of a therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof, wherein the one or more doses of the anti-PD-1 antibody or antigen-binding fragment thereof 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.

[0039] In certain embodiments, each dose of the anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof is administered in more than 1 fractions, *e.g.*, in 2-5 fractions ("split dosing") within the given dosing period. The anti-MUC16/anti-CD3 bispecific antibody or antigen-binding fragment thereof may be administered in split doses to reduce or eliminate the cytokine "spikes" induced in response to administration of the antibody. Cytokine spikes refer to the clinical symptoms of the cytokine release syndrome ("cytokine storm") and infusion related reactions. In certain embodiments, the methods of the present disclosure comprise administering one or more doses of anti-PD-1 antibody or antigen-binding fragment thereof in combination with one or more doses of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a subject in need thereof, wherein a dose of the bispecific antibody or antigen-binding fragment thereof is administered as split doses, or in more than 1 fractions, *e.g.*, as 2 fractions, as 3 fractions, as 4 fractions or as 5 fractions within the given dosing period. In certain embodiments, a dose of the bispecific antibody or antigen-binding fragment thereof is split into 2 or more fractions, wherein each fraction comprises an amount of the antibody or antigen-binding fragment thereof equal to the other fractions. For example, a dose of anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof comprising 1000 micrograms may be administered once a week, wherein the dose is administered in 2 fractions within the week, each fraction comprising 500 micrograms. In certain embodiments, a dose of the bispecific antibody or antigen-binding fragment thereof 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. For example, a dose of anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof comprising 1000 micrograms may be administered once a week, wherein the dose is administered in 2 fractions within the week, wherein the first fraction comprises 700 micrograms and the second fraction comprises 300 micrograms. As another

example, a dose of anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof comprising 1000 micrograms may be administered once in 2 weeks, wherein the dose is administered in 3 fractions within the 2-week period, wherein the first fraction comprises 400 micrograms, the second fraction comprises 300 micrograms and the third fraction comprises 300 micrograms.

[0040] In certain embodiments, the present disclosure provides a method of treating a MUC16-expressing cancer (*e.g.*, endometrial cancer, including cancers refractory to multiple rounds of prior therapy as discussed herein) in a subject in need thereof, comprising administering to the subject a bispecific antibody comprising a first antigen-binding domain that specifically binds mucin 16 (MUC16), and a second antigen-binding domain that specifically binds human CD3, wherein the bispecific antibody is administered in a dosing regimen comprising: (i) administering 1 mg of the bispecific antibody in week 1, optionally wherein the dose is split into a first fraction of about 0.5 mg and a second fraction of about 0.5 mg; (ii) administering 20 mg of the bispecific antibody in week 2, optionally wherein the dose is split into a first fraction of about 10 mg and a second fraction of about 10 mg; and (iii) administering 250 mg of the bispecific antibody in week 3, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg. In some cases, the method further comprises administering the bispecific antibody at a dose of about 250 mg once every week from week 4 onwards. In some cases, the method further comprises administering the bispecific antibody at a dose of about 250 mg once every three weeks from week 4 onwards. In some cases, the method further comprises administering the bispecific antibody at a dose of about 800 mg once every three weeks from week 4 onwards. In some cases, the method further comprises administering an anti-PD-1 antibody to the subject at a dose of from 300 to 400 mg (*e.g.*, 350 mg) once every three weeks.

[0041] 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 therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof to a subject in need thereof.

[0042] 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 an endometrial cancer a therapeutically effective amount of an anti-PD-1 antibody or antigen-binding fragment thereof prior to administering a therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or

antigen-binding fragment thereof, wherein the anti-PD-1 antibody or antigen-binding fragment thereof 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, more than 7 days, or more than 8 days prior to the bispecific antibody or antigen-binding fragment thereof. 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 with the bispecific antibody or antigen-binding fragment thereof prior to the anti-PD-1 antibody or antigen-binding fragment thereof.

[0043] In certain embodiments, the methods of the present disclosure comprise administering a therapeutically effective amount of a bispecific anti-CD3xMUC16 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof to a subject with an endometrial cancer. In specific embodiments, the endometrial cancer is serous cancer. In further embodiments, the endometrial cancer is indolent or aggressive. In certain embodiments, the subject is not responsive to prior therapy or has relapsed after prior therapy (*e.g.*, platinum-based therapy). In some embodiments, the subject has a CA-125 level that is equal to or greater than 2 times the upper limit of normal (ULN) (*e.g.*, equal to or greater than about 60 U/ml). In various embodiments, the subject's serum CA-125 level (prior to treatment) is at or greater than 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650 or 700 U/ml. In certain embodiments, the methods of the present disclosure further comprise administering an additional therapeutic agent to the subject.

[0044] In certain embodiments, the methods of the present disclosure comprise administering a therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a subject with a MUC16+ cancer. In specific embodiments, the cancer is an endometrial cancer. In further embodiments, the endometrial cancer is indolent or aggressive. In some embodiments, the cancer is a platinum-resistant endometrial cancer. In some embodiments, the cancer is a taxol-resistant endometrial cancer. In some embodiments, the cancer is fallopian tube cancer. In some embodiments, the cancer is primary peritoneal cancer, optionally in which the patient has elevated levels of serum CA-125 (*e.g.*, at least 2x ULN). In certain embodiments, the subject is not responsive to prior therapy or has relapsed after prior therapy (*e.g.*, chemotherapy).

[0045] In certain embodiments, the methods of the present disclosure comprise administering an anti-PD-1 antibody or antigen-binding fragment thereof in combination with a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a subject in need thereof as a

"first line" treatment (*e.g.*, initial treatment). In other embodiments, an anti-PD-1 antibody or antigen-binding fragment thereof in combination with a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof is administered as a "second line" treatment (*e.g.*, after prior therapy). For example, an anti-PD-1 antibody or antigen-binding fragment thereof in combination with a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof is administered as a "second line" treatment to a subject that has relapsed after prior therapy with, *e.g.*, chemotherapy (*e.g.*, platinum-based chemotherapy).

[0046] 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-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof to a subject in need thereof.

[0047] The methods of the present disclosure, according to certain embodiments, comprise administering to a subject a therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof and, optionally, a third therapeutic agent. The third therapeutic agent may be an agent selected from the group consisting of, *e.g.*, radiation, chemotherapy, surgery, a cancer vaccine, 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 (*e.g.*, CA9, CA125, melanoma-associated antigen 3 (MAGE3), carcinoembryonic antigen (CEA), vimentin, tumor-M2-PK, prostate-specific antigen (PSA), mucin-1, MART-1, and CA19-9), a vaccine (*e.g.*, Bacillus Calmette-Guerin), granulocyte-macrophage colony-stimulating factor, a cytotoxin, a chemotherapeutic agent, an IL-6R inhibitor (sarilumab), 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 (*e.g.*, paclitaxel, carboplatin, doxorubicin, cyclophosphamide, cisplatin, gemcitabine or docetaxel), radiation and surgery. As used herein, the phrase "in combination with" means that the antibodies are administered to the subject at the same time as, just before, or just after administration of the third therapeutic agent. In certain embodiments, the third therapeutic agent is administered as a co-formulation with the antibodies.

[0048] In certain embodiments, the methods of the present disclosure comprise administering to a subject in need thereof a therapeutically effective amount of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof. Where the combination is administered, the administration of the antibodies (or fragments) 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 (or fragment) as monotherapy. In certain embodiments, the administration of an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof leads to increased tumor regression, tumor shrinkage and/or disappearance. In certain embodiments, the administration of an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof 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 (or fragment) as monotherapy. In certain embodiments, administration of an anti-PD-1 antibody or antigen-binding fragment thereof in combination with a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof 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 than an untreated subject or a subject which is administered either antibody (or fragment) as monotherapy. In certain embodiments, administration of the antibodies in combination increases progression-free survival or overall survival. In certain embodiments, administration of an anti-PD-1 antibody or antigen-binding fragment thereof in combination with a bispecific anti-MUC16/anti-CD3 antibody

or antigen-binding fragment thereof 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 (or fragment) as monotherapy. In certain embodiments, administration of an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a subject with an endometrial cancer leads to complete disappearance of all evidence of tumor cells ("complete response"). In certain embodiments, administration of an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a subject with an endometrial cancer leads to at least 30% or more decrease in tumor cells or tumor size ("partial response"). In certain embodiments, administration of an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof to a subject with an endometrial 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 an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof produces a synergistic anti-tumor effect that exceeds the combined effects of the two agents when administered alone.

[0049] In certain embodiments, the combination of administered antibodies (or fragments) is safe and well-tolerated by a patient wherein there is no increase in an adverse side effect (e.g., increased cytokine release ("cytokine storm") or increased T-cell activation) as compared to a patient administered with the bispecific antibody (or fragment) as monotherapy.

[0050] 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.

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

[0051] According to certain exemplary embodiments of the present disclosure, the methods comprise administering a therapeutically effective amount of an anti-PD-1 antibody or antigen-binding fragment thereof. The term "anti-PD-1 antibody or antigen-binding fragment thereof" refers to and is used interchangeably with the term "antibody or antigen-binding fragment thereof that specifically binds to PD-1." 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, the FRs of the anti-IL-4R 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.

[0052] 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.

[0053] 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.

[0054] 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.

[0055] 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)).

[0056] The term "antibody," as used herein, also includes multispecific (e.g., bispecific) antibodies. A multispecific antibody or antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format may be adapted for use in the context of an antibody or antigen-binding fragment of an antibody of the present disclosure using routine techniques available in the art. For example, the present disclosure includes methods comprising the use of bispecific antibodies wherein one arm of an immunoglobulin is specific for PD-1 or a fragment thereof, and the other arm of the immunoglobulin is specific for a second therapeutic target or is conjugated to a therapeutic moiety. 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 Mab.sup.2 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). Bispecific antibodies can also be constructed using peptide/nucleic acid conjugation, e.g., wherein unnatural amino acids with orthogonal chemical reactivity are used to generate site-specific antibody-oligonucleotide conjugates which then self-assemble into multimeric complexes with defined composition, valency and geometry. (See, e.g., Kazane et al., J. Am. Chem. Soc. [Epub: Dec. 4, 2012]).

[0057] The antibodies used in the methods of the present disclosure 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.

[0058] The antibodies used in the methods of the present disclosure 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 (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), 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.

[0059] 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.

[0060] According to certain exemplary embodiments of the present disclosure, the anti-PD-1 antibody, or antigen-binding fragment thereof comprises a heavy chain variable region (HCVR), light chain variable region (LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the anti-PD-1 antibodies as set forth in US Patent No. 9,987,500. In certain exemplary embodiments, 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: 33 and the light chain complementarity determining regions (LCDRs) of a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 34. 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: 35; the HCDR2 comprises the amino acid sequence of SEQ ID NO: 36; the HCDR3 comprises the amino acid sequence of SEQ ID NO: 37; the LCDR1 comprises the amino acid sequence of SEQ ID NO: 38; the LCDR2 comprises the amino acid sequence of SEQ ID NO: 39; and the LCDR3 comprises the amino acid sequence of SEQ ID NO: 40. In yet other embodiments, the anti-PD-1 antibody or antigen-binding fragment thereof comprises an HCVR comprising SEQ ID NO: 33 and an LCVR comprising SEQ ID NO: 34. 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: 41. In some embodiments, the anti-PD-1 antibody comprises a light chain comprising the amino acid sequence of SEQ ID NO: 42. An exemplary antibody comprising a HCVR comprising the amino acid sequence of SEQ ID NO: 33 and a LCVR comprising the amino acid sequence of SEQ ID NO: 34 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.

[0061] Other anti-PD-1 antibodies that can be used in the context of the methods of the present disclosure include, *e.g.*, the antibodies referred to and known in the art as nivolumab (U.S. Pat. No. 8,008,449), pembrolizumab (U.S. Pat. No. 8,354,509), MEDI0608 (U.S. Pat. No. 8,609,089), pidilizumab (U.S. Pat. No. 8,686,119), or any of the anti-PD-1 antibodies as set forth in U.S. Pat. Nos. 6,808,710, 7,488,802, 8,168,757, 8,354,509, 8,779,105, or 8,900,587.

[0062] The anti-PD-1 antibodies used in the context of the methods of the present disclosure may have pH-dependent binding characteristics. For example, an anti-PD-1 antibody for use in

the methods of the present disclosure may exhibit reduced binding to PD-1 at acidic pH as compared to neutral pH. Alternatively, an anti-PD-1 antibody of the disclosure may exhibit enhanced binding to its antigen at acidic pH as compared to neutral pH. The expression "acidic pH" includes pH values less than about 6.2, e.g., about 6.0, 5.95, 5.9, 5.85, 5.8, 5.75, 5.7, 5.65, 5.6, 5.55, 5.5, 5.45, 5.4, 5.35, 5.3, 5.25, 5.2, 5.15, 5.1, 5.05, 5.0, or less. As used herein, the expression "neutral pH" means a pH of about 7.0 to about 7.4. The expression "neutral pH" includes pH values of about 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, and 7.4.

[0063] In certain instances, "reduced binding to PD-1 at acidic pH as compared to neutral pH" is expressed in terms of a ratio of the K_D value of the antibody binding to PD-1 at acidic pH to the K_D value of the antibody binding to PD-1 at neutral pH (or vice versa). For example, an antibody or antigen-binding fragment thereof may be regarded as exhibiting "reduced binding to PD-1 at acidic pH as compared to neutral pH" for purposes of the present disclosure if the antibody or antigen-binding fragment thereof exhibits an acidic/neutral K_D ratio of about 3.0 or greater. In certain exemplary embodiments, the acidic/neutral K_D ratio for an antibody or antigen-binding fragment of the present disclosure can be about 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 20.0, 25.0, 30.0, 40.0, 50.0, 60.0, 70.0, 100.0, or greater.

