METHODS OF TREATING CANCER WITH ANTI-PD-1 ANTIBODIES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims benefit of U.S. Provisional Application No. 62/444,336, filed January 9, 2017, U.S. Provisional Application No. 62/477,423, filed March 27, 2017, U.S. Provisional Application No. 62/491,220, filed April 27, 2017, and U.S. Provisional Application No. 62/556,386, filed September 9, 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-006 SEQ LIST_ST25" that was generated on January 8, 2018, and is 14,555 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 anti-programmed death-1 protein (PD-1) (e.g., PD-1 binding agents) are useful for treating disorders such as cancer.

[0004a] In one aspect, the present disclosure refers to a use of a therapeutically effective dose of an (IgG4) humanized monoclonal agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) antibody signaling in the manufacture of a medicament for treating a ~~disorder~~ cancer in a ~~subject~~human, wherein the therapeutically effective dose is~~:~~ ~~about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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 once every 3 weeks (Q3W) for 4 cycles, followed by a second dose of~~; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg~~ once every 6 weeks (Q6W), wherein the antibody comprises an immunoglobulin heavy chain whose amino acid comprises SEQ ID NO:3 and an immunoglobulin light chain whose amino acid comprises SEQ ID NO:4.

~~**[0004b]** In another aspect, the present disclosure refers to use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of a medicament for increasing T cell activation of T cell effector function in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

~~**[0004c]** In another aspect, the present disclosure refers to use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of a medicament for reducing tumors or inhibiting the growth of tumor cells in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

~~**[0004d]** In another aspect, the present disclosure refers to use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of a medicament for inducing an immune response in a subject, wherein~~

~~the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~**~~[0004e]~~** ~~In another aspect, the present disclosure refers to use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of medicament for enhancing an immune response of increasing the activity of an immune cell in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

[0005] In examples, a PD-1 inhibitor is a PD-1 binding agent. In examples, a PD-1 binding agent is an antibody, an antibody conjugate, or an antigen-binding fragment thereof. In examples, a PD-1 binding agent is an antibody agent (i.e., an anti- PD-1 antibody agent).

[0006] In examples, a PD-1 binding agent is an anti-PD-1 antibody. In examples, a PD-1 binding agent comprises a heavy chain variable region with one or more CDR sequences having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 9, 10, or 11. In examples, a PD-1 binding agent comprises a heavy chain variable region with two or three CDR sequences having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 9, 10, or 11.

[0007] In examples, a PD-1 binding agent comprises a light chain variable region with one or more CDR sequences having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 12, 13, and 14. In examples, a PD-1 binding agent comprises a light chain variable region with two or three

CDR sequences having at least about 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 12, 13, and 14.

[0008] In some examples, a PD-1-binding agent comprises a heavy chain variable region with one or more CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one or more CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding agent comprises a heavy chain variable region with two or more CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with two or more CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding agent comprises a heavy chain variable region with three CDRs that have sequences of SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with three CDRs that have sequences of SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding agent comprises a heavy chain variable region with three CDRs that have sequences of SEQ ID NOs: 9, 10, and 11 and a light chain variable region with three CDRs that have sequences of SEQ ID NOs: 12, 13, and 14.

[0009] In some examples, a PD-1-binding agent comprises an immunoglobulin heavy chain variable domain comprising an 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 some examples, a PD-1-binding agent comprises an immunoglobulin heavy chain variable domain comprising an 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. In some examples, a PD-1-binding agent comprises an immunoglobulin heavy chain variable domain comprising an 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: 7.

[0010] In some examples, a PD-1-binding agent comprises an immunoglobulin light chain variable domain comprising an 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, a PD-1-binding agent comprises an immunoglobulin light chain variable domain comprising an 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. In some examples, a PD-1-binding agent comprises an immunoglobulin light chain variable domain comprising an 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: 8.

[0011] In some examples, a PD-1-binding 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.

[0012] In some examples, a PD-1-binding agent comprises an immunoglobulin heavy chain comprising an 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: 3.

[0013] In some examples, a PD-1-binding agent comprises an immunoglobulin light chain comprising an 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: 4.

[0014] In some examples, a PD-1-binding 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.

[0015] The PD-1 binding agents can be any PD-1 binding agent known in the art. In some examples, a PD-1-binding agent 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, or GLS-010, or any of the PD-1 antibodies disclosed in WO2014/179664.

[0016] In some examples, a PD-1-binding agent (e.g., anti-PD-1 antibody agent) binds an epitope of PD-1 which blocks the binding of PD-1 to any one or more of its putative ligands. In some examples, a PD-1-binding agent (e.g., anti-PD-1 antibody agent) binds an epitope of PD-1 which blocks the binding of PD-1 to two or more of its putative ligands. In a some examples, a PD-1-binding agent (e.g., anti-PD-1 antibody agent) binds an epitope of a PD-1 protein which blocks the binding of PD-1 to PD-Ll and/or PD-L2. PD-1-binding agents (e.g., anti-PD-1 antibody agents) of the present disclosure may comprise a heavy chain constant region (F_c) of any suitable class. In some examples, a PD-1-binding agent (e.g., anti-PD-1 antibody agent) comprises a heavy chain constant region that is based upon wild-type IgGl, IgG2, or IgG4 antibodies, or variants thereof.

[0017] The present disclosure provides methods of treating a disorder in a subject comprising administering a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling. In examples, a therapeutically

effective dose is: about 1, 3 or 10 mg/kg. In examples, a therapeutically effective dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). 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 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a therapeutically effective dose is about 1000 mg. In examples, a PD-1 inhibitor is any PD-1 binding agent described herein (e.g., any anti-PD-1 antibody described herein).

[0018] The present disclosure provides methods of increasing T cell activation or T cell effector function in a subject, which method comprises administering a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling. In examples, a therapeutically effective dose is: about 1, 3 or 10 mg/kg. In examples, a therapeutically effective dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). 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 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a therapeutically effective dose is about 1000 mg. In examples, a PD-1 inhibitor is any PD-1 binding agent described herein (e.g., any anti-PD-1 antibody described herein).

