METHODS OF TREATING CANCER WITH ANTI-TIM-3 ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. Provisional Application No. 62/444,354, filed January 9, 2017, and U.S. Provisional Application No. 62/582,272, filed November 6, 2017, each of which is incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The present specification makes reference to a Sequence Listing provided in electronic form as an ASCII.txt file named "TSR-002 SEQ LIST_ST25" that was generated on January 8, 2018, and is 39,647 bytes in size.

BACKGROUND

[0003] Cancer is a serious public health problem, with about 600,920 people in the United States of America expected to die of cancer in 2017 alone according to the American Cancer Society, Cancer Facts & Figures 2017 (https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html). Accordingly, there continues to be a need for effective therapies to treat cancer patients.

SUMMARY

[0004] The present disclosure encompasses a recognition that certain dosage regimens for agents that are capable of inhibiting T Cell Immunoglobulin and Mucin Domain-3 (TIM-3) signaling (e.g., anti-TIM-3 antibody agents) are useful for treating disorders such as cancer. In one aspect, the present disclosure relates to a use of a T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) binding agent in the manufacture of a medicament for treating cancer in a human, wherein the TIM-3 binding agent is to be administered at a flat dose of between 100 mg and 1500 mg.

[0005] In some examples, the present disclosure provides methods of treating disorders such as cancer that include administering compositions that deliver particular TIM-3 inhibitors (e.g., anti-TIM-3 antibody agents) according to dosing regimens that may achieve clinical benefit in at least some patients.

[0006] In examples, a TIM-3 inhibitor is a TIM-3 binding agent. In examples, a TIM-3 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In examples, a TIM-3 binding agent is an antibody agent (i.e., an anti-TIM-3 antibody agent).

[0007] In examples, an anti-TIM-3 antibody agent comprises a heavy chain variable region with one or more CDR sequences selected from SEQ ID NOs: 21, 22, and 23 and/or a light chain variable region with one or more CDR sequences selected from SEQ ID NOs: 24, 25, and 26. In examples, an anti-TIM-3 antibody agent comprises a heavy chain variable region with two or three CDR sequences selected from SEQ ID NOs: 21, 22, and 23 and/or a light chain variable region with two or three CDR sequences selected from SEQ ID NOs: 24, 25, and 26. In examples, an anti-TIM-3 antibody agent comprises a heavy chain variable region with three CDR sequences of SEQ ID NOs: 21, 22, and 23 and/or a light chain variable region with three CDR sequences of SEQ ID NOs: 24, 25, and 26. In examples, an anti-TIM-3 antibody agent comprises a heavy chain variable region with three CDR sequences of SEQ ID NOs: 21, 22, and 23 and a light chain variable region with three CDR sequences of SEQ ID NOs: 24, 25, and 26.

[0008] In examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:1 or SEQ ID NO:7. In examples, an anti-TIM-3 antibody agent comprises an immunoglobulin light chain variable domain whose amino acid sequence having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:2 or SEQ ID NO:8. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO: 7 and/or an immunoglobulin light chain variable domain whose amino acid sequence comprises SEQ ID NO: 2 or SEQ ID NO: 8. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO: 7 and an immunoglobulin light chain variable domain whose amino acid sequence comprises SEQ ID NO: 2 or SEQ ID NO: 8.

[0009] In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain polypeptide comprising an amino acid sequence having about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:3. In

some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin light chain polypeptide comprising an amino acid sequence having about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO:4. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain whose amino acid sequence comprises SEQ ID NO: 3 and/or an immunoglobulin light chain whose amino acid sequence comprises SEQ ID NO: 4. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain whose amino acid sequence comprises SEQ ID NO: 3 and an immunoglobulin light chain whose amino acid sequence comprises SEQ ID NO: 4.

[0010] The present disclosure provides, in some examples, methods of treating a disorder in a subject that is responsive to T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) inhibition comprising administering a therapeutically effective dose of an agent that is capable of inhibiting TIM-3 signaling. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 100 - 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a therapeutically effective dose is about 3 mg/kg. In examples, a therapeutically effective dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 100 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 300 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0011] The present disclosure provides, in some examples, methods of increasing T cell activation or T cell effector function in a subject that is responsive to T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) inhibition comprising administering a therapeutically effective dose of an agent that is capable of inhibiting TIM-3 signaling. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 100 - 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically

effective dose is a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a therapeutically effective dose is about 3 mg/kg. In examples, a therapeutically effective dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 100 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 300 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 900 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0012] The present disclosure provides, in some examples, methods of reducing tumors or inhibiting the growth of tumor cells in a subject that is responsive to T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) inhibition comprising administering a therapeutically effective dose of an agent that is capable of inhibiting TIM-3 signaling. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 100 - 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a therapeutically effective dose is about 3 mg/kg. In examples, a therapeutically effective dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 100 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 300 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 900 mg of a TIM-3

inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0013] The present disclosure provides, in some examples, methods of inducing an immune response in a subject that is responsive to T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) inhibition comprising administering a therapeutically effective dose of an agent that is capable of inhibiting TIM-3 signaling. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 100 - 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a therapeutically effective dose is about 3 mg/kg. In examples, a therapeutically effective dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 100 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 300 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 900 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0014] The present disclosure provides, in some examples, methods of enhancing an immune response or increasing the activity of an immune cell in a subject that is responsive to T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) inhibition comprising administering a therapeutically effective dose of an agent that is capable of inhibiting TIM-3 signaling. In examples, an immune response is a humoral or cell mediated immune response. In examples, an immune response is a CD4 or CD8 T cell response. In examples, an immune response is a B cell response. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 100 - 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat

dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a therapeutically effective dose is about 3 mg/kg. In examples, a therapeutically effective dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 100 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 300 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 900 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0015] The present disclosure provides, in some examples, methods of treating cancer that comprises administering to a patient in need of treatment an anti-T Cell Immunoglobulin and Mucin Domain-3 (TIM-3) at a therapeutically effective dose. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 100 - 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a therapeutically effective dose is about 3 mg/kg. In examples, a therapeutically effective dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 100 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 300 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 900 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of a

TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0016] The present disclosure provides, in some examples, methods of treating cancer comprising administering to a patient in need of treatment an anti-T Cell Immunoglobulin and Mucin Domain-3 (TIM-3) antibody at a therapeutically effective dose at an administration interval for a period sufficient to achieve clinical benefit. In examples, an anti-TIM-3 antibody comprises a heavy chain comprising three CDRs that have sequences of SEQ ID NOs: 21, 22, or 23; and/or a light chain comprising three CDRs that have sequences of SED ID NOs: 24, 25, or 26. In examples, an anti-TIM-3 antibody comprises an immunoglobulin heavy chain variable domain comprising SEQ ID NO: 1 or SEQ ID NO: 7 and an immunoglobulin light chain variable domain comprising SEQ ID NO:2 or SEQ ID NO: 8. In examples, an anti-TIM-3 antibody comprises a heavy chain polypeptide comprising SEQ ID NO: 3 and a light chain polypeptide comprising SEQ ID NO: 4. In examples, a therapeutically effective dose is about 1, 3 or 10 mg/kg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is about 100 - 1500 mg of an anti-TIM-3 antibody In examples, a therapeutically effective dose is a flat dose about 100 mg; a flat dose about 200 mg; a flat dose about 300 mg; a flat dose about 400 mg; a flat dose about 500 mg; a flat dose about 600 mg; a flat dose about 700 mg; a flat dose about 800 mg; a flat dose about 900 mg; a flat dose about 1000 mg; a flat dose about 1100 mg; a flat dose about 1200 mg; a flat dose about 1300 mg; a flat dose about 1400 mg; or a flat dose about 1500 mg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is about 1 mg/kg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is about 3 mg/kg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is about 10 mg/kg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is a flat dose about 100 mg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is a flat dose about 300 mg of an anti-TIM-3 antibody. In examples, a therapeutically effective dose is a flat dose about 500 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 900 mg of a TIM-3 inhibitor. In examples, a therapeutically effective dose is a flat dose about 1200 mg of an anti-TIM-3 antibody.