[0064] Antibodies with pH-dependent binding characteristics may be obtained, e.g., by screening a population of antibodies for reduced (or enhanced) binding to a particular antigen at acidic pH as compared to neutral pH. Additionally, modifications of the antigen-binding domain at the amino acid level may yield antibodies with pH-dependent characteristics. For example, by substituting one or more amino acids of an antigen-binding domain (e.g., within a CDR) with a histidine residue, an antibody with reduced antigen-binding at acidic pH relative to neutral pH may be obtained. As used herein, the expression "acidic pH" means a pH of 6.0 or less.

Bispecific Anti-MUC16/Anti-CD3 Antibodies and Antigen-Binding Fragments Thereof

[0065] According to certain exemplary embodiments of the present disclosure, the methods comprise administering a therapeutically effective amount of a bispecific antibody or antigen-binding fragment thereof that specifically binds CD3 and MUC16. Such antibodies and fragments may be referred to herein as, e.g., "anti-MUC16/anti-CD3," or "anti-MUC16xCD3" or "MUC16xCD3" bispecific antibodies or antigen-binding fragments thereof, or other similar terminology.

[0066] 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.*, MUC16), and the second antigen-binding domain specifically binds a second, distinct antigen (*e.g.*, CD3). Each antigen-binding domain of a bispecific antibody comprises a heavy chain variable domain (HCVR) and a light chain variable domain (LCVR), each comprising three 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.

[0067] 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.

[0068] 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.

[0069] Any bispecific antibody format or technology may be used to make the bispecific antigen-binding molecules 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 antigen-binding molecule. 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).

[0070] 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 antigen-binding molecules 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 antigen-binding molecule 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.

[0071] The present disclosure also includes bispecific antigen-binding molecules 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 bi-specific 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.

[0072] In certain embodiments, the Fc domain may be chimeric, combining Fc sequences derived from more than one immunoglobulin isotype. For example, a chimeric Fc domain 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 Fc domain 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 Fc domain that can be included in any of the antigen-binding molecules 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 Fc domain that can be included in any of the antigen-binding molecules 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 Fc domains that can be included in any of the antigen-binding molecules of the present disclosure are described in US Patent Publication No. 20140243504, which is herein incorporated in its entirety. Chimeric Fc domains having these general structural arrangements, and variants thereof, can have altered Fc receptor binding, which in turn affects Fc effector function.

[0073] According to certain exemplary embodiments of the present disclosure, the bispecific anti-MUC16/anti-CD3 antibody, or antigen-binding fragment thereof comprises heavy chain variable regions (A-HCVR and B-HCVR), light chain variable regions (A-LCVR and B-LCVR), and/or complementarity determining regions (CDRs) comprising any of the amino acid sequences of the bispecific anti-MUC16/anti-CD3 antibodies as set forth in US Patent Publication No. 20180112001. In certain exemplary embodiments, the bispecific anti-MUC16/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 comprising 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: 2; and (b) a second antigen-binding arm comprising 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: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 or SEQ ID NO: 7, 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: 2. According to certain embodiments, the A-HCDR1 comprises the amino acid sequence of SEQ ID NO: 8; the A-HCDR2 comprises the amino acid sequence of SEQ ID NO: 9; the A-HCDR3 comprises the amino acid sequence of SEQ ID NO: 10; the A-LCDR1 comprises the amino acid sequence of SEQ ID NO: 11; the A-LCDR2 comprises the amino acid sequence of SEQ ID NO: 12; the A-LCDR3 comprises the amino acid sequence of SEQ ID NO: 13; the B-HCDR1 comprises the amino acid sequence of SEQ ID NO: 14, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 23, or SEQ ID NO: 26; the B-HCDR2 comprises the amino acid sequence of SEQ ID NO: 15, SEQ ID NO: 18, SEQ ID NO: 21, SEQ ID NO: 24, or SEQ ID NO: 27; and the B-HCDR3 comprises the amino acid sequence of SEQ ID NO: 16, SEQ ID NO: 19, SEQ ID NO: 22, SEQ ID NO: 25, or SEQ ID NO: 28; and the B-LCDR1 comprises the amino

acid sequence of SEQ ID NO: 11; the B-LCDR2 comprises the amino acid sequence of SEQ ID NO: 12; the B-LCDR3 comprises the amino acid sequence of SEQ ID NO: 13. In yet other embodiments, the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof comprises: (a) a first antigen-binding arm comprising a HCVR (A-HCVR) comprising SEQ ID NO: 1 and a LCVR (A-LCVR) comprising SEQ ID NO: 2; and (b) a second antigen-binding arm comprising a HCVR (B-HCVR) comprising SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, and a LCVR (B-LCVR) comprising SEQ ID NO: 2. In certain exemplary embodiments, the bispecific anti-CD3xMUC16 antibody comprises a MUC16-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, and a CD3-binding arm comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 31 and a light chain comprising the amino acid sequence of SEQ ID NO: 30. In certain exemplary embodiments, the bispecific anti-CD3xMUC16 antibody comprises a MUC16-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, and a CD3-binding arm comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 32 and a light chain comprising the amino acid sequence of SEQ ID NO: 30. An exemplary bispecific anti-MUC16/anti-CD3 antibody that may be used in the methods of the present disclosure and comprises A-HCVR of SEQ ID NO: 1, B-HCVR of SEQ ID NO: 3 and LCVR of SEQ ID NO: 2 is REGN4018 (ubamatamab).

[0074] Other bispecific anti-MUC16/anti-CD3 antibodies that can be used in the context of the methods of the present disclosure include, *e.g.*, any of the antibodies as set forth in US Patent Publication No. 20180112001.

Combination Therapies

[0075] The methods of the present disclosure, according to certain embodiments, comprise administering to the subject an anti-MUC16/anti-CD3 bispecific antibody or antigen-binding fragment thereof in combination with an anti-PD-1 antibody or antigen-binding fragment thereof. In certain embodiments, the methods of the present disclosure comprise administering the antibodies (or fragments) for additive or synergistic activity to treat cancer, for example, an endometrial cancer. As used herein, the expression "in combination with" means that the anti-MUC16/anti-CD3 bispecific antibody or antigen-binding fragment thereof is administered before, after, or concurrent with the anti-PD-1 antibody or antigen-binding fragment thereof. The term "in combination with" also includes sequential or concomitant administration of anti-PD-1

antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof. For example, when administered "before" the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof, the anti-PD-1 antibody or antigen-binding fragment thereof 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 bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof. When administered "after" the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof, the anti-PD-1 antibody or antigen-binding fragment thereof may be administered about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours, about 72 hours, or more than 72 hours after the administration of the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof. Administration "concurrent" with the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof means that the anti-PD-1 antibody or antigen-binding fragment thereof is administered to the subject in a separate dosage form within less than 5 minutes (before, after, or at the same time) of administration of the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof, or administered to the subject as a single combined dosage formulation comprising both the anti-PD-1 antibody or antigen-binding fragment thereof and the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof.

[0076] In certain embodiments, the methods of the present disclosure comprise administration of a third therapeutic agent wherein the third therapeutic agent is an anti-cancer drug. In certain embodiments, the methods of the present disclosure comprise administration of an additional therapy wherein the additional therapy is surgery. In certain embodiments, the methods of the disclosure comprise administering an anti-PD-1 antibody or antigen-binding fragment thereof and an anti-MUC16/anti-CD3 bispecific antibody or antigen-binding fragment thereof in combination with radiation therapy to generate long-term durable anti-tumor responses and/or enhance survival of patients with cancer.

[0077] In some embodiments, the methods of the disclosure comprise administering radiation therapy prior to, concomitantly or after administering an anti-PD-1 antibody or antigen-binding fragment thereof and a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof 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 antibodies (or fragments). 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 an anti-PD-1 antibody or antigen-binding fragment thereof and/or a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof.

[0078] 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 administration of the bispecific antibody.

Pharmaceutical Compositions and Administration

[0079] The present disclosure includes methods which comprise administering a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof to a subject wherein the antibody or antibodies (or fragments) 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. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell *et al.* "Compendium of excipients for parenteral formulations" PDA (1998) *J Pharm Sci Technol* 52:238-311.

[0080] Various delivery systems are known and can be used to administer the pharmaceutical composition 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, by absorption through epithelial or mucocutaneous linings (*e.g.*, oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents.

[0081] 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.

[0082] 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.

[0083] 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.

[0084] 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 such as an alcohol (*e.g.*, ethanol), a polyalcohol (*e.g.*, propylene glycol, polyethylene glycol), a nonionic surfactant [*e.g.*, polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, *e.g.*, sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0085] Advantageously, the pharmaceutical compositions for oral or parenteral 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, tablets, pills, capsules, injections (ampoules), suppositories, etc.

Administration Regimens and Dosage

[0086] According to certain embodiments of the present disclosure, multiple doses of an antigen-binding molecule (*e.g.*, a bispecific antibody or antigen-binding fragment thereof that specifically binds MUC16 and CD3, or an anti-PD-1 antibody or antigen-binding fragment thereof) 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 multiple doses of an antigen-binding molecule of the disclosure. As used herein, "sequentially administering" means that each dose of an antigen-binding molecule 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 antigen-binding molecule, followed by one

or more secondary doses of the antigen-binding molecule, and optionally followed by one or more tertiary doses of the antigen-binding molecule.

[0087] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the antigen-binding molecule (*e.g.*, a bispecific anti-MUC16 x CD3 antibody or anti-PD-1 antibody) of the disclosure. 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 doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of the antigen-binding molecule, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of an antigen-binding molecule 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, two or more (*e.g.*, 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"). In any of the embodiments, the initial dose (*e.g.*, first weekly dose) may be split into two doses administered on separate days (*e.g.*, consecutive days) no more than three days apart. In any of the embodiments, the first nominal dose (*i.e.*, the secondary dose) may be split into two doses administered on separate days (*e.g.*, consecutive days) no more than three days apart. For example, if the initial dose or the secondary dose is 6 mg, the dose may be split into two 3 mg doses administered on, *e.g.*, consecutive days, or on separate days no more than three days apart. In various embodiments, the dose (*e.g.*, the dose administered weekly, as a single dose or as two split fractions of the dose) is, or is at least, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg, 10 mg, 11 mg, 12 mg, 13 mg, 14 mg, 15 mg, 16 mg, 17 mg, 18 mg, 19 mg, 20 mg, 21 mg, 22 mg, 23 mg, 24 mg, 25 mg, 26 mg, 27 mg, 28 mg, 29 mg, 30 mg, 31 mg, 32 mg, 33 mg, 34 mg, 35 mg, 36 mg, 37 mg, 38 mg, 39 mg, 40 mg, 41 mg, 42 mg, 43 mg, 44 mg, 45 mg, 46 mg, 47 mg, 48 mg, 49 mg, 50 mg, 51 mg, 52 mg, 53 mg, 54 mg, 55 mg, 56 mg, 57 mg, 58 mg, 59 mg, 60 mg, 61 mg, 62 mg, 63 mg, 64 mg, 65 mg, 66 mg, 67 mg, 68 mg, 69 mg, 70 mg, 71 mg, 72 mg, 73 mg, 74 mg, 75 mg, 76 mg, 77 mg, 78 mg, 79 mg, 80 mg, 81 mg, 82 mg, 83 mg, 84 mg, 85 mg, 86 mg, 87 mg, 88 mg, 89 mg, 90 mg, 91 mg, 92 mg, 93 mg, 94 mg, 95 mg, 96 mg, 97 mg, 98 mg, 99 mg, 100 mg, 105 mg, 110 mg, 115 mg, 120 mg, 125 mg, 130 mg, 135 mg, 140 mg, 145 mg, 150 mg, 155 mg, 160 mg, 165 mg, 170 mg, 175 mg, 180 mg, 185 mg, 190 mg, 195 mg, 200 mg, 205 mg, 210 mg, 215 mg, 220 mg, 225 mg, 230 mg, 235 mg, 240 mg, 245 mg, 250 mg, 255 mg, 260 mg, 265 mg, 270 mg, 275 mg, 280 mg, 285

mg, 290 mg, 295 mg, 300 mg, 305 mg, 310 mg, 315 mg, 320 mg, 325 mg, 330 mg, 335 mg, 340 mg, 345 mg, 350 mg, 355 mg, 360 mg, 365 mg, 370 mg, 375 mg, 380 mg, 385 mg, 390 mg, 395 mg, 400 mg, 405 mg, 410 mg, 415 mg, 420 mg, 425 mg, 430 mg, 435 mg, 440 mg, 445 mg, 450 mg, 455 mg, 460 mg, 465 mg, 470 mg, 475 mg, 480 mg, 485 mg, 490 mg, 495 mg, 500 mg, 510 mg, 520 mg, 530 mg, 540 mg, 550 mg, 560 mg, 570 mg, 580 mg, 590 mg, 600 mg, 610 mg, 620 mg, 630 mg, 640 mg, 650 mg, 660 mg, 670 mg, 680 mg, 690 mg, 700 mg, 710 mg, 720 mg, 730 mg, 740 mg, 750 mg, 760 mg, 770 mg, 780 mg, 790 mg, 800 mg, 810 mg, 820 mg, 830 mg, 840 mg, 850 mg, 860 mg, 870 mg, 880 mg, 890 mg, 900 mg, 910 mg, 920 mg, 930 mg, 940 mg, 950 mg, 960 mg, 970 mg, 980 mg, 990 mg, 1000 mg, 1.5 g, 2 g, 2.5 g, 3 g, 3.5 g, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g, 10 g, or more. Any of these amounts may be used to define a range for the initial, secondary or tertiary doses discussed herein and are encompassed within the scope of this disclosure. In some embodiments, all doses are given as single doses (e.g., single infusions), including the doses administered in weeks one and two of a dosing regimen. For example, an initial dose of from 1 mg to 5 mg may be administered as a single dose in week one, a secondary dose of from 3 mg to 400 mg may be administered as a single dose in week two, and a tertiary dose of from 50 mg to 800 mg may be administered as a single dose in week three, and thereafter during a weekly dosing portion of a dosing regimen. In another example, an initial dose of 5 mg may be administered as a single dose in week one, a secondary dose of 25 mg may be administered as a single dose in week two, and a tertiary dose of from 50 mg to 800 mg may be administered as a single dose in week three, and thereafter during a weekly dosing portion of a dosing regimen. In some cases, the dosing schedule may thereafter (e.g., following 12 to 16 weeks) include administration every two weeks, every three weeks, once per month, or the like.