[0019] The present disclosure provides methods of reducing tumors or inhibiting the growth of tumor cells in a subject, which method comprises administering a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling. In examples, a therapeutically effective dose is: about 1, 3 or 10 mg/kg. In

examples, a therapeutically effective dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). 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 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a therapeutically effective dose is about 1000 mg. In examples, a PD-1 inhibitor is any PD-1 binding agent described herein (e.g., any anti-PD-1 antibody described herein).

[0020] The present disclosure provides methods of inducing an immune response in a subject, which method comprises administering a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling. In examples, a therapeutically effective dose is: about 1, 3 or 10 mg/kg. In examples, a therapeutically effective dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). 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 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a therapeutically effective dose is about 1000 mg. In examples, a PD-1 inhibitor is any PD-1 binding agent described herein (e.g., any anti-PD-1 antibody described herein).

[0021] The present disclosure provides methods of enhancing an immune response or increasing the activity of an immune cell in a subject, which method comprises administering a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) 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. In examples, a therapeutically effective dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). 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 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a therapeutically effective dose is about 1000 mg. In examples, a PD-1 inhibitor is any PD-1 binding agent described herein (e.g., any anti-PD-1 antibody described herein).

[0022] The present disclosure provides methods of treating cancer that include administering compositions that deliver particular PD-1-binding agents. In examples, a PD-1 binding agent in administered in an amount that is about 1, 3 or 10 mg/kg. In examples, a PD-1 binding agent in administered in an amount that is about 100 - 2000 mg (e.g., about 100 mg; about 200 mg; about 300 mg; about 400 mg; about 500 mg; about 600 mg; about 700 mg about 800 mg; about 900 mg about 1000 mg; about 1100 mg; about 1200 mg; about 1300 mg; about 1400 mg; about 1500 mg; about 1600 mg; about 1700 mg; about 1800 mg; about 1900 mg; or about 2000 mg). In examples, a PD-1 binding agent in administered in an amount that is about 1 mg/kg. In examples, a PD-1 binding agent in administered in an amount that is about 3 mg/kg. In examples, a PD-1 binding agent in administered in an amount that is about 10 mg/kg. In examples, a PD-1 binding agent in administered in an amount that is about 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a PD-1 binding agent in administered in an amount that is about 1000 mg. In examples, a PD-1 inhibitor is any PD-1 binding agent described herein (e.g., any anti-PD-1 antibody described herein).

[0023] The present disclosure provides methods of treating cancer comprising administering to a patient in need of treatment an anti-programmed death-1 protein (PD-1) antibody at a therapeutically effective dose at an administration interval for a period sufficient to achieve clinical benefit. In examples, an anti-PD-1 antibody comprises a heavy

chain variable region comprising CDR sequences of SEQ ID NOs: 9, 10, and 11 and a light chain variable region comprising CDR sequences of SEQ ID NOs: 12, 13, and 14. In examples, an anti-PD-1 antibody 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 examples, an anti-PD-1 antibody comprises an immunoglobulin heavy chain polypeptide whose amino acid sequence comprises SEQ ID NO:3 and/or an immunoglobulin light chain polypeptide whose amino acid sequence comprises SEQ ID NO:4. In examples, a therapeutically effective dose is: about 1, 3 or 10 mg/kg. In examples, a therapeutically effective dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). 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 500 mg. In examples, a therapeutically effective dose is about 800 mg. In examples, a therapeutically effective dose is about 1000 mg.

[0024] The present disclosure provides methods of treating cancer comprising administering to a patient in need of treatment an anti-programmed death-1 protein (PD-1) antibody at a first dose at a first interval for a first period; and administering to the patient the anti-PD-1 antibody at a second dose at a second interval for a second period. In examples, an anti-PD-1 antibody comprises a heavy chain variable region comprising CDR sequences of SEQ ID NOs: 9, 10, and 11 and a light chain variable region comprising CDR sequences of SEQ ID NOs: 12, 13, and 14. In examples, an anti-PD-1 antibody 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 examples, an anti-PD-1 antibody comprises an immunoglobulin heavy chain polypeptide whose amino acid sequence comprises SEQ ID NO:3 and/or an immunoglobulin light chain polypeptide whose amino acid sequence comprises SEQ ID NO:4. In examples, a dose is: about 1, 3 or 10 mg/kg. In

examples, a dose is a flat dose of about 100 - 2000 mg (e.g., 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; or a flat dose about 2000 mg). In examples, a therapeutically effective dose is about 1 mg/kg. In examples, a dose is about 3 mg/kg. In examples, a dose is about 10 mg/kg. In examples, a therapeutically effective dose is a flat dose about 500 mg. In examples, a therapeutically effective dose is a flat dose about 800 mg. In examples, a therapeutically effective dose is about 1000 mg. In examples, the first dose and second dose are different. In examples, the first dose is about 500 mg and the second dose is about 1000 mg. In examples, the first interval and the second interval are different. In examples, the first interval is once every three weeks and the second interval is once every six weeks. In examples, anti-PD-1 antibody is administered at the first dose of 500 mg once every three weeks for the first period of 2-6 dosing cycles (e.g., the first 3, 4, or 5 dosing cycles), and at the second dose of 1000 mg once every six weeks until therapy is discontinued (e.g., due to disease progression, an adverse event, or as determined by a physician). In examples, anti-PD-1 antibody is administered at the first dose of 500 mg once every three weeks for the first three dosing cycles, and at the second dose of 1000 mg once every six weeks or more until therapy is discontinued (e.g., due to disease progression, an adverse event, or as determined by a physician). In examples, anti-PD-1 antibody is administered at the first dose of 500 mg once every three weeks for the first four dosing cycles, and at the second dose of 1000 mg once every six weeks or more until therapy is discontinued (e.g., due to disease progression, an adverse event, or as determined by a physician). In examples, anti-PD-1 antibody is administered at the first dose of 500 mg once every three weeks for the first five dosing cycles, and at the second dose of 1000 mg once every six weeks or more until therapy is discontinued (e.g., due to disease progression, an adverse event, or as determined by a physician). In examples, the second dose is administered once every six weeks.