[0017] In any of the methods described herein, a therapeutically effective dose is about 1 mg/kg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective

dose is about 3 mg/kg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 5 mg/kg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0018] In any of the methods described herein, a therapeutically effective dose is about 100 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 200 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 300 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 400 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 500 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 600 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 700 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 800 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 900 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 1000 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 1100 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 1200 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 1300 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 1400 mg of a TIM-3 inhibitor. In any of the methods described herein, a therapeutically effective dose is about 1500 mg of a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0019] In examples, a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once a week (Q1W), once every 2 weeks (Q2W), once every 3 weeks (Q3W), once every 4 weeks (Q4W), once every 5 weeks (Q5W), or once every 6 weeks (Q6W). In examples, a TIM-3 inhibitor is administered for a period of at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks, or more. In examples, a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once a week (Q1W). In examples, a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once every 2 weeks (Q2W). In examples, a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once every three weeks (Q3W). In examples,

a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once every 4 weeks (Q4W). In examples, a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once every 5 weeks (Q5W). In examples, a TIM-3 inhibitor is administered at an administration interval (or treatment cycle) of once every 6 weeks (Q6W).

[0020] In examples, a TIM-3 inhibitor (e.g., a therapeutically effective dose of about 100 mg, 300 mg, 500 mg, or 900 mg) is administered at an administration interval (or treatment cycle) of once every 3 weeks. In examples, a therapeutically effective dose of about 100 mg is administered at an administration interval (or treatment cycle) of once every 3 weeks. In examples, a therapeutically effective dose of about 300 mg is administered at an administration interval (or treatment cycle) of once every 3 weeks. In examples, a therapeutically effective dose of about 500 mg is administered at an administration interval (or treatment cycle) of once every 3 weeks. In examples, a therapeutically effective dose of about 900 mg is administered at an administration interval (or treatment cycle) of once every 3 weeks.

[0021] In examples, a TIM-3 inhibitor is administered on the first day of a treatment cycle or within 1, 2, or 3 days of the first day of a treatment cycle. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0022] In examples, a TIM-3 inhibitor described herein is administered according to dosing regimens demonstrated to achieve a clinical benefit in some patients (for example, according to a regimen as determined by a physician, including dosing modifications). In examples, a TIM-3 inhibitor described herein is administered until treatment is discontinued due to, e.g., disease progression or an adverse reaction or as determined by a physician. In examples, a clinical benefit is stable disease ("SD"), a partial response ("PR") and/or a complete response ("CR"). In examples, a clinical benefit is stable disease ("SD"). In examples, a clinical benefit is a partial response ("PR"). In examples, a clinical benefit is a complete response ("CR"). In examples, PR or CR is determined in accordance with Response Evaluation Criteria in Solid Tumors (RECIST). In examples, a TIM-3 inhibitor is administered for a longer period to maintain clinical benefit. In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0023] In examples, a TIM-3 inhibitor is administered periodically to a subject at a dose of about 100 mg, about 300 mg, or about 1200 mg. In examples, a TIM-3 inhibitor is

administered periodically to a subject at a dose of about 100 mg (e.g., once every three weeks (Q3W) and/or for 2, 3, 4, 5, 6, or more cycles). In examples, a TIM-3 inhibitor is administered periodically to a subject at a dose of about 300 mg (e.g., once every three weeks (Q3W) and/or for 2, 3, 4, 5, 6, or more cycles). In examples, a TIM-3 inhibitor is administered periodically to a subject at a dose of about 1200 mg (e.g., once every three weeks (Q3W) and/or for 2, 3, 4, 5, 6, or more cycles). In examples, a TIM-3 inhibitor is any anti-TIM-3 antibody agent described herein.

[0024] In examples, a subject has been further administered or will be administered a further therapeutic agent, such that the subject receives a TIM-3 inhibitor (e.g., any anti-TIM-3 antibody agent described herein) and a further therapeutic agent (e.g., one, two, three, four, or more further therapeutic agents).

[0025] In examples, a subject has been further administered or will be administered an immune checkpoint inhibitor, such that the subject receives a TIM-3 inhibitor (e.g., any anti-TIM-3 antibody agent described herein) and an immune checkpoint inhibitor. That is, a subject can be administered a TIM-3 inhibitor in combination with at least one immune checkpoint inhibitor.

[0026] In examples, a checkpoint inhibitor is an agent capable of inhibiting any of the following: PD-1 (e.g., inhibition via anti-PD-1, anti-PD-L1, or anti-PD-L2 therapies), CTLA-4, TIM-3, TIGIT, LAGs (e.g., LAG-3), CEACAM (e.g., CEACAM-1, -3 and/or -5), VISTA, BTLA, LAIR1, CD160, 2B4, CD80, CD86, B7-H3 (CD276), B7-H4 (VTCN1), HVEM (TNFRSF14 or CD270), KIR, A2aR, MHC class I, MHC class II, GALS, adenosine, TGFR (e.g., TGFR beta), B7-H1, B7-H4 (VTCN1), OX-40, CD137, CD40, IDO, or CSF-1R. In examples, a checkpoint inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In examples, a checkpoint inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.

[0027] In examples, an immune checkpoint inhibitor is an agent that inhibits programmed death-1 protein (PD-1) signaling,, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and ITIM domain (TIGIT), indoleamine 2,3-dioxygenase (IDO), or colony stimulating factor 1 receptor (CSF1R).

[0028] In examples, an immune checkpoint inhibitor is a PD-1 inhibitor. In examples, a PD-1 inhibitor is a PD-1 binding agent (e.g., an antibody, an antibody conjugate,

or an antigen-binding fragment thereof). In examples, a PD-1 binding agent is nivolumab, pembrolizumab, TSR-042, PDR-001, tislelizumab (BGB-A317), cemiplimab (REGN2810), LY-3300054, JNJ-63723283, MGA012, BI-754091, IBI-308, camrelizumab (HR-301210), BCD-100, JS-001, CX-072, AMP-514 / MEDI-0680, AGEN-2034, CS1001, TSR-042, Sym-021, PF-06801591, LZM009, KN-035, AB122, genolimzumab (CBT-501), AK 104, or GLS-010, or derivatives thereof. In examples, a PD-1 inhibitor is a PD-L1 or PD-L2 binding agent (e.g., an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In examples, a PD-1 inhibitor is a PD-L1 or PD-L2 binding agent is durvalumab, atezolizumab, avelumab, BGB-A333, SHR-1316, FAZ-053, CK-301, or, PD-L1 millamolecule, or derivatives thereof. In examples, PD-1 inhibitor (e.g., TSR-042) is administered to the subject periodically at a dose of about 500 mg or 1000 mg. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered to the subject periodically at a dose of about 500 mg or 1000 mg. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered to the subject periodically at a dose of about 500 mg. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered to the subject once every 3 weeks. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered for 2, 3, 4, 5, 6, or more cycles. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered for 4 cycles. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered to the subject periodically at a dose of about 1000 mg. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered to the subject once every 6 weeks. In examples, a PD-1 inhibitor (e.g., TSR-042) is administered at a first dose of about 500 mg once every 3 weeks for 4 cycles followed by a second dose of about 1000 mg once every 6 weeks (e.g., until treatment is discontinued).

[0029] In examples, an immune checkpoint inhibitor is a CTLA-4 inhibitor (e.g., an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In examples, a CTLA-4 inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In examples, a CTLA-4 inhibitor is a small molecule. In examples, a CTLA-4 inhibitor is a CTLA-4 binding agent. In examples, a CTLA-4 inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In examples, a CTLA-4 inhibitor is ipilimumab (Yervoy), AGEN1884, or tremelimumab.

[0030] In examples, an immune checkpoint inhibitor is a LAG-3 inhibitor (e.g., an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In examples, a LAG-3 inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a

carbohydrate, a lipid, a metal, or a toxin. In examples, a LAG-3 inhibitor is a small molecule. In examples, a LAG-3 inhibitor is a LAG-3 binding agent. In examples, a LAG-3 inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In examples, a LAG-3 inhibitor is a IMP321, BMS-986016, GSK2831781, Novartis LAG525, or a LAG-3 inhibitor described in WO 2016/126858, WO 2017/019894, or WO 2015/138920, each of which is hereby incorporated by reference in its entirety.

[0031] In examples, an immune checkpoint inhibitor is a TIGIT inhibitor (e.g., an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In examples, a TIGIT inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In examples, a TIGIT inhibitor is small molecule. In examples, a TIGIT inhibitor is a TIGIT binding agent. In examples, a TIGIT inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In examples, a TIGIT inhibitor is MTIG7192A, BMS-986207, or OMP-31M32.

[0032] In examples, an immune checkpoint inhibitor is an IDO inhibitor. In examples, an IDO inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In examples, an IDO inhibitor is small molecule. In examples, an IDO inhibitor is an IDO binding agent. In examples, an IDO inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.