[0088] In one exemplary embodiment of the present disclosure, each secondary and/or tertiary dose is administered 1 to 26 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) 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 antigen-binding molecule which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0089] The dose of antibody (or fragment thereof) administered to a patient may vary depending upon the age and the size of the patient, conditions, route of administration, and the like. The preferred dose is typically calculated according to body weight or body surface area.

When an antibody (or fragment thereof) of the present disclosure is used for treating endometrial cancer in an adult patient, methods of treating can include intravenously administering the antibody of the present disclosure at a single dose of about 0.01 to about 100 mg/kg body weight, or more. In some cases, the dose is about 0.01 mg/kg, 0.05 mg/kg, 0.1 mg/kg, 0.5 mg/kg, 1 mg/kg, 2 mg/kg, 3 mg/kg, 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 20 mg/kg, 30 mg/kg, 40 mg/kg, 50 mg/kg, 60 mg/kg, 70 mg/kg, 80 mg/kg, 90 mg/kg, 100 mg/kg, or more. Depending on the severity of the endometrial cancer, the concentration of the dose, the frequency and/or the duration of the treatment can be adjusted. Treatment methods can include 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more doses of a presently disclosed antibody administered weekly, biweekly, or triweekly over 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 11 weeks, 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, 21 weeks, 22 weeks, 23 weeks, 24 weeks, 26 weeks, 27 weeks, 28 weeks, 29 weeks, 30 weeks, 31 weeks, 32 weeks, 33 weeks, 34 weeks, 35 weeks, 36 weeks, 37 weeks, 38 weeks, 39 weeks, 40 weeks, 41 weeks, 42 weeks, 43 weeks, 44 weeks, 45 weeks, 46 weeks, 47 weeks, 48 weeks, 49 weeks, 50 weeks, 51 weeks, 52 weeks, 13 months, 14 months, 15 months, 16 months, 17 months, 18 months, 19 months, 20 months, 21 months, 22 months, 23 months, 24 months, 25 months, 26 months, 27 months, 28 months, 29 months, 30 months, 31 months, 32 months, 33 months, 34 months, 35 months, 36 months, 37 months, 38 months, 39 months, 40 months, 41 months, 42 months, 43 months, 44 months, 45 months, 46 months, 47 months, 48 months, 49 months, 50 months, 51 months, 52 months, 53 months, 54 months, 55 months, 56 months, 57 months, 58 months, 59 months, 60 months, or over a longer duration of time. Scheduling for dosing can be modified, *e.g.*, from weekly to biweekly, vice versa, or otherwise, as needed. Effective dosages and schedules for administering antibodies may be determined empirically; for example, patient progress can be monitored by periodic assessment, and the dose adjusted accordingly. Moreover, interspecies scaling of dosages can be performed using well-known methods in the art (*e.g.*, Mordenti *et al.*, *Pharmaceut Res* 8:1351 (1991)).

[0090] 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 antigen-binding molecule (*e.g.*, a bispecific anti-MUC16 x CD3 antibody, or an anti-PD-1 antibody). For example, in certain embodiments, only a single secondary 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 are administered to the patient. Likewise, in certain embodiments, only a single tertiary 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.

[0091] 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 to 2 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 2 to 4 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.

[0092] The present disclosure includes methods comprising administering to a subject a bispecific anti-MUC16 x CD3 antibody or antigen-binding fragment thereof and/or an anti-PD-1 antibody or antigen-binding fragment thereof 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 nine weeks, once every ten weeks, once every eleven weeks, once every twelve weeks, or less frequently so long as a therapeutic response is achieved.

[0093] According to certain embodiments of the present disclosure, multiple doses of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with an anti-PD-1 antibody or antigen-binding fragment thereof 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-MUC16/anti-CD3 antibody or antigen-binding fragment thereof alone, or in combination with one or more doses of an anti-PD-1 antibody or antigen-binding fragment thereof. As used herein, "sequentially administering" means that each dose of the antibody or antigen-binding fragment thereof 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 or antigen-binding fragment thereof, followed by one or more secondary doses of the antibody or antigen-binding fragment thereof, and optionally followed by one or more tertiary doses of the antibody or antigen-binding fragment thereof.

[0094] The amount of bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment

thereof, and optionally anti-PD-1 antibody or antigen-binding fragment thereof, administered to a subject according to the methods of the present disclosure is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means an amount of antibody or antigen-binding fragment thereof (anti-PD-1 antibody or bispecific anti-MUC16/anti-CD3 antibody) that results in one or more of: (a) a reduction in the severity or duration of a symptom of a cancer (*e.g.*, endometrial 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) inhibit or retard or stop tumor metastasis; (e) prevention of recurrence of tumor growth; (f) increase in survival of a subject with cancer (*e.g.*, endometrial cancer); and/or (g) a reduction in the use or need for conventional anti-cancer therapy (*e.g.*, reduced or eliminated use of chemotherapeutic or cytotoxic agents) as compared to an untreated subject or a subject administered with either antibody (or fragment) as monotherapy.

[0095] In the case of a bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof, a therapeutically effective amount can be from about 0.1 milligrams (mg) to about 1000 mg, *e.g.*, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.5 mg, about 1 mg, about 3 mg, about 5 mg, about 10 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 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 225 mg, about 250 mg, about 275 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-MUC16/anti-CD3 antibody or antigen-binding fragment thereof. In some cases, the dose is about 1 mg. In some cases, the dose is about 2 mg. In some cases, the dose is about 20 mg. In some cases, the dose is about 25 mg. In some cases, the dose is about 250 mg. In some cases, the dose is about 800 mg. Any of these doses may be the initial dose, the intermediate or transitional dose, or the full dose.

[0096] In some cases, the bispecific anti-MUC16/anti-CD3 antibody is administered to the subject at a dose of at least 1 mg weekly or every two weeks, at least 1.5 mg weekly or every two weeks, at least 2.0 mg weekly or every two weeks, at least 2.5 mg weekly or every two weeks, at least 3.0 mg weekly or every two weeks, at least 3.5 mg weekly or every two weeks, at least 4 mg weekly or every two weeks, at least 5 mg weekly or every two weeks, at least 6 mg weekly or every two weeks, at least 7 mg weekly or every two weeks, at least 8 mg weekly or every two weeks, at least 9 mg weekly or every two weeks, at least 10 mg weekly or every

two weeks, at least 15 mg weekly or every two weeks, at least 20 mg weekly or every two weeks, at least 25 mg weekly or every two weeks, at least 30 mg weekly or every two weeks, at least 35 mg weekly or every two weeks, at least 40 mg weekly or every two weeks, at least 45 mg weekly or every two weeks, at least 50 mg weekly or every two weeks, at least 55 mg weekly or every two weeks, at least 60 mg weekly or every two weeks, at least 65 mg weekly or every two weeks, at least 70 mg weekly or every two weeks, at least 75 mg weekly or every two weeks, at least 80 mg weekly or every two weeks, at least 85 mg weekly or every two weeks, at least 90 mg weekly or every two weeks, at least 95 mg weekly or every two weeks, at least 100 mg weekly or every two weeks, at least 150 mg weekly or every two weeks, at least 200 mg weekly or every two weeks, at least 250 mg weekly or every two weeks, at least 300 mg weekly or every two weeks, at least 350 mg weekly or every two weeks, at least 400 mg weekly or every two weeks, at least 450 mg weekly or every two weeks, at least 500 mg weekly or every two weeks, at least 550 mg weekly or every two weeks, at least 600 mg weekly or every two weeks, at least 650 mg weekly or every two weeks, at least 700 mg weekly or every two weeks, at least 750 mg weekly or every two weeks, at least 800 mg weekly or every two weeks, at least 850 mg weekly or every two weeks, or at least 900 mg weekly or every two weeks.

[0097] In the case of an anti-PD-1 antibody or antigen-binding fragment thereof, a therapeutically effective amount can be 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 or antigen-binding fragment thereof. In certain embodiments, 350 mg of an anti-PD-1 antibody or antigen-binding fragment thereof is administered.

[0098] In some cases, the anti-PD-1 antibody is administered to the subject at a dose of at least 1 mg weekly or every two weeks, at least 1.5 mg weekly or every two weeks, at least 2.0 mg weekly or every two weeks, at least 2.5 mg weekly or every two weeks, at least 3.0 mg weekly or every two weeks, at least 3.5 mg weekly or every two weeks, at least 4 mg weekly or

every two weeks, at least 5 mg weekly or every two weeks, at least 6 mg weekly or every two weeks, at least 7 mg weekly or every two weeks, at least 8 mg weekly or every two weeks, at least 9 mg weekly or every two weeks, at least 10 mg weekly or every two weeks, at least 15 mg weekly or every two weeks, at least 20 mg weekly or every two weeks, at least 25 mg weekly or every two weeks, at least 30 mg weekly or every two weeks, at least 35 mg weekly or every two weeks, at least 40 mg weekly or every two weeks, at least 45 mg weekly or every two weeks, at least 50 mg weekly or every two weeks, at least 55 mg weekly or every two weeks, at least 60 mg weekly or every two weeks, at least 65 mg weekly or every two weeks, at least 70 mg weekly or every two weeks, at least 75 mg weekly or every two weeks, at least 80 mg weekly or every two weeks, at least 85 mg weekly or every two weeks, at least 90 mg weekly or every two weeks, at least 95 mg weekly or every two weeks, at least 100 mg weekly or every two weeks, at least 150 mg weekly or every two weeks, at least 200 mg weekly or every two weeks, at least 250 mg weekly or every two weeks, at least 300 mg weekly or every two weeks, at least 350 mg weekly or every two weeks, at least 400 mg weekly or every two weeks, at least 450 mg weekly or every two weeks, at least 500 mg weekly or every two weeks, at least 550 mg weekly or every two weeks, at least 600 mg weekly or every two weeks, at least 650 mg weekly or every two weeks, at least 700 mg weekly or every two weeks, at least 750 mg weekly or every two weeks, at least 800 mg weekly or every two weeks, at least 850 mg weekly or every two weeks, or at least 900 mg weekly or every two weeks.

[0099] In any of the various embodiments of the dosing regimen, the initial dose of the bispecific anti-MUC16/anti-CD3 antibody and/or the anti-PD-1 antibody is from 1 mg to 5 mg. In any of the various embodiments of the dosing regimen, the secondary dose is from 3 mg to 400 mg. In any of the various embodiments of the dosing regimen, the tertiary dose is from 3 mg to 800 mg. In some embodiments, the initial dose is 5 mg, the secondary dose is 25 mg, and the tertiary dose is from 50 mg to 800 mg. In some cases, the dosing regimen includes administration of the tertiary dose weekly for at least 12 weeks (e.g., 12 weeks, 13 weeks, 14 weeks, 15 weeks, 16 weeks, 17 weeks, 18 weeks, 19 weeks, 20 weeks, or more) during a weekly dosing period of the dosing regimen. In some cases, the dosing regimen further includes administration of the tertiary dose once every two weeks during a biweekly dosing period of the dosing regimen that follows the weekly period of the dosing regimen. In some cases, the dosing regimen further includes administration of the tertiary dose one every three weeks, or once every four weeks. In various embodiments, the dose may be at least 1 mg weekly or every two weeks, at least 1.5 mg weekly or every two weeks, at least 2.0 mg weekly or every two weeks, at least 2.5 mg weekly or every two weeks, at least 3.0 mg weekly or every two weeks, at least

3.5 mg weekly or every two weeks, at least 4 mg weekly or every two weeks, at least 5 mg weekly or every two weeks, at least 6 mg weekly or every two weeks, at least 7 mg weekly or every two weeks, at least 8 mg weekly or every two weeks, at least 9 mg weekly or every two weeks, at least 10 mg weekly or every two weeks, at least 15 mg weekly or every two weeks, at least 20 mg weekly or every two weeks, at least 25 mg weekly or every two weeks, at least 30 mg weekly or every two weeks, at least 35 mg weekly or every two weeks, at least 40 mg weekly or every two weeks, at least 45 mg weekly or every two weeks, at least 50 mg weekly or every two weeks, at least 55 mg weekly or every two weeks, at least 60 mg weekly or every two weeks, at least 65 mg weekly or every two weeks, at least 70 mg weekly or every two weeks, at least 75 mg weekly or every two weeks, at least 80 mg weekly or every two weeks, at least 85 mg weekly or every two weeks, at least 90 mg weekly or every two weeks, at least 95 mg weekly or every two weeks, at least 100 mg weekly or every two weeks, at least 150 mg weekly or every two weeks, at least 200 mg weekly or every two weeks, at least 250 mg weekly or every two weeks, at least 300 mg weekly or every two weeks, at least 350 mg weekly or every two weeks, at least 400 mg weekly or every two weeks, at least 450 mg weekly or every two weeks, at least 500 mg weekly or every two weeks, at least 550 mg weekly or every two weeks, at least 600 mg weekly or every two weeks, at least 650 mg weekly or every two weeks, at least 700 mg weekly or every two weeks, at least 750 mg weekly or every two weeks, at least 800 mg weekly or every two weeks, at least 850 mg weekly or every two weeks, or at least 900 mg weekly or every two weeks.