[0025] In any of the methods described herein, a therapeutically effective dose is about 1 mg/kg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 3 mg/kg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 10 mg/kg of a PD-1 binding agent. In examples, a PD-1 binding agent is any anti-PD-1 antibody described herein.

[0026] In any of the methods described herein, a therapeutically effective dose is about 100 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 200 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 300 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 400 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 500 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 600 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 700 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 800 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 900 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1000 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1100 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1200 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1300 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1400 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1500 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1600 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1700 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1800 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 1900 mg of a PD-1 binding agent. In any of the methods described herein, a therapeutically effective dose is about 2000 mg of a PD-1 binding agent. In examples, a PD-1 binding agent is any anti-PD-1 antibody described herein.

[0027] In examples, a PD-1 binding agent 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 PD-1 binding agent is administered at an administration interval (or treatment cycle) of once a week (Q1W). In examples, a PD-1 binding agent is administered at an administration interval (or treatment cycle) of once every 2 weeks (Q2W). In examples,

a PD-1 binding agent is administered at an administration interval (or treatment cycle) of once every three weeks (Q3W). In examples, a PD-1 binding agent is administered at an administration interval (or treatment cycle) of once every 4 weeks (Q4W). In examples, a PD-1 binding agent is administered at an administration interval (or treatment cycle) of once every 5 weeks (Q5W). In examples, a PD-1 binding agent is administered at an administration interval (or treatment cycle) of once every 6 weeks (Q6W). In examples, a PD-1 binding agent 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 PD-1 binding agent 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 PD-1 binding agent is any anti-PD-1 antibody described herein.

[0028] In examples, a PD-1 binding agent 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 PD-1 binding agent 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 PD-1 binding agent is administered for a longer period to maintain clinical benefit. In examples, a PD-1 binding agent is any anti-PD-1 antibody described herein.

[0029] In examples, a PD-1 binding agent is administered periodically to a subject at a dose of about 500 mg or about 1000 mg. In examples, a PD-1 binding agent is administered periodically to a subject at a dose of about 500 mg (e.g., once every three weeks (Q3W) and/or for 2, 3, 4, 5, 6, or more cycles). In examples, a PD-1 binding agent is administered periodically to a subject at a dose of about 1000 mg (e.g., once every three weeks (Q3W) and/or for 2, 3, 4, 5, 6, or more cycles). In examples, a PD-1 binding agent is administered to a subject at a dose of about 500 mg according once every three weeks (Q3W) for 3 cycles. In examples, a PD-1 binding agent is administered to a subject at a dose of about 500 mg according once every three weeks (Q3W) for 4 cycles. In examples, a PD-1 binding agent is administered to a subject at a dose of about 500 mg according once every three weeks (Q3W) for 5 cycles. In examples, a PD-1 binding agent is administered to a subject at a dose of

about 1000 mg according once every six weeks or more (Q3W). In examples, a PD-1 binding agent is administered to a subject at a dose of about 1000 mg according once every six weeks (Q3W). In examples, a PD-1 binding agent 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., until treatment is discontinued). In examples, a PD-1 binding agent 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). In examples, a PD-1 binding agent 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., until treatment is discontinued). In examples, a second dose is of about 1000 mg once every six weeks (e.g., until treatment is discontinued). In examples, a PD-1 binding agent is any anti-PD-1 antibody described herein.

[0030] In examples, a subject has been further administered or will be administered a further therapeutic agent, such that the subject receives a PD-1 binding agent and a further therapeutic agent (e.g., one, two, three, four, or more further therapeutic agents). In examples, a PD-1 binding agent is any anti-PD-1 antibody described herein.

[0031] In examples, a subject has been further administered or will be administered an immune checkpoint inhibitor, such that the subject receives a PD-1 binding agent and an immune checkpoint inhibitor. That is, a subject can be administered a PD-1 binding agent in combination with at least one immune checkpoint inhibitor. In examples, a PD-1 binding agent is any anti-PD-1 antibody described herein.

[0032] In examples, an immune 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.

[0033] In examples, an immune checkpoint inhibitor is an agent that inhibits T cell immunoglobulin and mucin protein 3 (TIM-3), 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).

[0034] In examples, an immune checkpoint inhibitor is a TIM-3 inhibitor. In examples, a TIM-3 inhibitor is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, a toxin, or a binding agent. In examples, a TIM-3 inhibitor is a TIM-3 binding agent (e.g., an antibody, an antibody conjugate, or an antigen-binding fragment thereof). In examples, a TIM-3 inhibitor is a TIM-3 inhibitor described in WO 2016/161270, which is hereby incorporated by reference in its entirety. In examples, a TIM-3 inhibitor is TSR-022. For example, a TIM-3 inhibitor (e.g., TSR-022) can be administered in a dose of about 1, 3 or 10 mg/kg (e.g., about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg) or a flat dose between about 100 - 1500 mg (e.g., 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).

[0035] 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.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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.

[0040] 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 PD-1 binding agent and a PARP inhibitor.

[0041] 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).

[0042] In examples, a subject is further administered or will be administered one or more immune checkpoint inhibitors (e.g., a TIM-3 inhibitor and/or a LAG-3 inhibitor) such that the subject receives treatment with a PD-1 binding agent, a PARP inhibitor (e.g., niraparib), and the one or more immune checkpoint inhibitors. In examples, a subject is administered a PD-1 binding agent, a PARP inhibitor (e.g., niraparib), and a TIM-3 inhibitor. In examples, a

subject is administered a PD-1 binding agent, a PARP inhibitor (e.g., niraparib), and a LAG-3 inhibitor. In examples, a subject is administered a PD-1 binding agent, a PARP inhibitor (e.g., niraparib), a TIM-3 inhibitor, and a LAG-3 inhibitor.

[0043] In examples, a therapeutic agent (e.g., a PD-1 binding agent, an immune checkpoint inhibitor, or a PARP 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).

[0044] 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 10% of patients achieve a clinical benefit. In some examples, at least 10% of patients achieve SD. In some examples, at least 10% of patients achieve at least a PR. In some examples, at least 20% of patients achieve a clinical benefit. In some examples, at least 20% of patients achieve SD.

[0045] 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.

[0046] In examples, a patient has a disorder that is a T-cell dysfunctional disorder.

