chemotherapeutic agents. Currently approved PD-1 antagonists include anti-PD-1 antibodies, Opdivo® and Keytruda®, and anti-PD-L1 antibody, Tecentriq™.

[0005] There remains a need for additional antagonists of PD-1 for treatment of cancer and other diseases and disorders.

SUMMARY

[0006] Antibodies that bind Programmed Death 1 (PD-1) are provided, wherein the antibodies bind human PD-1 and mouse PD-1, and wherein the antibodies block binding of PD-L1 and/or PD-L2 to PD-1.

[0007] In some examples, an isolated antibody that binds to Programmed Death 1 (PD-1) is provided, wherein the antibody binds to an epitope comprising amino acids 126 to 136 of human PD-1. In some examples, amino acids 126 to 136 are numbered according to SEQ ID NO: 1. In some examples, the antibody binds to human PD-1 of SEQ ID NO: 382 with at least 10-fold greater affinity than the antibody binds to one or more PD-1 variants selected from I126A, L128A, A132L, I134A, and E136A. In one example, there is provided an isolated antibody that binds to Programmed Death 1 (PD-1), wherein the antibody binds to an epitope comprising amino acids 126 to 136 of human PD-1, wherein amino acids 126 to 136 are numbered according to SEQ ID NO: 1.

[0008] In some examples, the antibody:

a) binds to human PD-1 ECD-Fc of SEQ ID NO: 401 with at least 10-fold greater affinity than the antibody binds to PD-1 variant I126A ECD-Fc (SEQ ID NO: 389); and/or

b) binds to human PD-1 ECD-Fc of SEQ ID NO: 401 with at least 10-fold greater affinity than the antibody binds to PD-1 variant L128A ECD-Fc (SEQ ID NO: 390); and/or

c) binds to human PD-1 ECD-Fc of SEQ ID NO: 401 with at least 10-fold greater affinity than the antibody binds to PD-1 variant A132L ECD-Fc (SEQ ID NO: 391); and/or

d) binds to human PD-1 ECD-Fc of SEQ ID NO: 401 with at least 10-fold greater affinity than the antibody binds to PD-1 variant I134A ECD-Fc (SEQ ID NO: 392); and/or

e) binds to human PD-1 ECD-Fc of SEQ ID NO: 401 with at least 10-fold greater affinity than the antibody binds to PD-1 variant E136A ECD-Fc (SEQ ID NO: 393).

[0009] In some examples, the antibody binds to mouse PD-1 ECD-Fc of SEQ ID NO: 403. In some examples, the antibody binds to mouse PD-1 ECD-Fc of SEQ ID NO: 403 with at least 10-fold greater affinity than the antibody binds to mouse PD-1 variant H129P ECD-Fc (SEQ I NO: 394). In some examples, the antibody binds to rat PD-1 variant P129H ECD-Fc (SEQ ID NO: 397) with at least 10-fold greater affinity than the antibody binds to rat PD-1 ECD-Fc (SEQ ID NO: 405).

[0010] In various examples, affinity is determined by biolayer interferometry.

[0011] In some examples, the antibody comprises (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 21; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 23; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 25; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 27. In some examples, the antibody comprises a heavy chain variable region (V_H) that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20 and a light chain variable region (V_L) that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 24. In some examples, the antibody comprises a V_H comprising the amino acid sequence of SEQ ID NO: 20 and a V_L comprising the amino acid sequence of SEQ ID NO: 24.

[0012] In one example, an antibody that binds to Programmed Death 1 (PD-1) is provided, wherein the antibody comprises:

i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 5; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 6; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 7; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 9; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 10; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 11; or

ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 13; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 14; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 15; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 17; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 18; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 19; or

iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 21; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 23; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 25; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 27; or

iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 29; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 30; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 31; (d) LCDR1 comprising the amino

selected from SEQ ID NOs: 294, 302, 310 and 318; (c) HCDR3 comprising an amino acid sequence selected from SEQ ID NOs: 295, 303, 311 and 319; (d) LCDR1 comprising an amino acid sequence selected from SEQ ID NOs: 297, 305, 313, and 321; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 298, 306, 314 and 322; and (f) LCDR3 comprising an amino acid sequence selected from SEQ ID NOs: 299, 307, 315, and 323.

[0012a] In one aspect, there is provided an antibody that binds to Programmed Death 1 (PD-1), wherein the antibody comprises:

i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 5; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 6; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 7; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 9; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 10; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 11; or

ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 13; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 14; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 15; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 17; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 18; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 19; or

iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 21; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 23; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 25; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 27; or

iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 29; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 30; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 31; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 33; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 34; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 35; or

v) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 37; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 38; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 39; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 41; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 42; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 43; or

vi) (a) HCDR1 comprising an amino acid sequence selected from SEQ ID NOs: 45, 53, 61, 101, and 109; (b) HCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 46, 54, 62, 102, and 110; (c) HCDR3 comprising an amino acid sequence selected from SEQ ID NOs: 47, 55, 63, 103, and 111; (d) LCDR1 comprising an amino acid sequence selected from SEQ ID NOs: 49, 57, 65, 105, and 113; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 50, 58, 66, 106, and 114; and (f) LCDR3 comprising an amino acid sequence selected from SEQ ID NOs: 51, 59, 67, 107, and 115.