[0100] The amount of bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof and optionally anti-PD-1 antibody or antigen-binding fragment thereof contained within the individual doses may be expressed in terms of milligrams of antibody or antigen-binding fragment thereof per kilogram of subject body weight (*i.e.*, mg/kg). In certain embodiments, the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof, and optionally the anti-PD-1 antibody or antigen-binding fragment thereof, used in the methods of the present disclosure may be administered to a subject at a dose of about 0.0001 to about 100 mg/kg of subject body weight. For example, the bispecific anti-MUC16/anti-CD3 antibody or antigen-binding fragment thereof may be administered at a dose of about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, to about 20 mg/kg of a patient's body

weight, and the optional anti-PD-1 antibody or antigen-binding fragment thereof may be administered at dose of about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1 mg/kg, about 2 mg/kg, about 3 mg/kg, about 4 mg/kg, about 5 mg/kg, about 6 mg/kg, about 7 mg/kg, about 8 mg/kg, about 9 mg/kg, about 10 mg/kg, about 11 mg/kg, about 12 mg/kg, about 13 mg/kg, about 14 mg/kg, about 15 mg/kg, about 16 mg/kg, about 17 mg/kg, about 18 mg/kg, about 19 mg/kg, to about 20 mg/kg of a patient's body weight.

[0101] A summary of the sequences and the corresponding SEQ ID NOs referenced herein is shown in Table 1, below.

Table 1: Summary of Sequences

SEQ ID NO:	Description
1	Anti-MUC16 Heavy Chain Variable Region
2	Anti-MUC16 and Anti-CD3 Light Chain Variable Region
3	Anti-CD3-G Heavy Chain Variable Region
4	Anti-CD3-G5 Heavy Chain Variable Region
5	Anti-CD3-G9 Heavy Chain Variable Region
6	Anti-CD3-G10 Heavy Chain Variable Region
7	Anti-CD3-G20 Heavy Chain Variable Region
8	Anti-MUC16 HCDR1
9	Anti-MUC16 HCDR2
10	Anti-MUC16 HCDR3
11	Anti-MUC16 and Anti-CD3 LCDR1
12	Anti-MUC16 and Anti-CD3 LCDR2
13	Anti-MUC16 and Anti-CD3 LCDR3
14	Anti-CD3-G HCDR1
15	Anti-CD3-G HCDR2
16	Anti-CD3-G HCDR3
17	Anti-CD3-G5 HCDR1
18	Anti-CD3-G5 HCDR2
19	Anti-CD3-G5 HCDR3
20	Anti-CD3-G9 HCDR1
21	Anti-CD3-G9 HCDR2

22	Anti-CD3-G9 HCDR3
23	Anti-CD3-G10 HCDR1
24	Anti-CD3-G10 HCDR2
25	Anti-CD3-G10 HCDR3
26	Anti-CD3-G20 HCDR1
27	Anti-CD3-G20 HCDR2
28	Anti-CD3-G20 HCDR3
29	Anti-MUC16 Heavy Chain
30	Anti-MUC16 and Anti-CD3 Light Chain
31	Anti-CD3-G Heavy Chain
32	Anti-CD3-G20 Heavy Chain
33	Anti-PD-1 Heavy Chain Variable Region
34	Anti-PD-1 Light Chain Variable Region
35	Anti-PD-1 HCDR1
36	Anti-PD-1 HCDR2
37	Anti-PD-1 HCDR3
38	Anti-PD-1 LCDR1
39	Anti-PD-1 LCDR2
40	Anti-PD-1 LCDR3
41	Anti-PD-1 Heavy Chain
42	Anti-PD-1 Light Chain

EXAMPLES

[0102] 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 disclosure, and are not intended to limit the scope of what the inventors regard as their disclosure. 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.

Example 1: Generation of Bispecific Antibodies that Bind MUC16 and CD3

[0103] The present disclosure provides methods of use comprising bispecific antigen-binding molecules that bind CD3 and MUC16; such bispecific antigen-binding molecules are also referred to herein as “anti-MUC16/anti-CD3 or anti-MUC16xCD3 bispecific molecules.” The anti-MUC16 portion of the anti-MUC16/anti-CD3 bispecific molecule is useful for targeting tumor cells that express MUC16 (also known as CA-125), and the anti-CD3 portion of the bispecific molecule is useful for activating T-cells. In certain preferred embodiments, the bispecific antigen-binding molecules are bispecific antibodies. The simultaneous binding of MUC16 on a tumor cell and CD3 on a T-cell facilitates directed killing (cell lysis) of the targeted tumor cell by the activated T-cell.

[0104] Bispecific antibodies comprising an anti-MUC16-specific binding domain and an anti-CD3-specific binding domain were constructed using standard methodologies, wherein the anti-MUC16 antigen binding domain and the anti-CD3 antigen binding domain each comprise different, distinct HCVRs paired with a common LCVR. In exemplified bispecific antibodies, the molecules were constructed utilizing a heavy chain from an anti-CD3 antibody, a heavy chain from an anti-MUC16 antibody and a common light chain from the anti-MUC16 antibody. In other instances, the bispecific antibodies may be constructed utilizing a heavy chain from an anti-CD3 antibody, a heavy chain from an anti-MUC16 antibody and a light chain from an anti-CD3 antibody or an antibody light chain known to be promiscuous or pair effectively with a variety of heavy chain arms.

[0105] Exemplified bispecific antibodies were manufactured having an IgG1 Fc domain (BSMUC16/CD3-001, -002, -003, and -004) or a modified (chimeric) IgG4 Fc domain (BSMUC16/CD3-005) as set forth in US Patent Application Publication No. US20140243504A1, published on August 28, 2014. An exemplary bispecific antibody comprising the VRs and CDRs of BSMUC16/CD3-001 is REGN4018 (ubamatamab). REGN4018 comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 29, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 31, and a common light chain comprising the amino acid sequence of SEQ ID NO: 30.

[0106] A summary of the component parts of the antigen-binding domains of the various anti-MUC16xCD3 bispecific antibodies constructed is set forth in Table 2.

Table 2: Summary of Component Parts of Anti-MUC16xCD3 Bispecific Antibodies

Bispecific Antibody Identifier	Anti-MUC16	Anti-CD3	Common Light Chain Variable Region
	Antigen-Binding Domain	Antigen-Binding Domain	

	Heavy Chain Variable Region	Heavy Chain Variable Region	
BSMUC16/CD3-001	(SEQ ID NO:1)	CD3-VH-G (SEQ ID NO:3)	(SEQ ID NO:2)
BSMUC16/CD3-002	(SEQ ID NO:1)	CD3-VH-G5 (SEQ ID NO:4)	(SEQ ID NO:2)
BSMUC16/CD3-003	(SEQ ID NO:1)	CD3-VH-G9 (SEQ ID NO:5)	(SEQ ID NO:2)
BSMUC16/CD3-004	(SEQ ID NO:1)	CD3-VH-G10 (SEQ ID NO:6)	(SEQ ID NO:2)
BSMUC16/CD3-005	(SEQ ID NO:1)	CD3-VH-G20 (SEQ ID NO:7)	(SEQ ID NO:2)

Example 2: Immuno-PET Imaging in Engineered Mice Showed Localization of the Anti-MUC16xCD3 Bispecific Antibody to T Cell-Rich Organs

[0107] The *in vivo* localization of BSMUC16/CD3-001 and BSMUC16/CD3-005 and the expression of MUC16 protein were assessed in wild type and genetically humanized mice using PET imaging. The biodistribution of the ⁸⁹Zr-labelled anti-MUC16 antibody (bivalent anti-MUC16 antibody generated using the same anti-MUC16 heavy and light chain as the bispecifics, herein referred to as “parental”) was similar in both wild type and humanized mice, suggesting low expression/availability of the humanized MUC16 protein to the antibody. In contrast, when mice were administered therapeutically relevant doses of a ⁸⁹Zr-labelled BSMUC16/CD3-001 bispecific antibody, distribution to the spleen and lymph nodes was evident due to recognition of CD3 positive T cells in these lymphoid organs (data not shown). *Ex vivo* biodistribution analyses in individual tissues confirmed localization to lymph nodes and spleen (data not shown). Uptake of ⁸⁹Zr-labelled BSMUC16/CD3-005 bispecific antibody in lymphoid tissues was greatly reduced relative to BSMUC16/CD3-001 due to its lower affinity for CD3. To assess whether BSMUC16/CD3-001 and BSMUC16/CD3-005 can accumulate in MUC16-expressing tumors, ⁸⁹Zr-labelled BSMUC16/CD3-001 and ⁸⁹Zr-labelled BSMUC16/CD3-005 were administered to mice bearing ID8-VEGF-huMUC16Δ tumors. Tumor uptake between the bispecific antibodies was not significantly different despite the higher lymphoid uptake of BSMUC16/CD3-001 (data not shown).

[0108] Preparation of immunoconjugate and small animal PET: BSMUC16/CD3-001 and control antibody were conjugated with DFO to glutamine residues at position 295 via transamidation by microbial transglutaminase following deglycosylation of the antibodies with PNGase F. DFO conjugated antibodies were then chelated with Zirconium-89 (^{89}Zr). Mice received antibody at a final dose of 0.5 mg/kg via tail vein injection. PET imaging was then performed to assess *in vivo* localization of the radioimmunoconjugate at day 6 post dosing, prior to *ex vivo* biodistribution studies. For experiments in tumor-bearing mice, mice were implanted subcutaneously with 10×10^6 ID8-VEGF-huMUC16 Δ tumor cells. Tumor bearing mice were dosed with ^{89}Zr radiolabeled antibodies 20 day post implantation when tumors averaged 150mm³.

[0109] A pre-calibrated Sofie Biosciences G8 PET/CT instrument (Sofie Biosciences (Culver city, CA) and Perkin Elmer) was used to acquire PET and CT images. The energy window ranged from 150 to 650 keV with a reconstructed resolution of 1.4 mm at the center of the field of view. On day 6 post dosing, mice underwent induction anesthesia using isoflurane and were kept under continuous flow of isoflurane during a 10-minute static PET acquisition. CT images were acquired following PET acquisition. The PET image was subsequently reconstructed using pre-configured settings. Decay-corrected PET data and CT data were processed using VivoQuant software (inviCRO Imaging Services) into false-colored co-registered PET-CT maximum intensity projections on a color scale calibrated to indicate a signal range of 0 to 30% of injected dose per volume, expressed as %ID/g. For *ex vivo* biodistribution analysis, mice were euthanized following imaging on day 6 post dosing. Blood was collected via cardiac puncture into counting tubes. Normal tissues (inguinal and axillary lymph nodes, thymus, spleen, heart, lungs, stomach, small intestine, liver, kidneys, bone and ovary) were then excised and placed into counting tubes. Tumors were similarly collected into counting tubes. All tubes had been pre-weighed and were subsequently re-weighed to determine the weight of the blood and tissues. The γ -emission radioactivity for all samples were then counted on an automatic gamma counter (Wizard 2470, Perkin Elmer) and results reported in in counts per minute (cpm). The %ID for each sample was the determined using samples counts relative to dose-standards counts prepared from the original injected material. Subsequently, the individual %ID/g values were derived by dividing the %ID value by the respective weight of the appropriate blood, tissues or tumor sample.

[0110] ^{89}Zr -labeled BSMUC16/CD3-001 and ^{89}Zr -labeled BSMUC16/CD3-005 demonstrated specific localization to MUC16+ tumors and CD3+ lymphoid tissues, with lymphoid distribution

correlating to relative CD3 affinity. Both MUC16xCD3 bispecifics demonstrated equivalent tumor localization in the presence of CD3+ tissues.

Example 3: Toxicology Studies in Cynomolgus Monkeys Showed No Overt Toxicity for the Anti-MUC16xCD3 Bispecific Antibody

[0111] BSMUC16/CD3-001 cross-reacts with monkey MUC16 and CD3. To determine the safety and tolerability, and characterize the pharmacokinetics of the bispecific antibody, a multidose toxicity study was conducted in cynomolgus monkeys. Six monkeys/sex/group received weekly administration of BSMUC16/CD3-001 for a total of five doses at 0.01, 0.1 or 1 mg/kg. At the completion of the dosing period, 3 animals/sex/group were euthanized and tissues examined for microscopic finding, while the remaining three animals/sex/group underwent 12 weeks of treatment-free recovery to assess the reversibility or persistence of any BSMUC16/CD3-001-related effects. BSMUC16/CD3-001 was well tolerated, and all animals survived to the time of scheduled necropsy. Toxicokinetic analysis demonstrated dose-proportional exposures and linear kinetics across the dose groups, with no gender differences observed (data not shown). Continuous exposure to BSMUC16/CD3-001 was observed throughout the dosing phase, and BSMUC16/CD3-001 exposure was maintained until the end of the recovery phase in all (n=6) and 50% of animals in the 0.1 and 1.0 mg/kg groups, respectively. BSMUC16/CD3-001 was not detected in the serum in any animal in the 0.01mg/kg group after recovery week 8. The elimination half-life of BSMUC16/CD3-001 was approximately 10 days.

[0112] There were no BSMUC16/CD3-001-related clinical observations, nor any changes in urinalysis parameters, peripheral blood immunophenotyping, food consumption, or body weight during the dosing or recovery periods. Importantly, BSMUC16/CD3-001 administration did not result in any changes in respiratory, neurologic, or cardiovascular safety pharmacology evaluations, including no changes in ECG parameters. No BSMUC16/CD3-001-related changes in organ weight were found, nor were any macroscopic changes noted at either terminal or recovery necropsy. Dose-related, reversible elevations of circulating inflammatory markers (C-reactive protein (CRP) and IL-6) were observed within 1 day after the initial dose of either 1.0 or 0.1 mg/kg, but these elevations were not apparent after subsequent doses (data not shown). In accordance with the minimal increase of serum cytokines, T cell redistribution was not detected after BSMUC16/CD3-001 administration (data not shown), in contrast to what has been described for several CD3 bispecific molecules against hematological tumors.

[0113] The cynomolgus monkey study was conducted in accordance to guidelines of the IACUC. Cynomolgus monkeys (6 animals/sex/group) were administered control article (diluted placebo) or BSMUC16/CD3-001 (0.01, 0.1, or 1mg/kg) once weekly via a 30-minute IV infusion. The control article was 10mM histidine with 10% sucrose and 0.05% polysorbate 20, pH 6, diluted with 0.9% sodium chloride for injection, USP (sterile saline). Blood samples or tissues were collected at various time points for clinical pathology and histopathology. BSMUC16/CD3-001 concentration was determined by ELISA and toxicokinetic analysis was performed using WinNonLin software. CRP was analyzed on a Roche Modular P 800 system. Cytokines were measured by MSD (Meso Scale Diagnostics, Rockville, MD). T cells were quantitated using flow cytometry. Briefly, blood was collected in potassium EDTA tubes, lysed, stained for CD3, CD4 and CD8 (BD Biosciences) and relative values for each phenotype are determined using a FACS Canto II. These values are then multiplied by the absolute lymphocyte values (via hematology analysis) to enumerate absolute cell counts for each phenotype.