[0047] In examples, a patient has a disorder that is cancer.

[0048] In examples, a cancer is associated with a high tumor mutation burden (TMB).

[0049] In examples, a cancer is microsatellite stable (MSS).

[0050] In examples a cancer is characterized by microsatellite instability.

[0051] In examples, a cancer has a high microsatellite instability status (MSI-H).

[0052] In examples, a cancer has a low microsatellite instability status (MSI-L).

[0053] In examples, a cancer is associated with high TMB and MSI-H.

[0054] 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.

[0055] In examples, a cancer has a defective DNA mismatch repair system.

[0056] In examples, a cancer has a defect in a DNA mismatch repair gene.

[0057] In examples, a cancer is a hypermutated cancer.

[0058] In examples, a cancer has homologous recombination repair deficiency/homologous repair deficiency ("HRD").

[0059] In examples, a cancer comprises a mutation in polymerase delta (POLD).

[0060] In examples, a cancer comprises a mutation in polymerase epsilon (POLE).

[0061] 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 (e.g., 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.

[0062] 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/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).

[0063] 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).

[0064] In some examples, a patient has cancer, such as 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 patient has an anal cancer, a fallopian tube cancer, an ovarian cancer, or a lung cancer. In some certain examples, a patient has a cancer of the anus. In some certain examples, a patient has a cancer of the fallopian tube(s). In some certain examples, a patient has an ovarian cancer. In some certain examples, a patient has a lung cancer.

[0065] 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 microsatellite instability is MSI-Low. In some examples, the microsatellite instability is microsatellite stable (e.g., MSS status). In some examples, a cancer with

microsatellite instability 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 with microsatellite instability is an anal cancer, a fallopian tube cancer, an ovarian cancer, or a lung cancer. In some certain examples, a patient has an endometrial cancer with microsatellite instability. In some examples, a patient has an endometrial cancer that is microsatellite stable (MSS).

[0066] 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.

[0067] 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”).

[0068] 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").

[0069] 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").

[0070] 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").

[0071] 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").

[0072] 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").

[0073] 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").

[0074] 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").

[0075] 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.

[0076] 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.

[0077] 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.

[0078] 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").

[0079] 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").

[0080] 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").

[0081] 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").

[0082] 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").

[0083] 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").

[0084] 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").

[0085] 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").

[0086] 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").

[0087] 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").

[0088] 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.

[0089] 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").

[0090] 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). 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).

[0091] 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.

[0092] In examples, a subject is resistant to treatment with an agent that inhibits PD-1.

[0093] In examples, a subject is refractory to treatment with an agent that inhibits PD-1.

[0094] In examples, a method described herein sensitizes a subject to treatment with an agent that inhibits PD-1.

[0095] In examples, a subject comprises an exhausted immune cell (e.g., an exhausted immune cell that is an exhausted T cell).

[0096] 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.

[0097] In examples, a PD-1 binding agent (e.g., any anti-PD-1 antibody) is administered intravenously (e.g., by intravenous infusion).

[0098] The present disclosure also provides, in some examples, methods of treating cancer that comprises administering to a patient in need of treatment an anti-programmed death-1 protein (PD-1) antibody at a therapeutically effective dose at an administration interval for a period sufficient to achieve clinical benefit. In examples, the anti-PD-1 antibody comprises a heavy chain variable region comprising CDR sequences of SEQ ID NOs: 9, 10, and 11 and a light chain variable region comprising CDR sequences of SEQ ID NOs: 12, 13, and 14. In examples, the heavy chain variable region comprises SEQ ID NO: 1 and the light chain variable domain comprises SEQ ID NO: 2. In examples, the heavy chain variable region comprises SEQ ID NO:7 and the light chain variable region comprises SEQ ID NO:8. In examples, the heavy chain variable region comprises SEQ ID NO: 3 and the light chain variable region comprises SEQ ID NO: 4.

[0099] 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 a PD-1-binding agent according to a regimen demonstrated to achieve a response rate in relevant patient population such that no more than 50% to 80% of patients show progressive disease after 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 weeks following initiation of treatment. In some examples, no more than 80% of patients show progressive disease after at least 10 weeks following initiation of treatment.

[00100] In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00101] 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 a PD-1-binding agent sufficient to achieve an average PD-1 receptor occupancy of at least about 50% to about 90% after 1, 2, 3, 4, or 5 days following a single dose of the composition. In some examples, administration of a composition that delivers a PD-1-binding agent is sufficient to achieve an average PD-1 receptor occupancy of at least 85% after 3 days following a single dose of the composition. In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00102] 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 a PD-1-binding agent sufficient to achieve an average stimulation ratio of at least 1 in a functional PD-1 receptor occupancy assay after 3 days following a single dose of the PD-1-binding agent. In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00103] 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 a PD-1-binding agent sufficient to achieve an average PD-1 receptor occupancy of at least 75% over a first period of time (e.g., about 15 days to about 60 days; in some examples about 29

days) following a single dose of the PD-1-binding agent. In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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] 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 a PD-1-binding agent sufficient to achieve an average stimulation ratio of at least 1 in a functional PD-1 receptor occupancy assay over a first period of time (e.g., about 15 days to about 60 days; in some examples about 29 days) following a single dose of the PD-1-binding agent. In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00105] In some examples, a patient for treatment with a composition for delivering a PD-1 binding agent has a tumor. 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 a metastatic solid tumor.

[00106] 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.

[00107] In some examples, the patient has an advanced stage cancer, including an advanced stage head and neck cancer, lung cancer (e.g., non-small cell lung cancer (NSCLC)), renal cancer, bladder cancer, melanoma, Merkel cell carcinoma, cervical cancer, vaginal cancer, vulvar cancer, uterine cancer, endometrial cancer, ovarian cancer, fallopian tube cancer, breast cancer, prostate cancer, salivary gland tumor, thymoma, adrenocortical carcinoma, esophageal cancer, gastric cancer, colorectal cancer, urothelial cell carcinoma, or 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 patient has an advanced stage anal cancer, fallopian tube cancer, ovarian cancer, breast cancer, endometrial cancer, or lung cancer. In some examples, the patient has an advanced stage cancer such as an advanced stage endometrial cancer, triple negative breast cancer, ovarian cancer, non-small cell lung cancer, squamous cell carcinoma of the lung, or squamous cell carcinoma of the anogenital region (e.g., squamous cell carcinoma of the anus, penis, cervix, vagina, or vulva).