[0033] In examples, an immune checkpoint inhibitor is a CSF1R inhibitor. In examples, a CSF1R inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In examples, a CSF1R inhibitor is small molecule. In examples, a CSF1R inhibitor is a CSF1R binding agent. In examples, a CSF1R inhibitor is an antibody, an antibody conjugate, or an antigen-binding fragment thereof.

[0034] In examples, a method comprises administering a TIM-3 inhibitor (e.g., any anti-TIM-3 antibody agent described herein) with at least two of the immune checkpoint inhibitors. In examples, a method comprises administering a third checkpoint inhibitor. In examples, a method comprises administering a TIM-3 inhibitor with a PD-1 inhibitor, and a LAG-3 inhibitor, such that the subject receives all three. In examples, a method comprises administering a TIM-3 inhibitor with a PD-1 inhibitor, a LAG-3 inhibitor, and a CTLA-4 inhibitor, such that the subject receives all four.

[0035] In examples, a subject has been further administered or will be administered an agent that inhibits poly (ADP-ribose) polymerase (PARP), such that the subject receives treatment with a TIM-3 inhibitor and a PARP inhibitor.

[0036] In examples, a PARP inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin. In examples, a PARP inhibitor is selected from the group consisting of: ABT-767, AZD 2461, BGB-290, BGP 15, CEP 8983, CEP 9722, DR 2313, E7016, E7449, fluzoparib, IMP 4297, INO1001, JPI 289, JPI 547, monoclonal antibody B3-LysPE40 conjugate, MP 124, niraparib, NU 1025, NU 1064, NU 1076, NU1085, olaparib, ONO2231, PD 128763, R 503, R554, rucaparib, SBP 101, SC 101914, simmiparib, talazoparib, veliparib, WW 46, 2-(4-(trifluoromethyl)phenyl)-7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidin-4-ol, and salts or derivatives thereof. In examples, a PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, or veliparib. In examples, a PARP inhibitor is niraparib (e.g., niraparib free base, niraparib tosylate, or niraparib tosylate monohydrate, or any combination thereof).

[0037] In examples, a subject is further administered or will be administered one or more immune checkpoint inhibitors (e.g., a PD-1 inhibitor and/or a LAG-3 inhibitor) such that the subject receives treatment with a TIM-3 inhibitor, a PARP inhibitor (e.g., niraparib), and the one or more immune checkpoint inhibitors. In examples, a subject is administered a TIM-3 inhibitor, a PD-1 inhibitor (e.g., TSR-042) and a PARP inhibitor (e.g., niraparib). In examples, a subject is administered a TIM-3 inhibitor, a PD-1 inhibitor (e.g., TSR-042), a LAG-3 inhibitor, and a PARP inhibitor (e.g., niraparib).

[0038] In examples, a patient has a disorder that is a T-cell dysfunctional disorder.

[0039] In examples, a patient has a disorder that is cancer.

[0040] In examples, a cancer is associated with a high tumor mutation burden (TMB).

[0041] In examples, a cancer is microsatellite stable (MSS).

[0042] In examples a cancer is characterized by microsatellite instability.

[0043] In examples, a cancer has a high microsatellite instability status (MSI-H).

[0044] In examples, a cancer has a low microsatellite instability status (MSI-L).

[0045] In examples, a cancer is associated with high TMB and MSI-H.

[0046] In examples, a cancer is associated with high TMB and MSI-L or MSS. In examples, a cancer is associated with high TMB and MSI-L. In examples, a cancer is associated with high TMB and MSS.

[0047] In examples, a cancer has a defective DNA mismatch repair system.

[0048] In examples, a cancer has a defect in a DNA mismatch repair gene.

[0049] In examples, a cancer is a hypermutated cancer.

[0050] In examples, a cancer has homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0051] In examples, a cancer comprises a mutation in polymerase delta (POLD).

[0052] In examples, a cancer comprises a mutation in polymerase epsilon (POLE).

[0053] In examples, a cancer is adenocarcinoma, endometrial cancer, breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, testicular cancer, primary peritoneal cancer, colon cancer, colorectal cancer, stomach cancer, small intestine cancer, squamous cell carcinoma of the anogenital region (e.g., squamous cell carcinoma of the anus, penis, cervix, vagina, or vulva), soft tissue sarcoma (e.g., leiomyosarcoma), melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, esophageal cancer, head and neck cancer, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer, mesothelioma, Merkel cell carcinoma, sarcoma, glioblastoma, a hematological cancer, multiple myeloma, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma (HL)/primary mediastinal B-cell lymphoma, chronic myelogenous leukemia, acute myeloid leukemia, acute lymphoblastic leukemia, non-Hodgkin's lymphoma, neuroblastoma, a CNS tumor, diffuse intrinsic pontine glioma (DIPG), Ewing's sarcoma, embryonal rhabdomyosarcoma, osteosarcoma, or Wilms tumor. In examples, a cancer is MSS or MSI-L, is characterized by microsatellite instability, is MSI-H, has high TMB, has high TMB and is MSS or MSI-L, has high TMB and is MSI-H, has a defective DNA mismatch repair system, has a defect in a DNA mismatch repair gene, is a hypermutated cancer, is an HRD cancer, comprises a mutation in polymerase delta (POLD) or comprises a mutation in polymerase epsilon (POLE).

[0054] In examples, a cancer is endometrial cancer (e.g., MSI-H or MSS/MSI-L endometrial cancer). In examples, a cancer is a MSI-H cancer comprising a mutation in

POLE or POLD (e.g., a MSI-H non-endometrial cancer comprising a mutation in POLE or POLD). In examples, a cancer is breast cancer (triple negative breast cancer (TNBC)). In examples, a cancer is lung cancer (e.g., non-small cell lung cancer). In examples, a cancer is melanoma. In examples, a cancer is colorectal cancer. In examples, a cancer is squamous cell carcinoma of the anus, squamous cell carcinoma of the penis, squamous cell carcinoma of the cervix, squamous cell carcinoma of the vagina, or squamous cell carcinoma of the vulva.

[0055] In examples, a cancer has homologous recombination repair deficiency/homologous repair deficiency ("HRD"). In examples, a cancer is acute myeloid leukemia. In examples, a cancer is acute lymphoblastic leukemia. In examples, a cancer is non-Hodgkin's lymphoma. In examples, a cancer is Hodgkin's lymphoma. In examples, a cancer is neuroblastoma. In examples, a cancer is a CNS tumor. In examples, a cancer is diffuse intrinsic pontine glioma (DIPG). In examples, a cancer is Ewing's sarcoma. In examples, a cancer is embryonal rhabdomyosarcoma. In examples, a cancer is osteosarcoma. In examples, a cancer is Wilms tumor. In examples, a cancer is a soft tissue sarcoma (e.g., leiomyosarcoma).

[0056] In some examples, a patient has cancer, such as: a non-small cell lung cancer (NSCLC), a hepatocellular cancer, a renal cancer, a melanoma, a cervical cancer, a colorectal cancer, a squamous cell carcinoma of the anogenital region, a head and neck cancer, a triple negative breast cancer, an ovarian cancer or an endometrial cancer. In some examples, a patient has a cancer with microsatellite instability. In some examples, the microsatellite instability is considered high, wherein the instability is significantly higher than that observed in a control cell (e.g., MSI-H status). In some examples, the patient has a solid tumor. In some examples, the patient has an advanced stage solid tumor. In some examples, a patient has an advanced stage solid tumor, such as a non-small cell lung cancer (NSCLC), a hepatocellular cancer, a renal cancer, a melanoma, a cervical cancer, a colorectal cancer, a squamous cell carcinoma of the anogenital region, a head and neck cancer, a triple negative breast cancer, an ovarian cancer or a endometrial cancer. In some examples, a patient has an advanced stage solid tumor with microsatellite instability.

[0057] In some examples, the patient has a hematological cancer. In some examples, the patient has a hematological cancer such as Diffuse large B cell lymphoma ("DLBCL"),

Hodgkin's lymphoma ("HL"), Non-Hodgkin's lymphoma ("NHL"), Follicular lymphoma ("FL"), acute myeloid leukemia ("AML"), acute lymphoblastic leukemia ("ALL"), or Multiple myeloma ("MM"). In some examples, a patient has a hematological cancer with microsatellite instability.