[0114] Immunohistochemical staining for MUC16 was present in expected tissues: pancreas (mesothelium, ductal epithelium), heart and ovary (data not shown) as well as salivary gland (goblet cells), liver (mesothelium, bile duct), lung (mesothelium, bronchiolar/bronchial epithelium), small intestine (mesothelium), testis (mesothelium, rete testis/efferent duct) and tonsil (epithelium, mucous glands) (not shown). BSMUC16/CD3-001-related microscopic changes, evaluated by hematoxylin and eosin (H&E) histologic staining, included inflammation (infiltration of white blood cells) and increased mesothelial cell size and cellularity leading to non-adverse thickening of the serosal lining and/or submesothelial connective tissue of multiple thoracic and peritoneal organs. These changes were generally focal or multi-focal in nature and were minimal to slight in severity and were considered to be on-target for BSMUC16/CD3-001, resulting from engagement of MUC16 expressed on serosal epithelial (mesothelial) cells and activation of T cells. Importantly, the serosal changes were reversed or trended towards reversal at the end of the recovery period (data not shown).

[0115] Toxicology studies in cynomolgus monkeys showed minimal and transient increases in serum cytokines and C-reactive protein following BSMUC16/CD3-001 administration, with no overt toxicity.

Example 4: MUC16 Expression in Humanized Mice and Effect of Anti-MUC16xCD3 Bispecific Antibodies on MUC16-Positive Tissues

[0116] To investigate the antitumor efficacy of BSMUC16/CD3-001 in a mouse with a fully intact immune system, mice were genetically engineered to express human CD3 on T cells and

a region of MUC16 covering the antibody binding region, both in the endogenous murine loci (knock-in mice). To validate these mice, MUC16 expression was examined by both RT-PCR and IHC. RNA expression was detected in the trachea as well as low levels in the lung, heart, ovary, pancreas and bladder (data not shown), similar to published data on murine MUC16 expression. To assess MUC16 protein expression, IHC was performed on selected tissues using an anti-human MUC16 antibody that recognizes a membrane-proximal region of MUC16. MUC16 protein expression was confirmed in the surface epithelium of the ovary and stomach in these mice. MUC16 was also observed in the tracheal lining/epithelium as well as the submucosal glands, as has been described in humans (data not shown).

[0117] Histology on mouse tissues: Tissues from humanized or WT mice were harvested and stained with an anti-MUC16 antibody binding the membrane proximal domain of MUC16 by IHC using the Ventana Discovery XT (Ventana; Tucson, AZ). 5µm Paraffin sections were cut onto Superfrost PLUS slides and baked for an hour at 60°C. The immunohistochemical staining was performed on the Discovery XT Automated IHC staining system using the Ventana DAB Map detection kit. Deparaffinization was performed using EZ Prep solution at 75°C for 8 minutes. Mild antigen retrieval was performed (95°C, 8 minutes followed by 100°C, 24 minutes) using Tris-EDTA buffer pH 9 (CC1) from Ventana. This was followed by multiple blocking steps. Tissue sections were incubated with the anti-MUC16 antibody (2µg/ml) for 8 hours at RT. An isotype control antibody recognizing an irrelevant non-binding antibody was used as the negative control. Primary antibody and negative control were applied manually. Biotinylated Goat Anti-Human IgG (Jackson ImmunoResearch) was used as the secondary antibody (1µg/ml) and samples were incubated for an hour at RT. The chromogenic signal was developed using the Ventana DAB MAP Kit. Slides were manually counterstained with Hematoxylin (2 minutes), dehydrated and coverslipped. Images were acquired on the Aperio AT 2 slide scanner (Leica Biosystems; Buffalo Grove, IL) and analyzed using Indica HALO software (Indica Labs; Corrales, NM). H&E staining were performed by Histoserv, Inc (Germantown, MD, USA).

[0118] The T cells in these mice are polyclonal, as assessed by T cell receptor (TCR) VB usage, express human CD3, and are present in similar numbers to wildtype mice (data not shown). To determine whether BSMUC16/CD3-001 induced any T cell activation or effects on normal tissues in these animals, non-tumor-bearing mice were injected with a high dose of BSMUC16/CD3-001 (10 mg/kg) and T cell numbers in blood, serum cytokines, and histopathology were then examined. Although T cells can be activated by an anti-human CD3 antibody (OKT3) as measured by T cell margination from the blood and increased levels of

serum cytokines (data not shown), BSMUC16/CD3-001 did not induce any such effects, suggesting limited accessibility of the MUC16 target (data not shown). To determine whether BSMUC16/CD3-001 induced any microscopic changes in MUC16-expressing tissues, MUC16 and CD3 humanized mice received two doses of BSMUC16/CD3-001 at 10 mg/kg on Day 0 and Day 3. On day 5, several MUC16-expressing tissues (trachea, stomach and ovary) were examined, and no cellular infiltration or necrosis was seen in these tissues following BSMUC16/CD3-001 administration (data not shown).

Histopathology examination revealed no inflammation or infiltration into MUC16-expressing tissues in mice after BSMUC16/CD3-001 administration at the time examined.

[0119] The results of this study, as well as the cynomolgus monkey study discussed in Example 5, demonstrate the safety profile of BSMUC16/CD3-001. BSMUC16/CD3-001 induced only minimal serum cytokines and, while there was focal induction of inflammation and thickening of the serosal lining in MUC16-expressing suggesting on-target activity, these effects were resolving by the end of the recovery period and consistent with inflammation and increased cellularity indicative of repair. The observed serosal changes were not correlated with any clinical observations, clinical pathology (except inflammatory response), or microscopic changes to the underlying parenchyma. Thus, studies in both genetically humanized mice and cynomolgus monkey show BSMUC16/CD3-001 was well-tolerated.

Example 5: Methods of Treating Endometrial Cancer with Anti-MUC16 x Anti-CD3 Bispecific Antibodies Alone or in Combination with Anti-PD-1 Antibody

[0120] A phase 1/2 study is being conducted to investigate the safety, pharmacokinetics (PK), and preliminary anti-tumor activity of REGN4018 (anti-MUC16 x anti-CD3 bispecific antibody; ubamatamab) alone or in combination with cemiplimab (anti-PD-1 antibody) in patients with advanced endometrial cancer after prior anti-PD1 and prior platinum-based therapy who have been selected based on demonstration of tumor MUC16 expression.

[0121] Patients with recurrent advanced endometrial cancer after 1-2 prior lines of therapy, including prior anti-PD-1 and prior platinum-based chemotherapy, will be included. The patients will include those with tumors that are likely to express MUC16. Only patients with elevated ($\geq 2 \times$ ULN) serum CA-125 levels will be included, as this serum CA-125 level is likely to reflect the presence of MUC16 on the tumor cells.

[0122] Objectives

[0123] The primary objective is to assess the preliminary efficacy of ubamatamab as a monotherapy, or in combination with cemiplimab, for treatment of endometrial cancer. In the

dose escalation phase, the primary objective is to assess the safety and pharmacokinetics (PK) in order to determine a maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of REGN4018 as monotherapy and in combination with cemiplimab. In the dose expansion phase, the primary objective is to assess the preliminary efficacy of REGN4018 as determined by the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

[0124] The secondary objectives include (1) in the dose escalation phase, to assess the preliminary efficacy of REGN4018 as monotherapy and in combination with cemiplimab as determined by RECIST 1.1; (2) in the dose expansion phase, to characterize the safety profile in each expansion cohort, to characterize the PK of REGN4018 as monotherapy and in combination with cemiplimab, and to assess the effect of REGN4018 as monotherapy and in combination with cemiplimab on patient-reported outcomes (PROs), including health-related quality of life (HRQoL), functioning, and symptoms; and (3) in both the dose escalation and dose expansion phases, to assess preliminary efficacy of REGN4018 as monotherapy and in combination with cemiplimab (separately by cohort) as measured by ORR based on immune-based therapy RECIST (iRESIST), best overall response (BOR), duration of response (DOR), disease control rate, CR rate, and progression-free survival (PFS) based on RECIST 1.1 and iRECIST, to assess efficacy of REGN4018 as monotherapy and in combination with cemiplimab as measured by CA-125 level, and immunogenicity of REGN4018 and cemiplimab.

[0125] The exploratory objectives of the study are:

(1) To assess preliminary efficacy of REGN4018 as monotherapy and in combination with cemiplimab (separately by cohort) as measured by ORR based on combined assessment of RECIST and CA-125 using the Gynecologic Cancer Intergroup (GCIg) Criteria;

(2) To evaluate biomarkers that may correlate with mechanism of action, increased understanding of disease/target, observed toxicity, and potential anti-tumor activity including, but not limited, to:

- Circulating proteins
- Circulating immune cells
- Gene expression changes in peripheral blood and tumor
- Tumor expression levels of proteins such as MUC16 and programmed cell death ligand 1 (PD-L1)

(3) Assessments of both tumor mutation burden and circulating tumor DNA;

(4) Where possible, to evaluate the relationship between exposure and efficacy and safety endpoints; and

(5) Overall survival (OS).

[0126] Study Design

[0127] Patients with histologically confirmed ($\geq 25\%$ of tumor cells MUC16+, as assessed by immunohistochemistry [IHC]) endometrial cancer that has progressed or is recurrent after prior anti-PD-1 therapy (≥ 60 days since last administration) and prior platinum-based chemotherapy will be enrolled. The first 20 patients enrolled in the endometrial cohort will receive ubamatamab 250 mg IV Q3W after initial step-up dosing (1 mg in week 1, and 20 mg in week 2, which may be split doses). If there are fewer than three objective responses, a further 20 patients may be enrolled to receive ubamatamab 800 mg IV Q3W. If there is evidence of monotherapy activity in the first 20 patients, an additional treatment arm may be opened to receive ubamatamab 250 mg IV Q3W + cemiplimab 250 mg or 350 mg IV Q3W, in parallel with the monotherapy cohort. To limit the risk of cytokine release syndrome, all arms will include weekly step-up dosing of ubamatamab prior to Q3W dosing. Cohorts will use a Simon 2-stage study design, with an interim analysis after the first 20 patients. Any treatment arm with ≥ 3 objective responses will be expanded to 50 patients.

[0128] The primary endpoint will be the objective response rate for each arm (RECIST v1.1). Secondary endpoints include evaluation of duration of response and progression-free survival, safety, PK, and change from baseline in quality of life and physical functioning. Exploratory endpoints include evaluation of baseline tumor MUC16 IHC expression and other biomarkers as predictors of response.

[0129] In addition, dosing will be evaluated through a 3-arm, randomized phase 2 cohort evaluating three doses: REGN4018 250 mg IV Q3W, REGN4018 800 mg IV Q3W as monotherapy, and REGN4018 250 mg (or highest tolerable dose in combination with cemiplimab if 250 mg QW is not tolerable) IV Q3W combined with cemiplimab 350 mg IV Q3W.

[0130] Study Duration: All REGN4018 monotherapy cycles will be approximately 6 weeks (42 days) long. In the combination therapy, cycle 1 will be approximately 28 or 35 days long, depending on when patients tolerate the full dose of REGN4018 without CRS. In the randomized phase 2 cohort, cycle 1 will be approximately 42-49 days in all arms, depending on when patients tolerate the full dose of REGN4018 without CRS. Subsequent cycles in all cohorts will be approximately 6 weeks (42 days). Treatment will continue until either disease progression, intolerable adverse events, withdrawal of consent, or other treatment withdrawal criterion is met. Post-treatment follow-up for patients who do not withdraw consent will be either approximately 90 days or 168 days, depending on the reason for treatment cessation.

[0131] Study Population: Up to approximately 100 patients with advanced endometrial cancer will be enrolled. The initial cohort will evaluate REGN4018 250 mg IV every 3 weeks after initial step-up dosing. Treatment will be identical to Arm 1 of the randomized phase 2 cohort. The cohort will follow a Simon 2 stage design. In stage 1, 20 patients will be enrolled. The enrollment of an additional 30 patients in stage 2 will occur only if there are 3 or more with unconfirmed PR or better by RECIST 1.1 in Simon stage 1. This study will enroll patients with recurrent or progressive endometrial cancer that has progressed or recurred after prior anti-PD-1 therapy and platinum-based chemotherapy is added.

[0132] If there is evidence of monotherapy activity defined as 3 or more with unconfirmed PR or better by RECIST 1.1 in the first 20 patients treated with REGN4018 250 mg IV Q3 weeks, an additional Simon 2-stage cohort of REGN4018 250 mg IV combined with cemiplimab 350 mg IV Q3W (Arm 3 of the randomized phase 2 cohort) may be opened in parallel with the monotherapy cohort.