[00108] 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.

[00109] In some examples, a patient has a cancer with microsatellite instability (e.g., MSI-H status). In some examples, the microsatellite instability is MSI-Low. In some examples, the microsatellite instability is microsatellite stable (e.g., MSS status). In some examples, the patient has endometrial cancer. In some examples, a patient has an endometrial cancer with microsatellite instability. In some examples, a patient has an advanced stage cancer with microsatellite instability. In some examples, an advanced stage cancer with microsatellite instability is an endometrial cancer, a triple negative breast cancer, an ovarian cancer, a non-small cell lung cancer, a squamous cell carcinoma of the lung, or a squamous cell carcinoma of the anogenital region (e.g., squamous cell carcinoma of the anus, penis, cervix, vagina, or vulva). In some examples, the patient has a solid tumor (e.g., an advanced stage solid tumor or a metastatic solid tumor). In some examples, the patient has a MSI-H solid tumor.

[00110] 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.

[00111] In some examples, the patient has not previously been treated with a cancer treatment modality.

[00112] 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 surgery, radiotherapy, chemotherapy or immunotherapy. In some examples, the patient has previously been treated with surgery. In some examples, the patient has previously been treated with chemotherapy (e.g., platinum-based chemotherapy). In some such examples, the platinum agent is selected from cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin tetranitrate, phenanthriplatin, picoplatin, or satraplatin. In some examples, a patient has a cancer that has responded to platinum induction therapy. In some examples, the cancer is platinum sensitive at the commencement of treatment. In some examples, the cancer responded to the most recent platinum-based chemotherapy regimen prior to commencement of treatment. In some examples, response to the most recent platinum-based chemotherapy regimen is a complete response. In some examples, response to the most recent platinum-based chemotherapy regimen is a partial response.

[00113] In some examples, a composition that delivers a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered in an amount that delivers a dose of 1, 3 or 10 mg/kg PD-1-binding agent. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers 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 delivers 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 delivers a dose of 1, 3 or 10 mg/kg every four weeks.

[00114] In some examples, a composition that delivers a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered in an amount that delivers a dose (e.g., a therapeutically effective dose) within a range of about 100 mg to about 2,000 mg of PD-1-binding agent. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose

ranging from about 100 mg to about 1,200 mg, such as a therapeutically effective dose that is about 100 mg, about 300 mg, about 500 mg, or about 1000 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of about 400 mg, about 500 mg, about 800 mg, and/or about 1000 mg of PD-1-binding agent. In some examples, a dose of a particular PD-1 binding agent is considered to be "a dose of about [an indicated amount]" if it achieves a relevant biological or pharmacological effect that is comparable to that achieved with a dose of the indicated amount of a particular reference PD-1 binding agent (e.g., a particular anti-PD-1 antibody, such as a particular anti-PD-1 monoclonal antibody or other anti-PD-1 antibody agent including, for example, an anti-PD-1 antibody exemplified herein). In some examples, such a dose of the particular PD-1 binding agent may be described as a dose "corresponding to" the indicated amount of the reference PD-1 binding agent.

[00115] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that includes a plurality of individual doses (e.g., as set forth above), separated from each other by a period of time. In some examples, individual doses may be separated from each other by a period of two weeks, three weeks, four weeks, five weeks, six weeks or more. In examples, the anti-PD-1 antibody is administered at the administration interval of once a week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, or once every 6 weeks. In examples, the administration interval is once every 3 weeks. In examples, the administration interval is once every 6 weeks. In examples, the anti-PD-1 antibody is administered for the period of at least 2, 4, 6, 8, 10, 12, 14, 16, 18, or 20 weeks.

[00116] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 100 mg of PD-1-binding agent. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 100 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 delivers a dose of 100 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 delivers a dose of 100 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 delivers a dose of 100 mg every five weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 100 mg every six weeks.

[00117] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 300 mg of PD-1-binding agent. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 300 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 delivers a dose of 300 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 delivers a dose of 300 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 delivers a dose of 300 mg every five weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 300 mg every six weeks.

[00118] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 400 mg of PD-1-binding agent. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 400 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 delivers a dose of 400 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 delivers a dose of 400 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 delivers a dose of 400 mg every five weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 400 mg every six weeks.

[00119] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered 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 delivers 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 delivers 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 delivers 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 delivers a dose of 500 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 delivers a dose of 500 mg every six weeks.

[00120] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 600 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 600 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 delivers a dose of 600 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 delivers a dose of 600 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 delivers a dose of 600 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 delivers a dose of 600 mg every six weeks.

[00121] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 700 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 700 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 delivers a dose of 700 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 delivers a dose of 700 mg every six weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 700 mg every seven weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 700 mg every eight weeks.

[00122] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 800 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 800 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 delivers a dose of 800 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 delivers a dose of 800 mg every six weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 800 mg every eight weeks.

[00123] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 900 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 900 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 delivers a dose of 900 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 delivers a dose of 900 mg every six weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 900 mg every seven weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 900 mg every eight weeks.

[00124] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered at a dose of 1,000 mg. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 1,000 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 delivers a dose of 1,000 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 delivers a dose of 1,000 mg every six weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 1,000 mg every seven weeks. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a dose of 1,000 mg every eight weeks.

[00125] In some particular examples, a PD-1 binding agent (e.g., an anti-PD1 antibody) is administered according to a regimen that comprises or consists of at least one cycle of: a single dose (e.g., a single 400 mg dose or a single 500 mg dose) once every two weeks, a single dose once every three weeks, a single dose once every four weeks, a single dose once every five weeks, a single dose once every six weeks, etc. In some examples, a cycle includes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more single doses. In some examples, a regimen includes a plurality of cycles. In some examples, individual cycles may be separated from one another by a period of rest (i.e., no dosing).

[00126] 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 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 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 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).