[0058] In some examples, a patient has a cancer characterized by PD-1 and/or PD-L1 expression. In some examples, a cancer has high PD-1 and/or PD-L1 expression (e.g., by high PD-1 and/or high PD-L1 expression). In some example, a cancer characterized by PD-1 and/or PD-L1 expression is a head and neck cancer, a lung cancer (e.g., a non-small cell lung cancer (NSCLC)), a renal cancer, a bladder cancer, a melanoma, Merkel cell carcinoma, a cervical cancer, a vaginal cancer, a vulvar cancer, a uterine cancer, a endometrial cancer, an ovarian cancer, a fallopian tube cancer, a breast cancer, a prostate cancer, a salivary gland tumor, a thymoma, a adrenocortical carcinoma, a esophageal cancer, a gastric cancer, a colorectal cancer, an appendiceal cancer, a urothelial cell carcinoma, or a squamous cell carcinoma (e.g., of the lung; of the anogenital region including anus, penis, cervix, vagina, or vulva; or of the esophagus). In some certain examples, a cancer characterized by PD-1 and/or PD-L1 expression is an anal cancer, a fallopian tube cancer, an ovarian cancer, or a lung cancer.

[0059] In some examples, the patient has a head and neck cancer, a lung cancer (e.g., a non-small cell lung cancer (NSCLC)), a renal cancer, a bladder cancer, a melanoma, Merkel cell carcinoma, a cervical cancer, a vaginal cancer, a vulvar cancer, a uterine cancer, an endometrial cancer, an ovarian cancer, a fallopian tube cancer, a breast cancer, a prostate cancer, a salivary gland tumor, a thymoma, an adrenocortical carcinoma, an esophageal cancer, a gastric cancer, a colorectal cancer, an appendiceal cancer, a urothelial cell carcinoma, or a squamous cell carcinoma.

[0060] In examples, a cancer is an advanced cancer. In examples, a cancer is a metastatic cancer. In examples, a cancer is a MSI-H cancer. In examples, a cancer is a MSS cancer. In examples, a cancer is a POLE-mutant cancer. In examples, a cancer is a POLD-mutant cancer. In examples, a cancer is a high TMB cancer. In examples, a cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0061] In examples, a cancer is a solid tumor. In examples, a solid tumor is advanced. In examples, a solid tumor is a metastatic solid tumor. In examples, a solid

tumor is a MSI-H solid tumor. In examples, a solid tumor is a MSS solid tumor. In examples, a solid tumor is a POLE-mutant solid tumor. In examples, a solid tumor is a POLD-mutant solid tumor. In examples, a solid tumor is a high TMB solid tumor. . In examples, a solid tumor is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0062] In examples, a cancer is a non-endometrial cancer (e.g., a non-endometrial solid tumor). In examples, a non-endometrial cancer is an advanced cancer. In examples, a non-endometrial cancer is a metastatic cancer. In examples, a non-endometrial cancer is a MSI-H cancer. In examples, a non-endometrial cancer is a MSS cancer. In examples, a non-endometrial cancer is a POLE-mutant cancer. In examples, a non-endometrial cancer is a solid tumor (e.g., a MSS solid tumor, a MSI-H solid tumor, a POLD mutant solid tumor, or a POLE-mutant solid tumor). In examples, a non-endometrial cancer is a high TMB cancer. In examples, a non-endometrial cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0063] In examples, a cancer is endometrial cancer (e.g., a solid tumor). In examples, an endometrial cancer is an advanced cancer. In examples, an endometrial cancer is a metastatic cancer. In examples, an endometrial cancer is a MSI-H endometrial cancer. In examples, an endometrial cancer is a MSS endometrial cancer. In examples, an endometrial cancer is a POLE-mutant endometrial cancer. In examples, an endometrial cancer is a POLD-mutant endometrial cancer. In examples, an endometrial cancer is a high TMB endometrial cancer. In examples, an endometrial cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0064] In examples, a cancer is a lung cancer (e.g., a solid tumor). In examples, a lung cancer is an advanced lung cancer. In examples, a lung cancer is a metastatic lung cancer. In examples, a lung cancer is squamous cell carcinoma of the lung. In examples, a lung cancer is small cell lung cancer (SCLC). In examples, a lung cancer is non-small cell lung cancer (NSCLC). In examples, a lung cancer is an ALK-translocated lung cancer (e.g., a lung cancer with a known ALK-translocation). In examples, a lung cancer is an EGFR-mutant lung cancer (e.g., a lung cancer with a known EGFR mutation). In examples, a lung cancer is a MSI-H lung cancer. In examples, a lung cancer is a MSS lung cancer. In examples, a lung cancer is a POLE-mutant lung cancer. In examples, a lung cancer is a

POLD-mutant lung cancer. In examples, a lung cancer is a high TMB lung cancer. In examples, a lung cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0065] In examples, a cancer is a colorectal (CRC) cancer (e.g., a solid tumor). In examples, a colorectal cancer is an advanced colorectal cancer. In examples, a colorectal cancer is a metastatic colorectal cancer. In examples, a colorectal cancer is a MSI-H colorectal cancer. In examples, a colorectal cancer is a MSS colorectal cancer. In examples, a colorectal cancer is a POLE-mutant colorectal cancer. In examples, a colorectal cancer is a POLD-mutant colorectal cancer. In examples, a colorectal cancer is a high TMB colorectal cancer. In examples, a colorectal cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0066] In examples, a cancer is a melanoma. In examples, a melanoma is an advanced melanoma. In examples, a melanoma is a metastatic melanoma. In examples, a melanoma is a MSI-H melanoma. In examples, a melanoma is a MSS melanoma. In examples, a melanoma is a POLE-mutant melanoma. In examples, a melanoma is a POLD-mutant melanoma. In examples, a melanoma is a high TMB melanoma. In examples, a melanoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0067] In examples, a cancer is squamous cell carcinoma of the anogenital region (e.g., of the anus, penis, cervix, vagina, or vulva). In examples, a squamous cell carcinoma of the anogenital region (e.g., of the anus, penis, cervix, vagina, or vulva) is an advanced cancer. In examples, a squamous cell carcinoma of the anogenital region (e.g., of the anus, penis, cervix, vagina, or vulva) is a metastatic cancer. In examples, a squamous cell carcinoma of the anogenital region (e.g., of the anus, penis, cervix, vagina, or vulva) is MSI-H. In examples, a squamous cell carcinoma of the anogenital region (e.g., of the anus, penis, cervix, vagina, or vulva) is MSS. In examples, a lung cancer is a POLE-mutant cancer. In examples, a squamous cell carcinoma of the anogenital region (e.g., of the anus, penis, cervix, vagina, or vulva) is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0068] In examples, a cancer is an ovarian cancer. In examples, an ovarian cancer is an advanced ovarian cancer. In examples, an ovarian cancer is a metastatic ovarian cancer.

In examples, an ovarian cancer is a MSI-H ovarian cancer. In examples, an ovarian cancer is a MSS ovarian cancer. In examples, an ovarian cancer is a POLE-mutant ovarian cancer. In examples, an ovarian cancer is a POLD-mutant ovarian cancer. In examples, an ovarian cancer is a high TMB ovarian cancer. In examples, an ovarian cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD"). In examples, an ovarian cancer is a serous cell ovarian cancer. In examples, an ovarian cancer is a clear cell ovarian cancer.

[0069] In examples, a cancer is a fallopian cancer. In examples, a fallopian cancer is an advanced fallopian cancer. In examples, a fallopian cancer is a metastatic fallopian cancer. In examples, a fallopian cancer is a MSI-H fallopian cancer. In examples, a fallopian cancer is a MSS fallopian cancer. In examples, a fallopian cancer is a POLE-mutant fallopian cancer. In examples, a fallopian cancer is a POLD-mutant fallopian cancer. In examples, a fallopian cancer is a high TMB fallopian cancer. In examples, a fallopian cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD"). In examples, a fallopian cancer is a serous cell fallopian cancer. In examples, a fallopian cancer is a clear cell fallopian cancer.

[0070] In examples, a cancer is a primary peritoneal cancer. In examples, a primary peritoneal cancer is an advanced primary peritoneal cancer. In examples, a primary peritoneal cancer is a metastatic primary peritoneal cancer. In examples, a primary peritoneal cancer is a MSI-H primary peritoneal cancer. In examples, a primary peritoneal cancer is a MSS primary peritoneal cancer. In examples, a primary peritoneal cancer is a POLE-mutant primary peritoneal cancer. In examples, a primary peritoneal cancer is a POLD-mutant primary peritoneal cancer. In examples, a primary peritoneal cancer is a high TMB primary peritoneal cancer. In examples, a primary peritoneal cancer is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD"). In examples, a primary peritoneal cancer is a serous cell primary peritoneal cancer. In examples, a primary peritoneal cancer is a clear cell primary peritoneal cancer.