[0133] Inclusion Criteria A patient must meet the following criteria to be eligible for inclusion in the study:

1. Women age 18 years or greater
2. Willing and able to comply with clinic visits and study-related procedures

Note: Patients must provide either a newly obtained biopsy (newly obtained biopsies at screening are required unless medically inappropriate and discussed with medical monitor) or archived tumor tissue.
3. Expansion cohorts only: Must have progression on prior therapy documented radiographically and must have at least 1 measurable lesion (not previously irradiated) that can be accurately measured by Response Evaluation Criteria in Solid Tumors (RECIST).
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
5. Adequate organ and bone marrow function as follows:
 - a. Hemoglobin ≥ 8.5 g/dL
 - b. Absolute neutrophil count $\geq 1.5 \times 10^9/L$
 - c. Platelet count $\geq 75 \times 10^9/L$
 - d. Serum creatinine $\leq 1.5 \times$ ULN or estimated glomerular filtration rate >50 mL/min/1.73m² (dose escalation cohorts) or estimated glomerular filtration rate >30 mL/min/1.73m² (dose expansion cohorts)
 - e. Total bilirubin $\leq 1.5 \times$ ULN

- f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 3 \times$ ULN or $\leq 5 \times$ ULN, if liver metastases
- g. Alkaline phosphatase $\leq 2.5 \times$ ULN (or $\leq 5.0 \times$ ULN, if liver or bone metastases)
- 6. Life expectancy of at least 3 months.
- 7. Provide informed consent signed by study patient or legally acceptable representative.
- 8. Histologically confirmed endometrial cancer that has progressed or recurrent after prior anti-PD1 therapy and platinum-based chemotherapy.
 - a. MUC16-positivity of $\geq 25\%$ of tumor cells by MUC16 Immunohistochemistry IHC Assay, for Investigational Use Only will be performed at the Ventana Clinical Laboratory Improvement Amendments certified and College of American Pathologists accredited laboratory in Tucson, Arizona, U.S.A.. May be performed on a biopsy performed during screening or archival tissue block within 2 years of screening.
 - b. Prior treatment with anti-PD-1 therapy and prior platinum-based chemotherapy
 - c. 1-2 prior lines of systemic therapy, does not include systemic adjuvant therapy administered >12 months before 1st treatment in the recurrent setting
 - d. 60 days (approximately 3 half-lives) since last administration of anti-PD-1

[0134] Exclusion Criteria - A patient who meets any of the following criteria will be excluded from the study:

- 1. Currently receiving treatment in another therapeutic study or has participated in a study of an investigational agent and received treatment, or used an investigational device within 4 weeks of first dose of study therapy, or received treatment with an approved systemic therapy within 3 weeks of first dose of study therapy, or has received any previous systemic therapy within 5 half-lives of first dose of study therapy (whichever is longer). Patients who have received or are enrolled in a study involving treatment with a minimal dose of an investigational immunoPET reagent are not excluded. Patients previously treated with bevacizumab are permitted after discussion with the sponsor, if no history of bowel perforation or wound complications on bevacizumab AND last dose >30 days from the first dose of REGN4018, and other non-investigational non-immunomodulatory antibodies with half-lives longer than 7 days are permitted after a discussion with the sponsor if at least 3 half-lives have elapsed since last treatment.
- 2. Prior anti-cancer immunotherapy as described below:

- a. Prior treatment with anti-PD-1/PD-L1 therapy given within 60 days (~3 half-lives) of first dose
- b. Prior CAR-T cell therapy within 30 days of first dose of study drug
3. Prior treatment with a MUC16-targeted therapy.
4. Expansion cohorts only: another malignancy that is progressing or requires active treatment with the exception of non-melanoma skin cancer that has undergone potentially curative therapy or in situ cervical carcinoma, or any other tumor that has been deemed to be effectively treated with definitive local control (with or without continued adjuvant hormonal therapy) for at least 2 years prior to enrollment.
5. Corticosteroid therapy (>10 mg prednisone/day or equivalent) within 1 week prior to the first dose of study drug. Patients who require a brief course of steroids (up to 2 days in the week before enrollment) are not excluded.
6. Treatment-related immune-mediated AEs from immune-modulatory agents (including but not limited to anti-PD-1/PD-L1 or anti-CTLA-4 monoclonal antibodies or PI3Kdelta inhibitors) that have not resolved to baseline at least 30 days prior to initiation of treatment with study therapy.

Note: Endocrine immune-mediated AEs controlled with hormonal or other non-immunosuppressive therapies (without resolution) or grade 1 imAEs affecting any organ system with resolution prior to enrollment are allowed.

7. Another malignancy that is progressing or requires active treatment with the exception of non-melanoma skin cancer that has undergone potentially curative therapy or in situ cervical carcinoma, or any other tumor that has been deemed to be effectively treated with definitive local control (with or without continued adjuvant hormonal therapy) for at least 2 years prior to enrollment.
8. Untreated or active primary brain tumor, CNS metastases, or spinal cord compression. Patients with previously treated central nervous system metastases or spinal cord compression may participate provided they are stable (ie, without evidence of progression by imaging for at least 4 weeks prior to the first dose of study treatment, and any neurologic symptoms have returned to baseline), and there is no evidence of new or enlarging central nervous system metastases, and the patient does not require any systemic corticosteroids for management of central nervous system metastases or spinal cord compression within 2 weeks prior to the first dose of study therapy.
9. Encephalitis, meningitis, or uncontrolled seizures in the year prior to informed consent.

10. Has a clinically significant abnormal ECG reading as determined by the investigator, and/or meets the following criteria:
 - a. QTc (Friedericia) interval >470 msec. In cases of asymptomatic prolonged QTc interval (>470 msec), the ECG can be repeated up to 2 times. If subsequent QTc interval is <470 msec, the patient may be enrolled but only after review and approval by a cardiologist.
 - b. Evidence of Second-Degree AV block type II (Mobitz type II) or AV block type III (complete heart block).
11. Left ventricular ejection fraction (LVEF) less than 50% as measured by echocardiogram at baseline. In cases of LVEF 45-50% in absence of clinical symptoms, after review and clearance by cardiologist, the patient may be enrolled.
12. History of clinically significant cardiac disease including but not limited to the following, within 6 months prior to screening:
 - Myocardial infarction
 - Unstable angina
 - Stroke or transient ischemic attack
 - Peripheral arterial disease event
 - Heart failure (NYHA class III and IV or ACC/AHA heart failure classification C or D)
13. History of any clinically significant arrhythmia including paroxysmal atrial fibrillation requiring intervention at any time or implantation of a pacemaker or defibrillator.
14. Any history of myocarditis.
15. Signs or symptoms of active angina, arrhythmia or heart failure.
16. Any moderate to severe valve abnormality (stenosis or regurgitation) and/or clinically significant valvular heart disease that has not already been managed surgically.
17. Moderate to large pericardial effusion (e.g., > approximately 100 mL) as measured by echocardiogram at baseline.
18. Patients requiring 2 or more therapeutic paracenteses in the month before screening.
19. Baseline serum troponin above institutional upper limit of normal. In cases of minimally elevated troponin in absence of clinical symptoms, after clearance by a cardiologist, the patient may be enrolled.
20. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for imAEs. The following are not exclusionary: vitiligo, childhood asthma that has

resolved, hypothyroidism that required only hormone replacement, type 1 diabetes or psoriasis that does not require systemic treatment.

21. Known history of, or any evidence of interstitial lung disease, or active, non-infectious pneumonitis (past 5 years).
22. Moderate to large pleural effusion that may require thoracentesis within the next 4 weeks due to size or rate of enlargement. Pre-existing chest tube is acceptable, if patient meets all other inclusion/exclusion criteria.
23. Uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency.

NOTES:

- Patients with HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted.
- Patients with hepatitis B surface antigen positive (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving antiviral therapy for hepatitis B) are permitted.
- Participants with HBsAg negative but total HBV core antibody positive (HBc Ab+) 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.

24. Active infection requiring systemic therapy including:
 - a. Infection requiring hospitalization or treatment with IV anti-infectives within 2 weeks of start of study therapy
 - b. 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.
 - c. History of invasive opportunistic infections including but not limited to histoplasmosis, coccidioidomycosis, pneumocystis jirovecii, or aspergillosis, or John Cunningham virus (progressive multifocal leukoencephalopathy)
25. Receipt of a live vaccine within 30 days of planned start of study medication.
26. Major surgical procedure, open biopsy or significant traumatic injury within 2 weeks prior to enrollment.
27. Prior allogeneic stem cell transplant.

28. Bowel obstruction, perforation or severe diverticulosis within the last 3 months or high risk for bowel obstruction (in the opinion of the investigator) or current need for parenteral nutrition.
29. Any medical condition that in the opinion of the investigator would make participation in the study not in the best interest of the patient.
30. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments.
31. Has known allergy or hypersensitivity to components of study drug.
32. Known psychiatric or substance abuse disorders that would interfere with participation with the requirements of the study.
33. Member of the clinical site study team or his/her immediate family.
34. Pregnant or breastfeeding women.
35. Severe and/or uncontrolled hypertension at screening. Patients taking anti-hypertensive medication must be on a stable anti-hypertensive regimen.

Example 6: Evaluation of MUC16 Expression by Immunohistochemistry

[0135] MUC16 expression was evaluated by immunohistochemistry (IHC) using (Abnova Clone X325) in clinically annotated hysterectomy specimens from patients with endometrial cancer. Assessment included apical and a combination of membrane and cytoplasmic expression. MUC16 expression was quantified by total protein score (TPS, number of MUC16+ cancer cells) and H-score that incorporates staining intensity. Clinical annotation included available demographics, highest serum CA125, next generation sequencing (NGS), p53 IHC and histology. Clinical correlations used Kruskal-Wallis, Spearman, and Wilcoxon tests.

[0136] 147 cases were evaluated. Patient demographics: 64% Black (n=94), 26% White (n=39), 10% (n=14) Other. Histology: 67 (46%) serous, 42 (29%) carcinosarcoma, 20 (13%) grade 3 endometrioid, and 18 (12%) mixed histology. By p53 IHC (n=72) 71% positive), NGS sequencing, (n=36) 14 (39%) had P53 mutations, no microsatellite instability. MUC16 analysis showed 97% (143/147) positive cases, overall median H-score 145 (interquartile range (IQR) 70, 205) and median TPS of 70%. 79% (117/147) had TPS $\geq$ 25%, an eligibility threshold for the study discussed in Example 5. H-scores varied by subtype (Kruskal Wallis $p = 0.00022$): serous: median 175 (IQR 90, 205); carcinosarcoma median 105 (IQR 12, 161); grade 3 endometrial: median 110 (IQR 16, 203); mixed serous and endometrioid: median 200 (IQR 120, 214); Mixed serous and clear cell: median 115 (IQR 10, 210); and mixed clear cell and grade 3 endometrial case H-score 155. Heterogeneous MUC16 expression was observed in mixed histology cases, especially carcinosarcoma, where MUC16 generally stained the epithelial component. No

difference in MUC16 H-score by p53 IHC status was observed. Among 106 patients with available CA125, 48% had elevation >70 u/mL; 25% had CA125 > 500 u/mL. In this study, CA125 did not correlate with MUC16 H-score.

[0137] MUC16 is broadly expressed in high-grade endometrial cancer.

[0138] The present disclosure is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the disclosure 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.

[0139] Sequences

SEQ ID NO: 1

QVQLVESGGGLVKPGGSLRLSCAASGFTFSNYYMSWVRQAPGKGLEWISYISGRGSTIFYADSVKGRITI
SRDNAKNSLFLQMNSLRAEDTAVYFCVKDRGGYSPYWGQGTLLVTVSS

SEQ ID NO: 2

DIQMTQSPSSLSASVGDRVTITCRASQSISTYLNWYQQKPKAPKLLIYTASSLQSGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQSYSTPPITFGQGTRLEIK

SEQ ID NO: 3

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADSVKGR
FTISRDNKNSLYLQMNSLRAEDTALYYCAKYGSYGKIFYHYGLDVWGQGTTTVTVSS

SEQ ID NO: 4

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGR
FTISRDNKNSLYLQMNSLRAEDTALYYCAKDGSYGKIFYHYGMDVWGQGTTTVTVSS

SEQ ID NO: 5

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADSVKGR
FTISRDNKNSLYLQMNSLRAEDTALYYCAKDGSYGKIFYHYGLDVWGQGTTTVTVSS

SEQ ID NO: 6

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADSVKGR
FTISRDNKNSLYLQMNSLRAEDTALYYCAKYGSYGKIFYHYGLDVWGQGTTTVTVSS

SEQ ID NO: 7

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGR
FTISRDNKNSLYLQMNSLRAEDTALYYCAKYGSYGKIFYHYGMDVWGQGTTTVTVSS

SEQ ID NO: 8

GFTFSNYY

SEQ ID NO: 9

ISGRGSTI

SEQ ID NO: 10

VKDRGGYSPY

SEQ ID NO: 11

QSISTY

SEQ ID NO: 12

TAS

SEQ ID NO: 13

QQSYSTPPIT

SEQ ID NO: 14

GFTFDDYS

SEQ ID NO: 15

ISWNSGSK

SEQ ID NO: 16

AKYGSGYGKIFYHYGLDV

SEQ ID NO: 17

GFTFDDYS

SEQ ID NO: 18

ISWNSGSI

SEQ ID NO: 19

AKDGSGYGKFYYYGMDV

SEQ ID NO: 20

GFTFDDYS

SEQ ID NO: 21

ISWNSGSK

SEQ ID NO: 22

AKDGSGYGKIFYHYGLDV

SEQ ID NO: 23

GFTFDDYS

SEQ ID NO: 24

ISWNSGSK

SEQ ID NO: 25

AKYGSGYGKFYYYGLDV

SEQ ID NO: 26

GFTFDDYS

SEQ ID NO: 27

ISWNSGSI

SEQ ID NO: 28

AKYGSYGKFFYYGMDV

SEQ ID NO: 29

QVQLVESGGGLVKPGGSLRLSCAASGFTFSNYYMSWVRQAPGKGLEWISYISGRGSTIFYADSVKGRITI
SRDNAKNSLFLQMNSLRAEDTAVYFCVKDRGGYSPYWGQGTLLTVSSASTKGPSVFPLAPCSRSTSES
TAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYTCNVDPKPSN
TKVDKRVESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPEVQFNWYVDG
VEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKGQPREPQVYTL
PPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRLTVDKSRWQE
GNVFSCSVMHEALHNHYTQKSLSLGLK

SEQ ID NO: 30

DIQMTQSPSSLSASVGDRVITICRASQSISTYLNWYQQKPGKAPKLLIYTASSLQSGVPSRFSGSGSGTD
FTLTISLQPEDFATYYCQQSYSTPITFGQGTREIKRTVAAPSVFIFPPSDEQLKSGTASVCLLNNFYF
REAKVQWKVDNALQSGNSQESVTEQDSKDYSLSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGE

SEQ ID NO: 31

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSKGYADSVKGR
FTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSYGKFFYYGMDVWGQGTITVTVSSASTKGPSVFPLA
PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYT
CNVDHKPSNTKVDKRVESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKG
QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRL
TVDKSRWQEGNVFSCSVMHEALHNRFTQKSLSLSPGK

SEQ ID NO: 32

EVQLVESGGGLVQPGRSLRLSCAASGFTFDDYSMHWVRQAPGKGLEWVSGISWNSGSIGYADSVKGR
FTISRDNAKNSLYLQMNSLRAEDTALYYCAKYGSYGKFFYYGMDVWGQGTITVTVSSASTKGPSVFPLA
PCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTKYT
CNVDHKPSNTKVDKRVESKYGPPCPPCPAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSDQEDPE
VQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTIKAKG
QPREPQVYTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSRL
TVDKSRWQEGNVFSCSVMHEALHNRFTQKSLSLSPGK

SEQ ID NO: 33

EVQLLESGLVLPVPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDITYFADSVKGRF
TISRDNKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGGQTLTVSS

SEQ ID NO: 34

DIQMTQSPSSLSASVGDSTITICRASLSINTFLNWYQQKPGKAPNLLIYAASSLHGGVPSRFSGSGSGTDF
TLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFR

SEQ ID NO: 35

GFTFSNFG

SEQ ID NO: 36

ISGGGRDT

SEQ ID NO: 37

VKWGNIYFDY

SEQ ID NO: 38

LSINTF

SEQ ID NO: 39

AAS

SEQ ID NO: 40

QQSSNTPFT

SEQ ID NO: 41

EVQLLES GGVLVQPGGSLRLSCAASGFTFSNFGMTWVRQAPGKGLEWVSGISGGGRDITYFADSVKGRF
TISRDN SKNTLYLQMNSLKGEDTAVYYCVKWGNIYFDYWGGGTLVTVSSASTKGPSVFPLAPCSRSTSE
STAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTYTCNVDHKPS
NTKVDKRVESKYGPCCPPCPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQFNWYV
DGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQV
YTLPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSRLTVDKSRW
QEGNVFSCSVMHEALHNHYTQKSLSLGLK

SEQ ID NO: 42

DIQMTQSPSSLSASVGDSITITCRASLSINTFLNWKYQQKPGKAPNLLIYAASSLHGGVPSRFSGSGSGTDF
TLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVDFRRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPR
EAKVQWKVDNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNR
GEC

What is claimed is:

1. A method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject a bispecific antibody comprising a first antigen-binding domain that specifically binds mucin 16 (MUC16), and a second antigen-binding domain that specifically binds human CD3, wherein the bispecific antibody is administered to the subject at a dose of at least 1 mg.
2. The method of claim 1, wherein the subject has previously been treated with a platinum-based chemotherapy.
3. The method of claim 1 or 2, wherein the subject has been previously treated with an antibody that binds human programmed death receptor-1 (PD-1).
4. The method of any one of claims 1-3, wherein the subject has received at least two prior lines of therapy to treat the endometrial cancer.
5. The method of any one of claims 1-4, wherein the endometrial cancer is advanced or recurrent endometrial cancer.
6. The method of any one of claims 1-5, wherein the endometrial cancer is MUC16-expressing cancer.
7. The method of any one of claims 1-6, wherein the first antigen-binding domain comprises:
 - (a) three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 1; and
 - (b) three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.
8. The method of claim 7, wherein the first antigen-binding domain comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 8, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 9, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 10.

9. The method of claim 7 or 8, wherein the first antigen-binding domain comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 11, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 12, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 13.

10. The method of any one of claims 7-9, wherein the first antigen-binding domain 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: 2.

11. The method of any one of claims 1-10, wherein the second antigen-binding domain comprises:

(a) three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 3; and

(b) three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 2.

12. The method of claim 11, wherein the second antigen-binding domain comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 14, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 15, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 16.

13. The method of claim 11 or 12, wherein the second antigen-binding domain comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 11, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 12, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 13.

14. The method of any one of claims 11-13, wherein the second antigen-binding domain comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 3, and a LCVR comprising the amino acid sequence of SEQ ID NO: 2.

15. The method of any one of claims 1-14, wherein the bispecific antibody comprises a human IgG heavy chain constant region.

16. The method of claim 15, wherein the human IgG heavy chain constant region is isotype IgG1.

17. The method of claim 15, wherein the human IgG heavy chain constant region is isotype IgG4.

18. The method of claim 16 or 17, wherein the bispecific antibody comprises a chimeric hinge that reduces Fcγ receptor binding relative to a wild-type hinge of the same isotype.

19. The method of any one of claims 15-18, 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.

20. The method of any one of claims 1-14, wherein the bispecific antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 29.

21. The method of any one of claims 1-14, wherein the bispecific antibody comprises a second heavy chain comprising the amino acid sequence of SEQ ID NO: 31.

22. The method of any one of claims 1-14, wherein the bispecific antibody comprises a first heavy chain comprising the amino acid sequence of SEQ ID NO: 29, a second heavy chain comprising the amino acid sequence of SEQ ID NO: 31, and a common light chain comprising the amino acid sequence of SEQ ID NO: 30.

23. The method of any one of claims 1-22, wherein the subject has a serum CA-125 level equal to or greater than 60 U/ml.

24. The method of any one of claims 1-23, further comprising administering a second therapeutic agent or therapeutic regimen.

25. The method of claim 24, wherein the second therapeutic agent or therapeutic regimen comprises an anti-PD-1 antibody or antigen-binding fragment thereof.

26. The method of claim 25, wherein the anti-PD-1 antibody or antigen-binding fragment comprises:

(a) three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 33; and

(b) three light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) contained within a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 34.

27. The method of claim 26, wherein the anti-PD-1 antibody or antigen-binding fragment comprises a HCDR1 comprising the amino acid sequence of SEQ ID NO: 35, a HCDR2 comprising the amino acid sequence of SEQ ID NO: 36, and a HCDR3 comprising the amino acid sequence of SEQ ID NO: 37.

28. The method of claim 26 or 27, wherein the anti-PD-1 antibody or antigen-binding fragment comprises a LCDR1 comprising the amino acid sequence of SEQ ID NO: 38, a LCDR2 comprising the amino acid sequence of SEQ ID NO: 39, and a LCDR3 comprising the amino acid sequence of SEQ ID NO: 40.

29. The method of any one of claims 26-28, wherein the anti-PD-1 antibody or antigen-binding fragment comprises a HCVR comprising the amino acid sequence of SEQ ID NO: 33, and a LCVR comprising the amino acid sequence of SEQ ID NO: 34.

30. The method of claim 29, wherein the anti-PD-1 antibody or antigen-binding fragment is an anti-PD-1 antibody comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 41 and a light chain comprising the amino acid sequence of SEQ ID NO: 42.

31. The method of any one of claims 25-30, wherein the anti-PD-1 antibody is cemiplimab.

32. The method of any one of claims 1-31, wherein the bispecific antibody is administered in a dosing regimen comprising a split initial dose.

33. The method of any one of claims 1-32, wherein the bispecific antibody is administered to the subject at a dose of from 10 mg to 1000 mg weekly.

34. The method of claim 33, wherein the bispecific antibody is administered to the subject at a dose of about 250 mg weekly, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg.

35. The method of claim 33, wherein the bispecific antibody is administered to the subject at a dose of about 800 mg weekly, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 750 mg.

36. The method of any one of claims 1-32, wherein the bispecific antibody is administered to the subject at a dose of from 10 mg to 1000 mg once every three weeks.

37. The method of claim 36, wherein the bispecific antibody is administered to the subject at a dose of about 250 mg once every three weeks, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg.

38. The method of claim 36, wherein the bispecific antibody is administered to the subject at a dose of about 800 mg once every three weeks, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 750 mg.

39. The method of claim 33, wherein the bispecific antibody is administered in a dosing regimen comprising: (i) administering 1 mg of the bispecific antibody in week 1, optionally wherein the dose is split into a first fraction of about 0.5 mg and a second fraction of about 0.5 mg; (ii) administering 20 mg of the bispecific antibody in week 2, optionally wherein the dose is split into a first fraction of about 10 mg and a second fraction of about 10 mg; and (iii) administering 250 mg of the bispecific antibody in week 3, optionally wherein the dose is split into a first fraction of about 50 mg, and a second fraction of about 200 mg.

40. The method of claim 39, further comprising administering the bispecific antibody at a dose of about 250 mg once every week from week 4 onwards.

41. The method of claim 39, further comprising administering the bispecific antibody at a dose of about 250 mg once every three weeks from week 4 onwards.

42. The method of claim 39, further comprising administering the bispecific antibody at a dose of about 800 mg once every three weeks from week 4 onwards.

43. The method of any one of claims 25-42, wherein the anti-PD-1 antibody is administered to the subject at a dose of from 300 to 400 mg once every three weeks.

44. The method of claim 43, wherein the anti-PD-1 antibody is administered to the subject at a dose of 350 mg once every three weeks.

45. The method of any one of claims 1-44, wherein the subject has stable disease, a partial response, or a complete response following administration of the bispecific antibody for at least one week at a dose of 1–800 mg.

46. The method of any one of claims 1-44, wherein the subject has stable disease, a partial response, or a complete response following administration of the bispecific antibody for at least one week at a dose of 20–800 mg.

47. The method of any one of claims 1-32, wherein the bispecific antibody is administered to the subject at a dose sufficient to achieve a serum concentration of at least 4 mg/L.

48. The method of any one of claims 1-47, wherein MUC16 is highly expressed in $\geq 25\%$ of tumor cells in the subject, as determined by immunohistochemical staining.

49. The method of any one of claims 1-47, wherein the subject has:

- a baseline MUC16 immunohistochemical staining score of 2 in a MUC16-expressing tumor; or
- a baseline MUC16 immunohistochemical staining score of 2+ in a MUC16-expressing tumor; or
- a baseline MUC16 immunohistochemical staining score of 3 in a MUC16-expressing tumor; or
- a baseline MUC16 immunohistochemical staining score of 3+ in a MUC16-expressing tumor; or
- a baseline MUC16 immunohistochemical staining score of 4 in a MUC16-expressing tumor; or
- a baseline MUC16 immunohistochemical staining score of 4+ in a MUC16-expressing tumor; or
- a baseline MUC16 immunohistochemical staining score of 5 in a MUC16-expressing tumor; or
- a tumor with MUC16-expression in $\geq 25\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 30\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 35\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 40\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 45\%$ of tumor cells; or

- a tumor with MUC16-expression in $\geq 50\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 55\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 60\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 65\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 70\%$ of tumor cells; or
- a tumor with MUC16-expression in $\geq 75\%$ of tumor cells.

50. The method of any one of claims 1-47, wherein the subject has:

- an H-score ≥ 100 ; or
- an H-score ≥ 105 ; or
- an H-score ≥ 110 ; or
- an H-score ≥ 115 ; or
- an H-score ≥ 120 ; or
- an H-score ≥ 125 ; or
- an H-score ≥ 130 ; or
- an H-score ≥ 135 ; or
- an H-score ≥ 140 ; or
- an H-score ≥ 145 ; or
- an H-score ≥ 150 ; or
- an H-score ≥ 155 ; or
- an H-score ≥ 160 ; or
- an H-score ≥ 165 ; or
- an H-score ≥ 170 ; or
- an H-score ≥ 175 ; or
- an H-score ≥ 180 ; or
- an H-score ≥ 185 ; or
- an H-score ≥ 190 ; or
- an H-score ≥ 195 ; or
- an H-score ≥ 200 ,

as determined by immunohistochemical staining.

51. The method of any one of claims 1-50, wherein the bispecific antibody is administered intravenously.

52. The method of any one of claims 1-50, wherein the bispecific antibody is administered subcutaneously.

53. The method of any one of claims 25-52, wherein the anti-PD-1 antibody or antigen-binding fragment is administered intravenously.