[0013] In some examples, an antibody that binds PD-1 is provided, which comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein:

i) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 4 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 8; or

ii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 12 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16; or

iii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 24; or

iv) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 28 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32; or

v) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 36 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 40; or

vi) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 44, 52, 60, 68, 76, 84, 92, 100, 108 and 116; and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 48, 56, 64, 72, 80, 88, 96, 104, 112, and 120; or

vii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 124, 132,

140, 148, 156, 164, 172, 180, 188, 196, 204, 212, 220, 228, 236, 244, 252, 260, 268, 276, and 284; and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 128, 136, 144, 152, 160, 168, 176, 184, 192, 200, 208, 216, 224, 232, 240, 248, 256, 264, 272, 280 and 288; or

viii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 292, 300, 308 and 316; and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 296, 304, 312, and 320.

[0014] In some examples, an antibody that binds PD-1 is provided, which comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein:

i) the V_H comprises the amino acid sequence of SEQ ID NO: 4 and the V_L comprises the amino acid sequence of SEQ ID NO: 8; or

ii) the V_H comprises the amino acid sequence of SEQ ID NO: 12 and the V_L comprises the amino acid sequence of SEQ ID NO: 16; or

iii) the V_H comprises the amino acid sequence of SEQ ID NO: 20 and the V_L comprises the amino acid sequence of SEQ ID NO: 24; or

iv) the V_H comprises the amino acid sequence of SEQ ID NO: 28 and the V_L comprises the amino acid sequence of SEQ ID NO: 32; or

v) the V_H comprises the amino acid sequence of SEQ ID NO: 36 and the V_L comprises the amino acid sequence of SEQ ID NO: 40; or

vi) the V_H comprises the amino acid sequence of SEQ ID NO: 44 and the V_L comprises the amino acid sequence of SEQ ID NO: 48; or

vii) the V_H comprises the amino acid sequence of SEQ ID NO: 52 and the V_L comprises the amino acid sequence of SEQ ID NO: 56; or

viii) the V_H comprises the amino acid sequence of SEQ ID NO: 60 and the V_L comprises the amino acid sequence of SEQ ID NO: 64; or

ix) the V_H comprises the amino acid sequence of SEQ ID NO: 68 and the V_L comprises the amino acid sequence of SEQ ID NO: 72; or

x) the V_H comprises the amino acid sequence of SEQ ID NO: 76 and the V_L comprises the amino acid sequence of SEQ ID NO: 80; or

xi) the V_H comprises the amino acid sequence of SEQ ID NO: 84 and the V_L comprises the amino acid sequence of SEQ ID NO: 88; or

xxix) the V_H comprises the amino acid sequence of SEQ ID NO: 228 and the V_L comprises the amino acid sequence of SEQ ID NO: 232; or

xxx) the V_H comprises the amino acid sequence of SEQ ID NO: 236 and the V_L comprises the amino acid sequence of SEQ ID NO: 240; or

xxxi) the V_H comprises the amino acid sequence of SEQ ID NO: 244 and the V_L comprises the amino acid sequence of SEQ ID NO: 248; or

xxxii) the V_H comprises the amino acid sequence of SEQ ID NO: 252 and the V_L comprises the amino acid sequence of SEQ ID NO: 256; or

xxxiii) the V_H comprises the amino acid sequence of SEQ ID NO: 260 and the V_L comprises the amino acid sequence of SEQ ID NO: 264; or

xxxiv) the V_H comprises the amino acid sequence of SEQ ID NO: 268 and the V_L comprises the amino acid sequence of SEQ ID NO: 272; or

xxxv) the V_H comprises the amino acid sequence of SEQ ID NO: 276 and the V_L comprises the amino acid sequence of SEQ ID NO: 280; or

xxxvi) the V_H comprises the amino acid sequence of SEQ ID NO: 284 and the V_L comprises the amino acid sequence of SEQ ID NO: 288; or

xxxvii) the V_H comprises the amino acid sequence of SEQ ID NO: 292 and the V_L comprises the amino acid sequence of SEQ ID NO: 296; or

xxxviii) the V_H comprises the amino acid sequence of SEQ ID NO: 300 and the V_L comprises the amino acid sequence of SEQ ID NO: 304; or

xxxix) the V_H comprises the amino acid sequence of SEQ ID NO: 308 and the V_L comprises the amino acid sequence of SEQ ID NO: 312; or

xl) the V_H comprises the amino acid sequence of SEQ ID NO: 316 and the V_L comprises the amino acid sequence of SEQ ID NO: 320.