[0071] In examples, a cancer is acute lymphoblastic leukemia ("ALL"). In examples, acute lymphoblastic leukemia is advanced acute lymphoblastic leukemia. In examples, acute lymphoblastic leukemia is metastatic acute lymphoblastic leukemia. In examples, acute lymphoblastic leukemia is MSI-H acute lymphoblastic leukemia. In

examples, acute lymphoblastic leukemia is MSS acute lymphoblastic leukemia. In examples, acute lymphoblastic leukemia is POLE-mutant acute lymphoblastic leukemia. In examples, acute lymphoblastic leukemia is POLD-mutant acute lymphoblastic leukemia. In examples, an acute lymphoblastic leukemia is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0072] In examples, a cancer is acute myeloid leukemia ("AML"). In examples, acute myeloid leukemia is advanced acute myeloid leukemia. In examples, acute myeloid leukemia is metastatic acute myeloid leukemia. In examples, acute myeloid leukemia is MSI-H acute myeloid leukemia. In examples, acute myeloid leukemia is MSS acute myeloid leukemia. In examples, acute myeloid leukemia is POLE-mutant acute myeloid leukemia. In examples, acute myeloid leukemia is POLD-mutant acute myeloid leukemia. In examples, an acute myeloid leukemia is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0073] In examples, a cancer is non-Hodgkin's lymphoma (NHL). In examples, non-Hodgkin's lymphoma is advanced non-Hodgkin's lymphoma. In examples, non-Hodgkin's lymphoma is metastatic non-Hodgkin's lymphoma. In examples, non-Hodgkin's lymphoma is MSI-H non-Hodgkin's lymphoma. In examples, non-Hodgkin's lymphoma is MSS non-Hodgkin's lymphoma In examples, non-Hodgkin's lymphoma is POLE-mutant non-Hodgkin's lymphoma. In examples, non-Hodgkin's lymphoma is POLD-mutant non-Hodgkin's lymphoma. In examples, non-Hodgkin's lymphoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0074] In examples, a cancer is Hodgkin's lymphoma (HL). In examples, Hodgkin's lymphoma is advanced Hodgkin's lymphoma. In examples, Hodgkin's lymphoma is metastatic Hodgkin's lymphoma. In examples, Hodgkin's lymphoma is MSI-H Hodgkin's lymphoma. In examples, Hodgkin's lymphoma is MSS Hodgkin's lymphoma In examples, Hodgkin's lymphoma is POLE-mutant Hodgkin's lymphoma. In examples, Hodgkin's lymphoma is POLD-mutant Hodgkin's lymphoma. In examples, Hodgkin's lymphoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0075] In examples, a cancer is a neuroblastoma (NB). In examples, a neuroblastoma is an advanced neuroblastoma. In examples, a neuroblastoma is a metastatic

neuroblastoma. In examples, neuroblastoma is a MSI-H neuroblastoma. In examples, a neuroblastoma is a MSS neuroblastoma. In examples, a neuroblastoma is a POLE-mutant neuroblastoma. In examples, a neuroblastoma is a POLD-mutant neuroblastoma. In examples, a neuroblastoma is a high TMB neuroblastoma. In examples, a neuroblastoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0076] In examples, a cancer is a CNS tumor. In examples, a CNS tumor is advanced. In examples, a CNS tumor is a metastatic CNS tumor. In examples, a CNS tumor is a MSI-H CNS tumor. In examples, a CNS tumor is a MSS CNS tumor. In examples, a CNS tumor is a POLE-mutant CNS tumor. In examples, a CNS tumor is a POLD-mutant CNS tumor. In examples, a CNS tumor is a high TMB CNS tumor. . In examples, a CNS tumor is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0077] In examples, a cancer is diffuse intrinsic pontine glioma (DIPG). In examples, a DIPG is an advanced DIPG. In examples, a DIPG is a metastatic DIPG. In examples, DIPG is a MSI-H DIPG. In examples, a DIPG is a MSS DIPG. In examples, a DIPG is a POLE-mutant DIPG. In examples, a DIPG is a POLD-mutant DIPG. In examples, a DIPG is a high TMB DIPG. In examples, a DIPG is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0078] In examples, a cancer is Ewing's sarcoma. In examples, Ewing's sarcoma is an advanced Ewing's sarcoma. In examples, Ewing's sarcoma is a metastatic Ewing's sarcoma. In examples, Ewing's sarcoma is a MSI-H Ewing's sarcoma. In examples, Ewing's sarcoma is a MSS Ewing's sarcoma. In examples, Ewing's sarcoma is a POLE-mutant Ewing's sarcoma. In examples, Ewing's sarcoma is a POLD-mutant Ewing's sarcoma. In examples, Ewing's sarcoma is a high TMB Ewing's sarcoma. In examples, Ewing's sarcoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0079] In examples, a cancer is an embryonal rhabdomyosarcoma (ERS). In examples, an embryonal rhabdomyosarcoma is an advanced embryonal rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is a metastatic embryonal rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is a MSI-H embryonal

rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is a MSS embryonal rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is a POLE-mutant embryonal rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is a POLD-mutant embryonal rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is a high TMB embryonal rhabdomyosarcoma. In examples, an embryonal rhabdomyosarcoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0080] In examples, a cancer is an osteosarcoma (OS). In examples, an osteosarcoma is an advanced osteosarcoma. In examples, an osteosarcoma is a metastatic osteosarcoma. In examples, an osteosarcoma is a MSI-H osteosarcoma. In examples, an osteosarcoma is a MSS osteosarcoma. In examples, an osteosarcoma is a POLE-mutant osteosarcoma. In examples, an osteosarcoma is a POLD-mutant osteosarcoma. In examples, an osteosarcoma is a high TMB osteosarcoma. In examples, an osteosarcoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0081] In examples, a cancer is a soft tissue sarcoma. In examples, a soft tissue sarcoma is an advanced soft tissue sarcoma. In examples, a soft tissue sarcoma is a metastatic soft tissue sarcoma. In examples, a soft tissue sarcoma is a MSI-H soft tissue sarcoma. In examples, a soft tissue sarcoma is a MSS soft tissue sarcoma. In examples, a soft tissue sarcoma is a POLE-mutant soft tissue sarcoma. In examples, a soft tissue sarcoma is a POLD-mutant soft tissue sarcoma. In examples, a soft tissue sarcoma is a high TMB soft tissue sarcoma. In examples, a soft tissue sarcoma is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD"). In examples, a soft tissue sarcoma is leiomyosarcoma.

[0082] In examples, a cancer is Wilms tumor. In examples, Wilms tumor is an advanced Wilms tumor. In examples, Wilms tumor is a metastatic Wilms tumor. In examples, Wilms tumor is a MSI-H Wilms tumor. In examples, Wilms tumor is a MSS Wilms tumor. In examples, Wilms tumor is a POLE-mutant Wilms tumor. In examples, Wilms tumor is a POLD-mutant Wilms tumor. In examples, Wilms tumor is a high TMB Wilms tumor. In examples, Wilms tumor is associated with homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0083] In examples, a subject has previously been treated with one or more different cancer treatment modalities (e.g., one or more of surgery, radiotherapy, chemotherapy, or immunotherapy).

[0084] In examples, a subject has previously been treated with one different cancer treatment modalities (e.g., one or more of surgery, radiotherapy, chemotherapy, or immunotherapy). In examples, a subject has previously been treated with two or more different cancer treatment modalities (e.g., one or more of surgery, radiotherapy, chemotherapy, or immunotherapy). In examples, a subject has been previously treated with a cytotoxic therapy. In examples, a subject has been previously treated with chemotherapy. In examples, a subject has previously been treated with two different cancer treatment modalities (e.g., one or more of surgery, radiotherapy, chemotherapy, or immunotherapy). In examples, a subject has previously been treated with three different cancer treatment modalities (e.g., one or more of surgery, radiotherapy, chemotherapy, or immunotherapy).

[0085] In examples of methods described herein, a method further comprises administering one or more of surgery, a radiotherapy, a chemotherapy, an immunotherapy, an anti-angiogenic agent, or an anti-inflammatory. In examples, a method further comprises administering a chemotherapy.