54. The method of any one of claims 1-53, wherein the bispecific antibody is REGN4018 (ubamatamab).

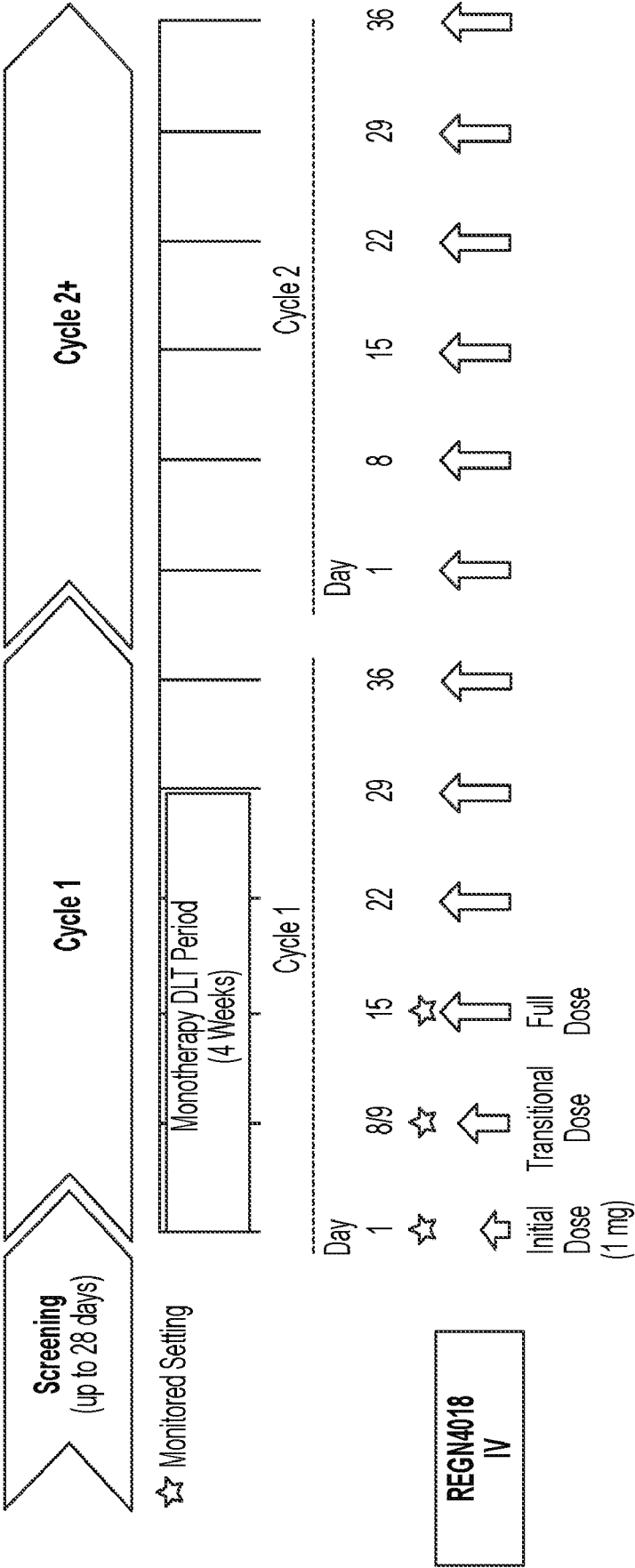


FIG. 1

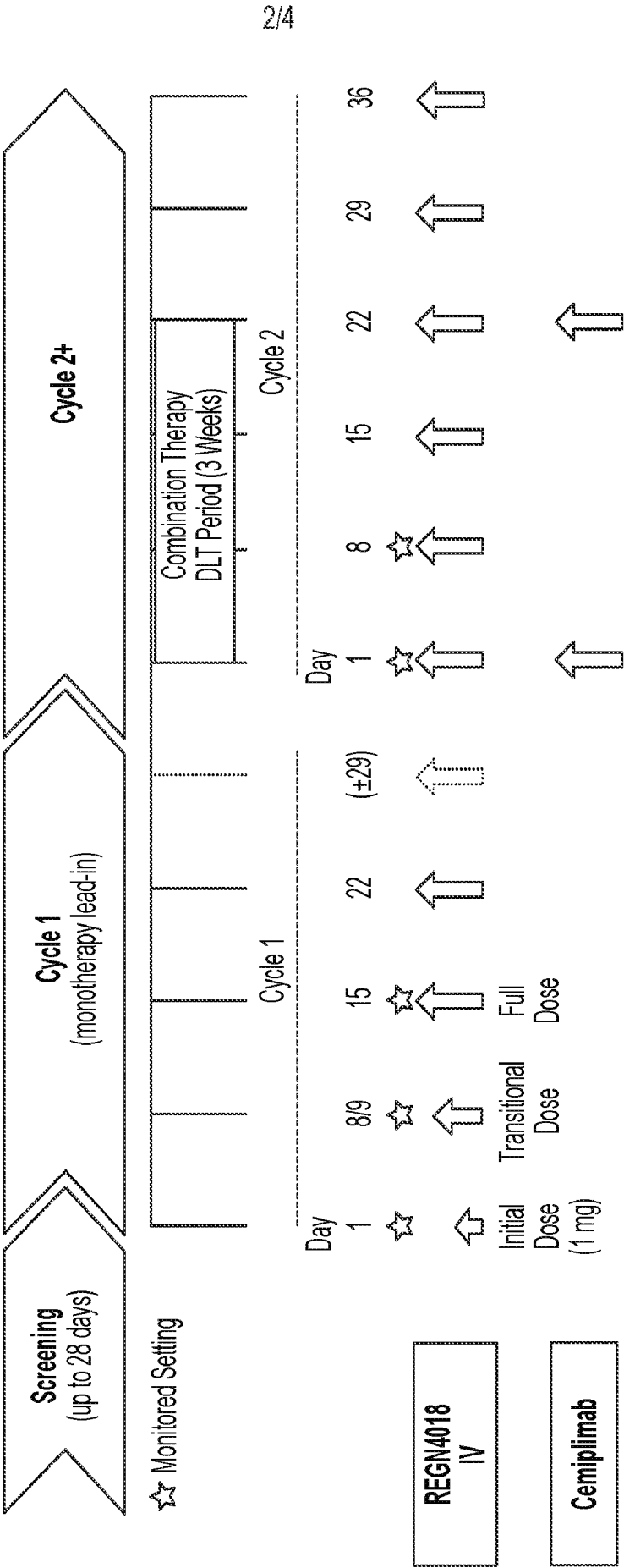


FIG. 2

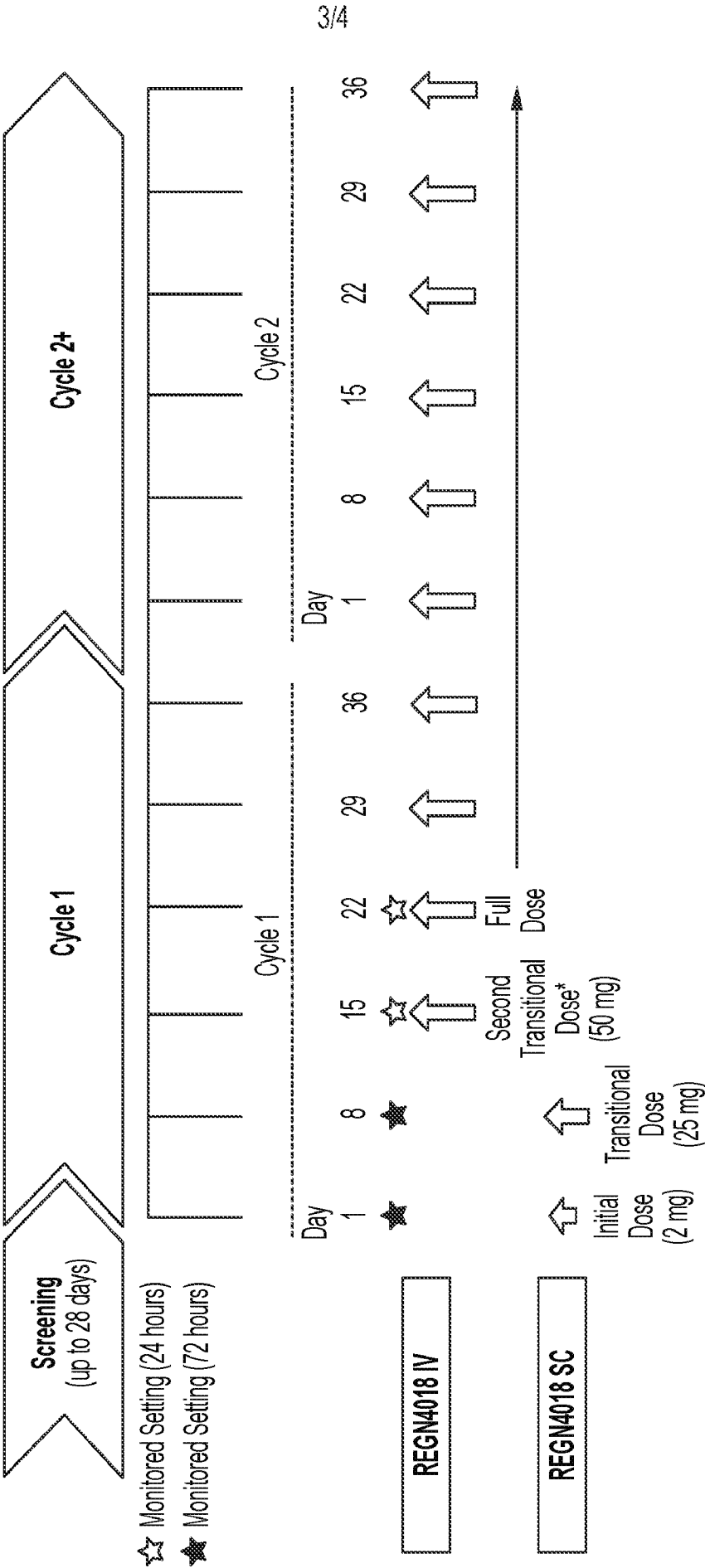


FIG. 3

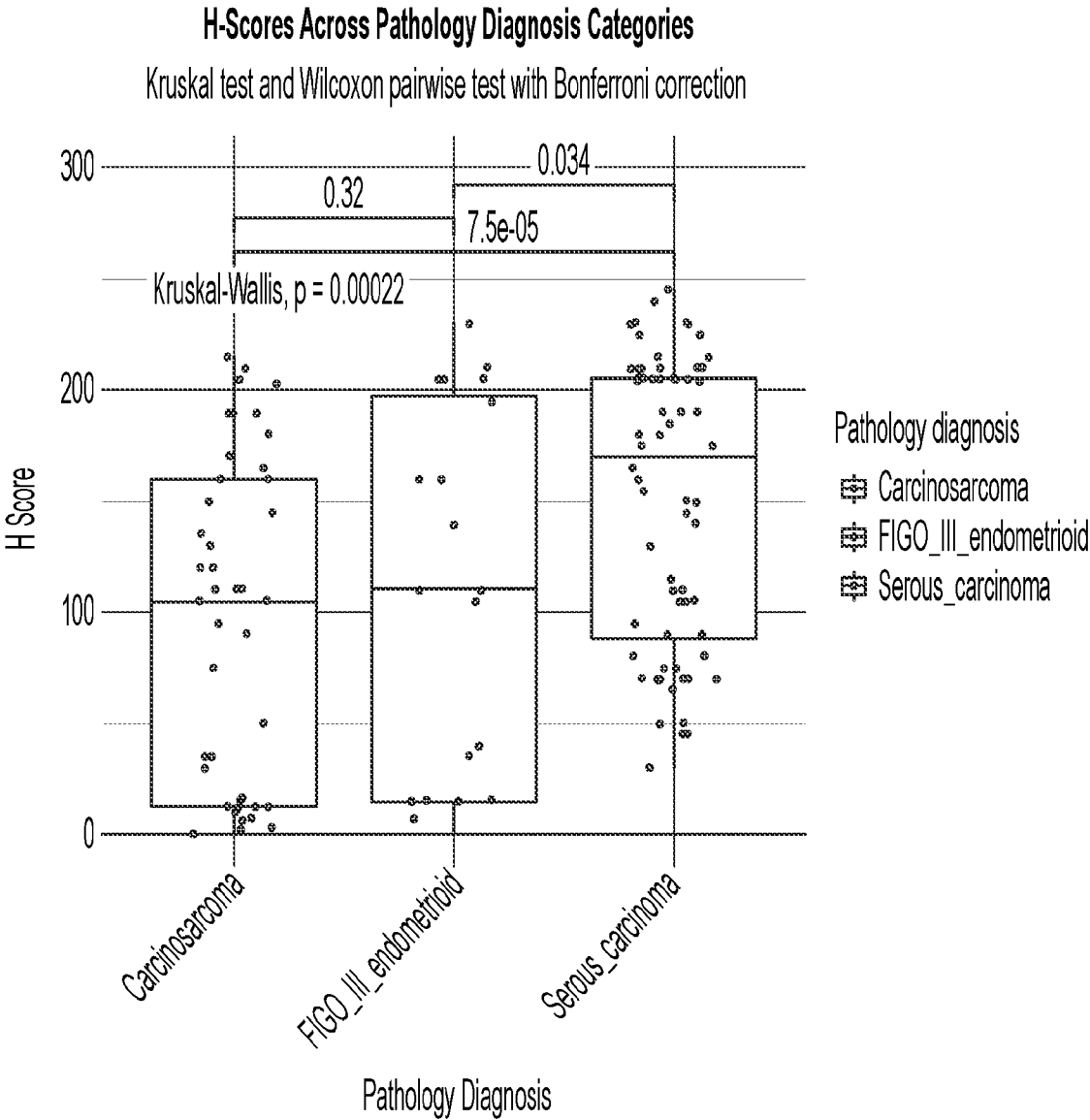


FIG. 4

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/059495

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07K16/28 C07K16/30 A61K39/395 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2020/399371 A1 (KIRSHNER JESSICA R [US] ET AL) 24 December 2020 (2020-12-24) paragraphs [0188], [0196]; claims 1,2; examples 3,2 -----	1 - 54
X	WO 2022/197907 A2 (MEMORIAL SLOAN KETTERING CANCER CENTER [US] ET AL.) 22 September 2022 (2022-09-22) paragraph [0288]; claims 1-18; examples 6,7 -----	1 - 54
X	WO 2023/133280 A1 (REGENERON PHARMA [US]) 13 July 2023 (2023-07-13) the whole document paragraph [0039]; claims 1,23-28 ----- - / - -	1 - 54



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 March 2025

Date of mailing of the international search report

18/03/2025

Name and mailing address of the ISA/

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Authorized officer

Siaterli, Maria

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2024/059495

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	LIU: "A phase I/II study of ubamatamab (REGN4018), a MUC16xCD3 bispecific antibody, administered alone or in combination with cemiplimab (anti-PD-1) in patients with recurrent ovarian cancer or MUC16+ endometrial cancer: Trial in progress update", GYNECOLOGIC ONCOLOGY., vol. 190, no. 1, 1 November 2024 (2024-11-01), page S284, XP093244398, GB ISSN: 0090-8258, DOI: https://doi.org/10.1016/j.ygyno.2024.07.422 Retrieved from the Internet: URL:https://pdf.sciencedirectassets.com/272587/1-s2.0-S0090825824X00128/1-s2.0-S0090825824007777/main.pdf?hash=d7509094d696e9585756a11bc59474a131d6fe0bca02a76778640e4eeb9c4a40&host=68042c943591013ac2b2430a89b270f6af2c76d8dfd086a07176afe7c76c2c61&pii=S0090825824007777&tid=spdf-f6e9a9be-5d4d-4ea0-9675-008> the whole document -----	1 - 54

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2024/059495

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)).

☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
2. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this report has been established to the extent that a meaningful search could be carried out without a WIPO Standard ST.26 compliant sequence listing.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

Information on patent family members

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