[00127] In some examples, administration of a dose may be achieved by administration of a single unit dose composition (i.e., of a single composition that comprises and/or delivers the relevant dose amount). In some examples, administration of a dose may be achieved by administration of a plurality of single unit dose compositions. In some examples, administration of a dose may be achieved by administration of a portion of a single unit dose composition.

[00128] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a first dose of PD-1-binding agent once every three weeks for the first 2-6 dosing cycles (e.g., the first 3, 4, or 5 dosing cycles), and then delivers a second dose of a PD-1-binding agent once every six weeks until disease progression. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a first dose of a PD-1-binding agent once every three weeks for the first 3, 4, or 5 dosing cycles, and then delivers a second dose of a PD-1-binding agent once every six weeks or more until disease progression. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that delivers a first dose of a PD-1-binding agent once every three weeks for the first 3, 4, or 5 dosing cycles, and then delivers a second dose of a PD-1-binding agent once every six weeks or more until disease progression. In some examples the first and/or second dose of a PD-1-binding agent (e.g., an anti-PD-1 antibody) is about 100 mg to about 2,000 mg. In some examples the first dose and the second dose are the same. In some examples, the first dose and the second dose are different.

[00129] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 500 mg dose every 3 weeks for 3, 4, or 5 doses followed by administering at least one 1,000 mg dose every six weeks after the third, fourth, or fifth 500 mg dose. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 500 mg dose every 3 weeks for 3 doses followed by administering at least one 1,000 mg dose every six weeks or more after the third 500 mg dose. In some examples, a

PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 500 mg dose every 3 weeks for 4 doses followed by administering at least one 1,000 mg dose every six weeks or more after the fourth 500 mg dose. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 500 mg dose every 3 weeks for 5 doses followed by administering at least one 1,000 mg dose every six weeks or more after the fifth 500 mg dose. In some examples, additional 1,000 mg doses are administered every six weeks or more after the first 1000 mg dose until no further clinical benefit is achieved. In some particular examples, a PD-1 binding agent (e.g., an anti-PD1 antibody) is administered according to a dosing regimen that includes 500 mg for 4 cycles Q3W followed by 1000 mg Q6W.

[00130] In some examples, the a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 300 mg dose every 3 weeks for 3, 4, or 5 doses followed by administering at least one 800 mg or 1000 mg dose every six weeks after the third, fourth, or fifth 300 mg dose. In some examples, additional 800 mg or 1000 mg doses are administered every six weeks after the first 800 mg or 1000 mg dose until no further clinical benefit is achieved. In some particular examples, a PD-1 binding agent (e.g., an anti-PD1 antibody) is administered according to a dosing regimen that includes 300 mg for 4 cycles Q3W followed by 800 mg or 1000 mg Q6W.

[00131] In some examples, the a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 400 mg dose every 3 weeks for 3, 4, or 5 doses followed by administering at least one 800 mg or 1000 mg dose every six weeks after the third, fourth, or fifth 400 mg dose. In some examples, additional 800 mg or 1000 mg doses are administered every six weeks after the first 800 mg or 1000 mg dose until no further clinical benefit is achieved. In some particular examples, a PD-1 binding agent (e.g., an anti-PD1 antibody) is administered according to a dosing regimen that includes 400 mg for 4 cycles Q3W followed by 800 mg or 1000 mg Q6W.

[00132] In some examples, the a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that comprises administering a 600 mg dose every 3 weeks for 3, 4, or 5 doses followed by administering at least one 800 mg or 1000 mg dose every six weeks after the third, fourth, or fifth 600 mg dose. In some examples, additional 800 mg or 1000 mg doses are administered every six weeks after the first 800 mg or 1000 mg dose until no further clinical benefit is achieved. In some particular examples, a PD-1 binding agent (e.g., an anti-PD1 antibody) is administered according to a dosing regimen that includes 600 mg for 4 cycles Q3W followed by 800 mg or 1000 mg Q6W.

[00133] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that is demonstrated to achieve an average C_{max} of PD-1-binding agent in a patient population that is within 10 μg/mL to 500 μg/mL. In some examples, the regimen is demonstrated to achieve an average C_{max} of PD-1-binding agent in a patient population that is about 20 μg/mL, about 65 μg/mL, or about 200 μg/mL. In some examples, the regimen is demonstrated to achieve an average C_{max} of PD-1-binding agent in a patient population that is about 140 μg/mL, about 180 μg/mL, about 200 μg/mL, about 230 μg/mL, about 290 μg/mL. In examples, the administration of the anti-PD-1 antibody results in an average C_{max} within 10 μg/mL to 500 μg/mL in the patient (e.g., an average C_{max} of about 20 μg/mL, about 65 μg/mL, or about 200 μg/mL in the patient).

[00134] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that is demonstrated to achieve an average $AUC_{0\text{-}336h}$ of PD-1-binding agent concentration-time curve in a patient population that is within 2500 h*μg/mL to 50000 h*μg/mL. In some examples, the regimen is demonstrated to achieve an average $AUC_{0\text{-}336h}$ of PD-1-binding agent concentration-time curve in a patient population that is about 3400 h*μg/mL, about 11000 h*μg/mL, or about 36800 h*μg/mL. In examples, the administration of the anti-PD-1 antibody results in an average $AUC_{0\text{-}336h}$ within 2500 h*μg/mL to 50000 h*μg/mL in the patient (e.g., an average $AUC_{0\text{-}336h}$ is about 3400 h*μg/mL, about 11000 h*μg/mL, or about 36800 h*μg/mL).

[00135] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered according to a regimen that is demonstrated to achieve a peak serum concentration of a PD-1-binding agent within 0.5-3 hours after administration.

[00136] In some examples, a PD-1 binding agent has a terminal half-life of approximately 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, or 18 days. In some examples, a PD-1 binding agent has a terminal half-life of approximately 12 days.

[00137] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered intravenously. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is administered by intravenous infusion.

[00138] In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is aseptically filled into a clear glass vial. In some examples, the glass vial is stoppered with a chlorobutyl elastomer stopper laminated with fluoropolymer and sealed with an aluminum overseal. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is stored at 2-8 ºC. In some examples, a PD-1-binding agent (e.g., an anti-PD-1 antibody) is free of preservatives.