[0086] In some examples, at least some of the patients in the cancer patient population have previously been treated with chemotherapy (e.g., platinum-based chemotherapy). For example, a patient who has received two lines of cancer treatment can be identified as a 2L cancer patient (e.g., a 2L NSCLC patient). In examples, a patient has received two lines or more lines of cancer treatment (e.g., a 2L+ cancer patient such as a 2L+ endometrial cancer patient). In examples, a patient has not been previously treated with an anti-PD-1 therapy. In examples, a patient previously received at least one line of cancer treatment (e.g., a patient previously received at least one line or at least two lines of cancer treatment). In examples, a patient previously received at least one line of treatment for metastatic cancer (e.g., a patient previously received one or two lines of treatment for metastatic cancer).

[0087] In examples, a subject is resistant to treatment with an agent that inhibits PD-1.

[0088] In examples, a subject is refractory to treatment with an agent that inhibits PD-1.

[0089] In examples, a method described herein sensitizes a subject to treatment with an agent that inhibits PD-1.

[0090] In examples, a subject comprises an exhausted immune cell (e.g., an exhausted immune cell that is an exhausted T cell).

[0091] In examples of methods described herein, a subject is an animal (e.g., a mammal). In examples, a subject is a human. In examples, a subject is a non-human mammal (e.g., mice, rats, rabbits, or non-human primates). Accordingly, methods described herein can be useful in both treatment of humans and in veterinary medicine.

[0092] In examples, a TIM-3 inhibitor is administered intravenously (e.g., by intravenous infusion).

[0093] The present disclosure provides, in some examples, methods of treating cancer in a patient in need thereof, the method comprising administering a composition that delivers an anti-TIM-3 antibody agent.

[0094] In some examples, the patient has not previously been treated with a cancer treatment modality.

[0095] In some examples, the patient has previously been treated with one or more different cancer treatment modalities. In some examples, the patient has previously been treated with one or more of radiotherapy, chemotherapy or immunotherapy. In some examples, the patient has previously been treated with chemotherapy (e.g., platinum-based chemotherapy).

[0096] In some examples, a composition that delivers a TIM-3 inhibitor (e.g., an anti-TIM-3 antibody agent) is administered at a dose of 1, 3 or 10 mg/kg. In some examples, the composition that delivers an anti-TIM-3 antibody agent is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every two weeks. In some examples, the composition that delivers an anti-TIM-3 antibody agent is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every three weeks. In some examples, the composition that delivers an anti-TIM-3 antibody agent is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every four weeks.

[0097] In some examples, a composition that delivers an anti-TIM-3 antibody agent at a fixed dose within a range of about 100 mg to about 1500 mg (e.g., about 100 mg to 1500 mg). In some examples, a composition that delivers an anti-TIM-3 antibody agent at a fixed dose within a range of about 100 mg to about 300 mg, about 300 mg to about 1,000 mg, or about 1000 mg to about 1200 mg. In examples, the fixed dose is about 100 mg. In examples, the

fixed dose is about 300 mg. In examples, the fixed dose is about 500 mg. In examples, the fixed dose is about 900 mg. In examples, the fixed dose is about 1200 mg. In some examples, the composition that delivers an anti-TIM-3 antibody agent is administered according to a regimen that includes a fixed dose every two weeks (Q2W). In some examples, the composition that delivers an anti-TIM-3 antibody agent is administered according to a regimen that includes a fixed dose every three weeks (Q3W). In some examples, the composition that delivers an anti-TIM-3 antibody agent is administered according to a regimen that includes a fixed dose every four weeks (Q4W). In examples, the anti-TIM-3 antibody is administered at the administration interval of once a week (Q1W), once every 2 weeks (Q2W), once every 3 weeks (S3W), once every 4 weeks (Q4W), once every 5 weeks (Q5W), or once every 6 weeks (Q6W). In examples, the anti-TIM-3 antibody is administered for the period of at least 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 weeks. In examples, a dose is administered as a monotherapy (e.g., a therapeutically effective amount of 1200 mg of an anti-TIM-3 antibody administered Q2W or Q3W) or a dose is administered in combination with one or more other therapies. For example, 100 mg, 300 mg, 500 mg, or 900 mg (e.g., 100 mg or 300 mg) of an anti-TIM-3 antibody can be administered in combination with an anti-PD-1 antibody according to regiments described herein (e.g., 500 mg of an anti-PD-1 antibody administered Q3W for four treatment cycles followed by administration of 1000 mg of the anti-PD-1 antibody Q6W until treatment is discontinued (e.g., due to disease progression)).

[0098] In some examples, the composition is administered intravenously. In some examples, the composition is administered by intravenous infusion.

[0099] In some examples, a clinical benefit is a complete response ("CR"), a partial response ("PR") or a stable disease ("SD"). In some examples, a clinical benefit corresponds to at least SD. In some examples, a clinical benefit corresponds to at least a PR. In some examples, a clinical benefit corresponds to a CR. In some examples, at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% or 95% of patients achieve a clinical benefit. In some examples, at least 5% of patients achieve a clinical benefit. In some examples, at least 5% of patients achieve SD. In some examples, at least 5% of patients achieve at least a PR. In some examples, at least 5% of patients achieve CR. In some examples, at least 20% of patients achieve a clinical benefit. In some examples, at least 20% of patients achieve SD.

[00100] In some examples, the clinical benefit (e.g., SD, PR and/or CR) is determined in accordance with Response Evaluation Criteria in Solid Tumors (RECIST). In some examples, the clinical benefit (e.g., SD, PR and/or CR) is determined in accordance RECIST guidelines. In some examples, the clinical benefit (e.g., SD, PR and/or CR) is determined in accordance RECIST guidelines (version 1.1). In some examples, the clinical benefit (e.g., SD, PR and/or CR) is determined in accordance immune-related RECIST (irRECIST) guidelines. In some examples, tumor response can be assessed by either irRECIST or RECIST version 1.1. In some examples, tumor response can be assessed by both irRECIST and RECIST version 1.1. When used herein, the term "RECIST guidelines" can refer to RECIST 1.0, RECIST 1.1 or ir RECIST interchangeably.

[00101] In some examples, the patient is receiving or will receive an additional therapy in combination with the anti-TIM-3 antibody agent. In some examples, the additional therapy is radiotherapy, chemotherapy or immunotherapy. In some examples, the additional therapy includes treatment with a composition that delivers a PD-1 inhibitor (e.g., a PD-1-binding agent) and/or a LAG-3-binding agent. In some examples, the additional PD-1 inhibitor is nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, TSR-042, PDR-001, tislelizumab (BGB-A317), cemiplimab (REGN2810), LY-3300054, JNJ-63723283, MGA012, BI-754091, IBI-308, camrelizumab (HR-301210), BCD-100, JS-001, CX-072, BGB-A333, AMP-514 (MEDI-0680), AGEN-2034, CS1001, Sym-021, SHR-1316, PF-06801591, LZM009, KN-035, AB122, genolimzumab (CBT-501), FAZ-053, CK-301, AK 104, GLS-010, PD-1VR or PD-1FL, or any of the PD-1 antibodies disclosed in WO2014/179664. In some examples, the additional therapy is a PARP inhibitor. In some examples, the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, and veliparib. . In some examples, the PARP inhibitor is niraparib.

[00102] The present disclosure provides, in some examples, methods of treating cancer in a patient in need thereof, the method comprising administering a one or more compositions that deliver an anti-TIM-3 antibody agent in combination with a PD-1-binding agent. In some examples, a patient or patient population is receiving a combination therapy that comprises administration of an anti-TIM-3 antibody agent and a PD-1-binding agent (e.g., an anti-PD-1 antibody).

[00103] In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO: 7 and an immunoglobulin light chain variable domain whose amino acid sequence comprises SEQ ID NO: 2 or SEQ ID NO: 8. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain whose amino acid sequence comprises SEQ ID NO: 3 and an immunoglobulin light chain whose amino acid sequence comprises SEQ ID NO: 4.

[00104] In some examples, a PD-1-binding agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence comprises SEQ ID NO: 11 or SEQ ID NO: 17 and an immunoglobulin light chain variable domain whose amino acid sequence comprises SEQ ID NO: 12 or SEQ ID NO: 18 ("PD-1VR"). In some examples, a PD-1-binding agent comprises an immunoglobulin heavy chain whose amino acid sequence comprises SEQ ID NO: 13 and an immunoglobulin light chain whose amino acid sequence comprises SEQ ID NO: 14 ("PD1-FL").

[00105] In some examples, an anti-TIM-3 antibody agent (e.g., an anti-TIM-3 antibody) is administered at a dose of about 1, 3 or 10 mg/kg. In some examples, an anti-TIM-3 antibody agent is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every two weeks. In some examples, an anti-TIM-3 antibody agent is administered according to a regimen that includes a dose of about 1, 3 or 10 mg/kg every three weeks. In some examples, an anti-TIM-3 antibody agent is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every four weeks. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose within a range of about 100 mg to 1,500 mg. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose within a range of about 300 mg to 1,000 mg, about 100 mg to about 500 mg, about 100 mg to about 1200 mg, or about 1000 mg to about 1500 mg. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose of about 100, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1000 mg, 1100 mg, 1200 mg, 1300 mg, 1400 mg, or 1500 mg. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose of about 100 mg. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose of about 300 mg. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose of about 500 mg. In some examples, an anti-TIM-3 antibody agent is administered at a fixed dose of about 900 mg. In some examples, an anti-TIM-3 antibody agent is administered at a

fixed dose of about 1200 mg. In some examples, an anti-TIM-3 antibody agent is administered according to a regimen that includes a fixed dose every two weeks (Q2W). In some examples, an anti-TIM-3 antibody agent is administered according to a regimen that includes a fixed dose every three weeks (Q3W). In some examples, an anti-TIM-3 antibody agent is administered according to a regimen that includes a fixed dose every four weeks (Q4W).

[00106] In some examples, a therapeutically effective dose is a dose of an anti-TIM-3 antibody of about 100 mg to about 1500 mg such as a dose that is about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, 1200 mg, 1300 mg, 1400 mg, or 1500 mg. In examples, a therapeutically effective dose is about 100 mg (e.g., administered Q2W or Q3W). In examples, a therapeutically effective dose is about 300 mg (e.g., administered Q2W or Q3W). In examples, a therapeutically effective dose is about 500 mg (e.g., administered Q2W or Q3W). In examples, a therapeutically effective dose is about 900 mg (e.g., administered Q2W or Q3W). In examples, a therapeutically effective dose is about 1200 mg (e.g., administered Q2W or Q3W). In examples, the anti-TIM-3 antibody is administered at the administration interval of once a week (Q1W), once every 2 weeks (Q2W), once every 3 weeks (S3W), once every 4 weeks (Q4W), once every 5 weeks (Q5W), or once every 6 weeks (Q6W). In examples, the anti-TIM-3 antibody is administered for the period of at least 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 weeks.

[00107] In examples, a therapeutically effective dose is about 100 mg, and the agent is administered at an administration interval of once every 2 weeks. In examples, a therapeutically effective dose is about 100 mg, and the agent is administered at an administration interval of once every 3 weeks.

[00108] In examples, a therapeutically effective dose is about 300 mg, and the agent is administered at an administration interval of once every 2 weeks. In examples, a therapeutically effective dose is about 300 mg, and the agent is administered at an administration interval of once every 3 weeks.

[00109] In examples, a therapeutically effective dose is about 500 mg, and the agent is administered at an administration interval of once every 2 weeks. In examples, a therapeutically effective dose is about 500 mg, and the agent is administered at an administration interval of once every 3 weeks.

[00110] In examples, a therapeutically effective dose is about 900 mg, and the agent is administered at an administration interval of once every 2 weeks. In examples, a therapeutically effective dose is about 900 mg, and the agent is administered at an administration interval of once every 3 weeks.

[00111] In examples, a therapeutically effective dose is about 1200 mg, and the agent is administered at an administration interval of once every 2 weeks. In examples, a therapeutically effective dose is about 1200 mg, and the agent is administered at an administration interval of once every 3 weeks.

[00112] In examples, a dose is administered as a monotherapy (e.g., a therapeutically effective amount of 1200 mg of an anti-TIM-3 antibody administered Q2W or Q3W) or a dose is administered in combination with one or more other therapies. For example, 100 mg or 300 mg of an anti-TIM-3 antibody can be administered in combination with an anti-PD-1 antibody according to regiments described herein (e.g., 500 mg of an anti-PD-1 antibody administered Q3W for four treatment cycles followed by administration of 1000 mg of the anti-PD-1 antibody Q6W until treatment is discontinued (e.g., due to disease progression)).

[00113] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 0.1, 1, 3 10, or 20 mg/kg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every two weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every three weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1, 3 or 10 mg/kg every four weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) at a dose of 500 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 500 mg every two weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 500 mg every three weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 500 mg every four weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 500 mg every three weeks for at least one treatment cycle (e.g., for at least one, two, three, or four treatment cycles), followed by

administration. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1000 mg every three weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1000 mg every four weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1000 mg every five weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 1000 mg every six weeks. In examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a dose of 500 mg every three weeks for four treatment cycles, followed by administration of a dose of 1000 mg every six weeks until treatment is discontinued (e.g., due to disease progression). In examples, an anti-TIM-3 antibody agent is administered Q2W or Q3W in a dose that is about 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1100, or 1200 mg or in a dose that is about 1-10 mg/kg (e.g, a dose that is about 1, about 3, or about 10 mg/kg). In examples, an anti-TIM-3 antibody agent is administered Q2W or Q3W in a dose that is about 100 mg. In examples, an anti-TIM-3 antibody agent is administered Q2W or Q3W in a dose that is about 300 mg.

[00114] In examples, a PD-1 inhibitor (e.g., any anti-PD-1 antibody described herein) is administered at a first dose of about 500 mg once every 3 weeks for 3, 4, or 5 cycles followed by a second dose of about 1000 mg once every 6 weeks or more (e.g., a second dose of about 1000 mg once every 6 weeks). In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 100 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 300 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 500 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 900 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is administered once every three weeks.

[00115] In examples, a PD-1 inhibitor (e.g., any anti-PD-1 antibody described herein) is administered at a first dose of about 500 mg once every 3 weeks for 3 cycles followed by a second dose of about 1000 mg once every 6 weeks or more (e.g., a second dose of about 1000 mg once every 6 weeks). In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 100 mg. In examples, a therapeutically effective

dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 300 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 500 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 900 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is administered once every three weeks.

[00116] In examples, a PD-1 inhibitor (e.g., any anti-PD-1 antibody described herein) is administered at a first dose of about 500 mg once every 3 weeks for 4 cycles followed by a second dose of about 1000 mg once every 6 weeks or more (e.g., a second dose of about 1000 mg once every 6 weeks). In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 100 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 300 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 500 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 900 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is administered once every three weeks.

[00117] In examples, a PD-1 inhibitor (e.g., any anti-PD-1 antibody described herein) is administered at a first dose of about 500 mg once every 3 weeks for 5 cycles followed by a second dose of about 1000 mg once every 6 weeks or more (e.g., a second dose of about 1000 mg once every 6 weeks). In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 100 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 300 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 500 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is a flat dose about 900 mg. In examples, a therapeutically effective dose of the agent (e.g., an anti-TIM-3 antibody) is administered once every three weeks.

[00118] The present disclosure provides, in some examples, compositions comprising an anti-TIM-3 antibody agent for use in treatment of cancer in a selected cancer patient population. In some examples, an anti-TIM-3 antibody agent comprises a heavy chain comprising three CDRs that have sequences of SEQ ID NOs: 21, 22, or 23. In some examples, an anti-TIM-3 antibody agent comprises a light chain comprising three CDRs that have sequences of SED ID NOs: 24, 25, or 26. In some examples, an anti-TIM-3 antibody agent comprises a heavy

chain comprising three CDRs that have sequences of SEQ ID NOs: 21, 22, or 23; and a light chain comprising three CDRs that have sequences of SED ID NOs: 24, 25, or 26. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO:7. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin light chain variable domain whose amino acid sequence comprises SEQ ID NO: 2 or SEQ ID NO: 8. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain variable domain whose amino acid sequence comprises SEQ ID NO: 1 or SEQ ID NO:7 and an immunoglobulin light chain variable domain whose amino acid sequence comprises SEQ ID NO: 2 or SEQ ID NO: 8. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain whose amino acid sequence comprises SEQ ID NO: 3. In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin light chain whose amino acid sequence comprises SEQ ID NO: 4.In some examples, an anti-TIM-3 antibody agent comprises an immunoglobulin heavy chain whose amino acid sequence comprises SEQ ID NO: 3 and an immunoglobulin light chain whose amino acid sequence comprises SEQ ID NO: 4.