[00139] In some examples, the patient is receiving or will receive an additional therapy in combination with the PD-1-binding agent. In some examples, the additional therapy is surgery, radiotherapy, chemotherapy or immunotherapy. In some examples, the additional therapy includes treatment with a composition that delivers a LAG-3-binding agent (e.g., any described in WO 2016/126858, WO 2017/019894, or WO 2015/138920, each of which is hereby incorporated by reference in its entirety) and/or a TIM-3 binding agent (e.g., any described in WO 2016/161270). In examples, an anti-TIM-3 therapy (e.g., an anti-TIM-3 antibody) can be administered at about 1, 3 or 10 mg/kg; a flat dose between about 100 - 1500 mg; 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; a flat dose about 1500 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg. In some examples, the additional therapy is a PARP inhibitor. In some examples, the PARP inhibitor is niraparib, olaparib, rucaparib, talazoparib, and veliparib.

[00140] In some examples, the present disclosure provides a method of administering a PD-1-binding agent in combination with niraparib to a patient having a recurrent and/or platinum sensitive cancer. In some examples, a recurrent and/or platinum sensitive cancer 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 recurrent and/or platinum sensitive cancer is an anal cancer, a fallopian tube cancer, an ovarian cancer, or a lung cancer. In some certain examples, a recurrent and/or platinum sensitive cancer is an endometrial cancer, triple negative breast cancer, ovarian cancer, non-small cell lung cancer (NSCLC), squamous cell carcinoma of the lung or squamous cell carcinoma of the anogenital region (e.g., squamous cell carcinoma of the anus, penis, cervix, vagina, or vulva).

[00141] In some examples, niraparib is administered to a patient at a dose of 5 mg to 500 mg. In some examples, niraparib is administered according to a regimen that comprises a once daily dose of 50 mg to 500 mg of niraparib. In some examples, a once daily dose of

niraparib comprises 100 mg to 300 mg. In some examples, a once daily dose of niraparib comprises 100 mg, 200 mg, or 300 mg. In some examples, a once daily dose of niraparib is administered orally.

[00142] In some examples, the method further comprises a step of reducing the therapeutically effective dose of the anti-PD-1 antibody and/or prolonging the administration interval after achieving the clinical benefit.

[00143] The present disclosure provides, in some examples, methods of treating cancer comprising administering to a patient in need of treatment an anti-programmed death-1 protein (PD-1) antibody at a first dose at a first interval for a first period; administering to the patient the anti-PD-1 antibody at a second dose at a second interval for a second period; wherein the anti-PD-1 antibody comprises a heavy chain variable region comprising CDR sequences of SEQ ID NOs: 9, 10, and 11 and a light chain variable region comprising CDR sequences of SEQ ID NOs: 12, 13, and 14. In some examples, the first dose and the second dose are different. In some examples, the first dose is 500 mg and the second dose is 1000 mg. In examples, the first interval and the second interval are different. In examples, the first interval is once every three weeks and the second interval is once every six weeks. In examples, the anti-PD-1 antibody is administered at the first dose once every three weeks for the first period of 2-6 dosing cycles (e.g., the first 3, 4, or 5 dosing cycles), and at the second dose once every six weeks until disease progression.

[00144] The present disclosure provides, in some examples, compositions comprising a PD-1-binding agent for use in treatment of cancer in a selected cancer patient population, wherein the composition is administered according to a regimen demonstrated to achieve a clinical benefit. In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00145] 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 in a patient population achieve a clinical benefit. In some examples, at least 5% of patients in a patient population achieve SD. In some examples, at least 5% of patients in a patient population achieve at least a PR. In some examples, at least 5% of patients achieve in a patient population CR. In some examples, at least 20% of patients in a patient population achieve a clinical benefit. In some examples, at least 20% of patients in a patient population achieve SD.

[00146] 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.

[00147] The present disclosure provides, in some examples, compositions comprising a PD-1-binding agent for use in treatment of cancer in a selected cancer patient population, wherein the composition is administered according to a regimen demonstrated to achieve an average PD-1 receptor occupancy of at least 50% to 85% within 1 to 5 days of administration of a single dose of the PD-1 binding agent. In some examples, a PD-1-binding agent comprises a heavy chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 9, 10, and 11 and/or a light chain variable region with one, two or three CDR sequences selected from SEQ ID NOs: 12, 13, and 14. In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00148] The present disclosure provides, in some examples, compositions comprising a PD-1-binding agent for use in treatment of cancer in a selected cancer patient population, wherein the composition is administered according to a regimen demonstrated to achieve an

average PD-1 receptor occupancy of at least 75% over the first period of time (e.g., about 15 days to about 60 days; in some examples about 29 days). In some examples, a PD-1-binding 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, a PD-1-binding 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.

[00149] 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 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, the patients in the cancer patient population each have a cancer such as an anal cancer, a fallopian tube cancer, an ovarian cancer, or a lung cancer.. In some examples, the patients in the cancer patient population each have a cancer with microsatellite instability (e.g., MSI-H status). In some examples, the microsatellite instability is MSI-Low. In some examples, the microsatellite instability is microsatellite stable (e.g., MSS status). In some examples, the patients in the cancer patient population each have endometrial cancer. In some examples, at least some of the patients in the cancer patient population have an endometrial cancer with microsatellite instability or an endometrial cancer that is microsatellite stable (MSS).

[00150] 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.

[00151] 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 surgery, 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).

[00152] 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.

BRIEF DESCRIPTION OF THE DRAWING

[00153] The Drawing included herein, which is composed of the following Figures, is for illustration purposes only not for limitation.

[00154] ***Figure 1*** depicts a graphical representation of log-linear mean concentration versus time profile following a single dose administration of an anti-PD-1 antibody. Dots represent a dose of 1 mg/kg, squares represent a dose of 3 mg/kg and triangles represent a dose of 10 mg/kg. The x-axis indicates time from administration (in hours) and the y-axis indicates the serum concentration of the anti-PD-1 antibody in ng/mL. Error bars represent ± standard deviation.

[00155] ***Figures 2A-2B*** depict graphical representations of log-linear mean concentration versus time profile following single dose administrations of an anti-PD-1 antibody at different dosages. (A) Dots represent a dose of 1 mg/kg, squares represent a dose of 3 mg/kg

CLAIMS

What is claimed is

1. Use of a therapeutically effective dose of an immunoglobulinG4 (IgG4) humanized monoclonal Programmed Death-1 Protein (PD-1) antibody in the manufacture of a medicament for treating a ~~disorder~~ cancer in a ~~subject~~human, wherein the therapeutically effective dose is~~: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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 once every 3 weeks (Q3W) for 4 cycles, followed by a second dose of~~; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg~~ once every 6 weeks (Q6W), wherein the antibody comprises an immunoglobulin heavy chain whose amino acid comprises SEQ ID NO:3 and an immunoglobulin light chain whose amino acid comprises SEQ ID NO:4.

~~2. Use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of a medicament for increasing T cell activation of T cell effector function in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

~~3. Use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of a medicament for reducing tumors or inhibiting the growth of tumor cells in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000~~

~~mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

~~4. Use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of a medicament for inducing an immune response in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

~~5. Use of a therapeutically effective dose of an agent that is capable of inhibiting Programmed Death-1 Protein (PD-1) signaling in the manufacture of medicament for enhancing an immune response of increasing the activity of an immune cell in a subject, wherein the therapeutically effective dose is: about 1, 3 or 10 mg/kg; a flat dose between about 100 - 2000 mg; 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; a flat dose about 1500 mg; a flat dose about 1600 mg; a flat dose about 1700 mg; a flat dose about 1800 mg; a flat dose about 1900 mg; a flat dose about 2000 mg; about 1 mg/kg; about 3 mg/kg; or about 10 mg/kg.~~

~~6. The use of any one of the preceding claims, wherein the medicament is to be administered at an administration interval of once a week, once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 5 weeks, once every 6 weeks, or more.~~

~~7. The use of claim 6, wherein the medicament is to be administered at the administration interval of once every 3 weeks or once every 6 weeks.~~

2. The use of claim 1, wherein the medicament is to be administered intravenously.

3. The use of claim 1, wherein the medicament is to be administered by intravenous infusion.

4. The use of claim 1, wherein the cancer is recurrent or advanced.

5. The use of claim 4, wherein the cancer is a solid tumor.

~~8. The use of any one of the preceding claims, wherein the medicament is to be administered for 2, 3, 4, 5, 6, or more cycles.~~

~~9. The use of any one of the preceding claims, wherein the medicament is to be administered for the period of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 weeks, or more.~~

~~10. The use of claim 1, wherein the disorder is a T-cell dysfunctional disorder.~~

~~11. The use of claim 1, wherein the disorder is cancer.~~

~~12~~6. The use of claim ~~11~~4, wherein the cancer ~~is:~~has

~~i) a cancer associated with a high tumor mutation burden (TMB);~~

~~ii) a cancer that is microsatellite stable (MSS),~~

~~iii) a cancer that is characterized by microsatellite instability,~~

~~iv) a cancer that~~ a defective DNA mismatch repair system or 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)~~7. The use of claim 6, wherein the 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 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, 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/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~~, 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)~~.

8. The use of claim 7, wherein the cancer is endometrial cancer.

9. The use of claim 7, wherein the cancer is non-small cell lung cancer.

10. The use of claim 7, wherein the cancer is colorectal cancer.

11. The use of claim 7, wherein the cancer is squamous cell carcinoma of the head and neck.

~~13~~12. The use of any one of the preceding claims, wherein the human~~subject~~ has been further administered or will be administered an immune checkpoint inhibitor, such that the human~~subject~~ receives the agent and the immune checkpoint inhibitor.

~~14~~13. The use of claim ~~13~~12, wherein the immune checkpoint inhibitor is an agent that inhibits T cell immunoglobulin and mucin protein 3 (TIM-3), 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).

14. The use of claim 13, wherein the immune checkpoint inhibitor is an agent that inhibits T cell immunoglobulin and mucin protein 3 (TIM-3), wherein the agent is an antibody.

15. The use of claim 14, wherein the antibody is TSR-022, wherein TSR-022 is administered at 100-1500 mg Q3W.

~~15~~16. The use of any one of the preceding claims, wherein the human~~subject~~ has further been administered or will be administered an agent that inhibits poly (ADP-ribose) polymerase (PARP).

~~16. The use of any one of the preceding claims, wherein the subject has previously been treated with one or more of surgery, radiotherapy, chemotherapy, or immunotherapy.~~

17. The use of any one of the preceding claims, wherein the human~~subject~~ has been previously been treated with one or more of surgery, a radiotherapy, a chemotherapy, an immunotherapy, an anti-angiogenic agent, or an anti-inflammatory.

18. The use of claim 17, wherein the human has been previously treated with a chemotherapy.

19. The use of claim 17, wherein the chemotherapy is a platinum-based chemotherapy.

20. The use of any of the preceding claims, wherein the human has previously received at least one line or at least two lines of cancer treatment.

~~18. The use of any one of the preceding claims, wherein the agent is a PD-1 binding agent.~~

~~19. The use of claim 18, wherein the PD-1 binding agent comprises a heavy chain variable region with one or more CDR sequences having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 9, 10, or 11.~~

~~20. The use of claim 18, wherein the PD-1 binding agent comprises a light chain variable region with one or more CDR sequences having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NOs: 12, 13, and 14.~~

~~21. The use of claim 18, wherein the PD-1 binding agent comprises a heavy chain variable region with three CDRs that have sequences of SEQ ID NOs: 9, 10, and 11 and/or a~~

~~light chain variable region with three CDRs that have sequences of SEQ ID NOs: 12, 13, and 14.~~

~~22. The use of claim 18, wherein the PD-1 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%, or 99% sequence identity to SEQ ID NO: 1 or SEQ ID NO:7; and/or an immunoglobulin light chain variable domain comprising an amino acid sequence having at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to SEQ ID NO: 2 or SEQ ID NO: 8.~~

~~23. The use of claim 18, wherein the PD-1 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%, or 99% 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%, or 99% sequence identity to SEQ ID NO: 4.~~