[00119] In some examples, the patients in the cancer patient population each have a tumor. In some examples, the patients in the cancer patient population each have a solid tumor. In some examples, at least some of the patients in the cancer patient population have an advanced stage solid tumor. In some examples, at least some of the patients in the cancer patient population have a metastatic solid tumor. In some examples, the patient has a MSI-H solid tumor. In some examples, the patients in the cancer patient population each have a cancer such as a non-small cell lung cancer (NSCLC), a hepatocellular cancer, a renal cancer, a melanoma, a cervical cancer, a colorectal cancer, a squamous cell carcinoma of the anogenital region (e.g., squamous cell carcinoma of the anus, penis, cervix, vagina, or vulva), a head and neck cancer, a triple negative breast cancer, an ovarian cancer or a endometrial cancer.

[00120] In examples, the patient has a lung cancer (e.g., non-small cell lung cancer (NSCLC). In examples, the patient has a melanoma.

[00121] In some examples, the patient has a cancer associated with a POLE (DNA polymerase epsilon) or a POLD (DNA polymerase delta) mutation. In some examples, the POLE or POLD mutation is in an exonuclease domain. In some examples, the POLE or POLD mutation is a germline mutation. In some examples, the POLE or POLD mutation is

a sporadic mutation. In some examples, a method described herein further comprises a step of first identifying the patient having the cancer with the POLE or POLD mutation. In some examples, a POLE or POLD mutation is identified using sequencing.

[00122] In some examples, the patients in the cancer patient population each have a cancer with microsatellite instability. In some examples, the microsatellite instability is considered high, wherein the instability is significantly higher than that observed in a control cell (e.g., MSI-H status). In some examples, the microsatellite instability is MSI-Low (MSI-L). In some examples, the microsatellite instability is microsatellite stable (e.g., MSS status). In some examples, a patient has an advanced stage solid tumor with microsatellite instability.

[00123] In some examples, the patients in the cancer patient population each have a hematological cancer. In some examples, the patients in the cancer patient population each have a hematological cancer such as Diffuse large B cell lymphoma ("DLBCL"), Hodgkin's lymphoma ("HL"), Non-Hodgkin's lymphoma ("NHL"), Follicular lymphoma ("FL"), acute myeloid leukemia ("AML"), acute lymphoblastic leukemia ("ALL"), or Multiple myeloma ("MM"). In some examples, the patients in the cancer patient population each have a hematological cancer with microsatellite instability.

[00124] In some examples, at least some of the patients in the cancer patient population have previously been treated with one or more different cancer treatment modalities. In some examples, at least some of the patients in the cancer patient population have previously been treated with one or more of radiotherapy, chemotherapy or immunotherapy. In some examples, at least some of the patients in the cancer patient population have previously been treated with chemotherapy (e.g., platinum-based chemotherapy).

[00125] In some examples, at least some of the patients in the cancer patient population have not previously been treated with one or more different cancer treatment modalities.

[00126] The present disclosure provides, in some examples, a combination therapy for use in treatment of cancer in a selected cancer patient population, wherein the combination therapy comprises administering an anti-TIM-3 antibody agent and a PD-1-binding agent.

BRIEF DESCRIPTION OF THE DRAWINGS

[00127] **Figure 1** depicts a schematic illustration, not to scale, of enhancement of immune cell activation by anti-TIM-3 and anti-PD1.

CLAIMS

What is claimed is

1. Use of a T Cell Immunoglobulin and Mucin Protein 3 (TIM-3) binding agent in the manufacture of a medicament for treating cancer in a human, wherein the TIM-3 binding agent is to be administered at a flat dose of between 100 mg and 1500 mg.
2. The use of claim 1, wherein the TIM-3 binding agent is to be administered at a flat dose of about 100 mg, 300 mg or 900 mg.
3. The use of claim 1 or claim 2, wherein the TIM-3 binding agent is to be administered once every three weeks (Q3W).
4. The use of claim 3, wherein the TIM-3 binding agent is to be administered at a dose of about 300 mg once every three weeks (Q3W).
5. The use of any of the preceding claims, wherein the TIM-3 binding agent is an antibody, an antibody conjugate, or an antigen binding fragment thereof.
6. The use of any of the preceding claims, wherein the TIM-3 binding agent comprises a heavy chain variable region with three CDR sequences of SEQ ID NOs: 21 (HCDR1), 22 (HCDR2) and 23 (HCDR3), and a light chain variable region with three CDR sequences of SEQ ID NOs: 24 (LCDR1), 25 (LCDR2) and 26 (LCDR3).
7. The use of claim 6, wherein the TIM-3 binding agent comprises an immunoglobulin heavy chain variable domain comprising an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:1 or SEQ ID NO:7 and/or an immunoglobulin light chain comprising an amino acid sequence having at least about 90%, 91% 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:2 or SEQ ID NO:8.
8. The use of claim 7, wherein the TIM-3 binding agent is an immunoglobulin G4 (IgG4) humanized monoclonal antibody.
9. The use of claim 7 or claim 8, wherein the TIM-3 binding agent comprises an immunoglobulin heavy chain comprising an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:3 and/or an immunoglobulin light chain comprising an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% sequence identity to SEQ ID NO:4.

10. The use of any of the preceding claims, wherein the TIM-3 binding agent is to be administered intravenously, optionally by intravenous infusion.
11. The use of any of the preceding claims, wherein the cancer is a solid tumour, optionally an advanced stage solid tumour.
12. The use of any of the preceding claims, wherein the cancer is:
    i. a cancer associated with a high tumour mutation burden (TMB);
    ii. a cancer that is microsatellite stable (MSS);
    iii. a cancer that is characterized by microsatellite instability;
    iv. a cancer that has a high microsatellite instability status (MSI-H);
    v. a cancer that has a low microsatellite instability status (MSI-L);
    vi. a cancer associated with high TMB and MSI-H;
    vii. a cancer associated with high TMB and MSI-L or MSS;
    viii. a cancer that has a defective DNA mismatch repair system;
    ix. a cancer that has a defect in a DNA mismatch repair gene;
    x. a hypermutated cancer;
    xi. a cancer comprising a mutation in polymerase delta (POLD);
    xii. a cancer comprising a mutation in polymerase epsilon (POLE);
    xiii. a cancer that has homologous recombination repair deficiency/homologous repair deficiency (HRD).
    xiv. adenocarcinoma, endometrial cancer, breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, testicular cancer, primary peritoneal cancer, colon cancer, colorectal cancer, stomach cancer, small intestine cancer, squamous cell carcinoma of the anus, squamous cell carcinoma of the penis, squamous cell carcinoma of the cervix, squamous cell carcinoma of the vagina, squamous cell carcinoma of the vulva, soft tissue sarcoma, melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, oesophageal cancer, head and neck cancer, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer, mesothelioma, Merkel cell carcinoma, sarcoma, glioblastoma, a haematological cancer, multiple myeloma, B-cell lymphoma, T-

cell lymphoma, Hodgkin's lymphoma/primary mediastinal B-cell lymphoma, chronic myelogenous leukaemia, acute myeloid leukaemia, non-Hodgkin's lymphoma, neuroblastoma, a CNS tumour, diffuse intrinsic pontine glioma (DIPG), Ewing's sarcoma, embryonal rhabdomyosarcoma, osteosarcoma, or Wilms tumour; or

xv. a cancer of xiv) wherein the cancer is MSS or MSI-L, is characterized by microsatellite instability, is MSI-H, has high TMB, has high TMB and is MSS or MSI-L, has high TMB and is MSI-H, has a defective DNA mismatch repair system, has a defect in a DNA mismatch repair gene, is a hypermutated cancer, is an HRD cancer, comprises a mutation in polymerase delta (POLD), or comprises a mutation in polymerase epsilon (POLE).

13. The use of any of the preceding claims, wherein the human has been administered or is to be administered an immune checkpoint inhibitor or an agent that inhibits poly (ADP-ribose) polymerase (PARP).
14. The use of any of the preceding claims, wherein the human is resistant or refractory to treatment with a PD-1 inhibitor.
15. The use of any of the preceding claims, wherein the human has previously been treated with one or more different cancer modalities, optionally one or more of surgery, radiotherapy, chemotherapy, or immunotherapy.