[0015] In another example, an antibody that competes with an antibody provided herein for binding to human PD-1 is provided, wherein the antibody binds to human PD-1 and mouse PD-1, and where in the antibody inhibits binding of human PD-1 to human PD-L1, inhibits binding of human PD-1 to human PD-L2, inhibits binding of mouse PD-1 to mouse PD-L1, and inhibits binding of mouse PD-1 to mouse PD-L2. In one aspect, there is provided an antibody that competes for binding to human PD-1 with an antibody provided herein, wherein the antibody binds to human PD-1 and mouse PD-1, and wherein the antibody inhibits binding of human PD-1 to human PD-L1, inhibits binding of human PD-1 to human PD-L2, inhibits binding of mouse PD-1 to mouse PD-L1, and inhibits binding of mouse PD-1 to mouse PD-L2.

[0016] In some examples, an antibody provided herein binds to human PD-1 with an affinity (K_D) of less than 5 nM. In some examples, an antibody provided herein binds to mouse PD-1 with an affinity (K_D) of less than 10 nM. In some examples, affinity is determined using biolayer interferometry.

[0017] In some examples, an antibody provided herein is a monoclonal antibody. In some examples, an antibody provided herein is a human antibody, chimeric antibody, or a

humanized antibody. In some examples, an antibody provided herein is an antibody fragment selected from a Fab, Fab', Fv, scFv or $(Fab')_2$ fragment. In some examples, an antibody provided herein is a full length antibody. In some examples, an antibody provided herein is an IgG1 or IgG4 antibody.

[0018] In some examples, an antibody provided herein binds human PD-1. In some examples, human PD-1 comprises the amino acid sequence of SEQ ID NO: 382. In some examples, an antibody provided herein binds mouse PD-1. In some examples, mouse PD-1 comprises the amino acid sequence of SEQ ID NO: 383. In some examples, an antibody provided herein binds cynomolgus monkey PD-1. In some examples, cynomolgus monkey PD-1 comprises the amino acid sequence of SEQ ID NO: 384.

[0019] In some examples, an antibody provided herein inhibits binding of PD-1 to PD-L1. In some examples, an antibody provided herein inhibits binding of PD-1 to PD-L2. In some examples, an antibody provided herein inhibits binding of PD-1 to PD-L1 and inhibits the binding of PD-1 to PD-L2.

[0020] In some examples, administration of an antibody provided herein to a mammal increases the level of at least one cytokine selected from IFNγ and IL-2. In some examples, an antibody provided herein increases the level of at least one cytokine selected from IFNγ and IL-2 by at least 2-fold. In some examples, the level of the cytokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody. In some examples, at least one cytokine is IFNγ. In some examples, at least one cytokine is IL-2. In some examples, the level of the chemokine is measured 24 hours after administration of the antibody.

[0021] In some examples, administration of an antibody provided herein to a mammal enhances an immune response in the mammal. In some examples, administration of an antibody provided herein to a mammal results in activation of T cells in the mammal. In some examples, administration of an antibody provided herein to a mammal reduces tumor size in a mammal with cancer. In some examples, the mammal is a human. In some examples, the human has cancer. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0022] In some aspects, an isolated nucleic acid is provided, which encodes an antibody provided herein. In some aspects, a vector is provided, which comprises the nucleic acid provided herein. In some aspects, a host cell is provided, which comprises the vector provided herein. In some aspects, a host cell is provided, which produces an antibody provided herein. In some aspects, a method for making an anti-PD-1 antibody is provided, comprising culturing the host cell provided herein under conditions suitable for expression of the antibody. In some examples, the method further comprises recovering the antibody produced by the host cell.

[0023] In some aspects, a pharmaceutical composition is provided, comprising an anti-PD-1 antibody provided herein and a pharmaceutically acceptable carrier.

[0024] In one aspect, there is provided use of the anti-PD-1 antibody provided herein or the pharmaceutical composition provided herein for the manufacture of a medicament for treating cancer in a mammal. In some examples, a method of treating cancer in a mammal is provided, comprising administering an effective amount of an anti-PD-1 antibody provided herein, or a pharmaceutical composition comprising an anti-PD-1 antibody provided herein and a pharmaceutically acceptable carrier. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0025] In one example, there is provided use of the anti-PD-1 antibody provided herein or the pharmaceutical composition provided herein for the manufacture of a medicament for enhancing an immune response in a mammal. In one aspect, there is provided use of the anti-PD-1 antibody provided herein or the pharmaceutical composition provided herein for the manufacture of a medicament for enhancing an immune response in a mammal with cancer. In some examples, a method of enhancing an immune response in a mammal is provided, comprising administering an effective amount of an anti-PD-1 antibody provided herein, or a pharmaceutical composition comprising an anti-PD-1 antibody provided herein and a pharmaceutically acceptable carrier.

[0026] In one example, there is provided use of the anti-PD-1 antibody provided herein or the pharmaceutical composition provided herein for the manufacture of a medicament for increasing activation of a T cell in a mammal. In one aspect, there is provided use of the anti-PD-1 antibody provided herein or the pharmaceutical composition provided herein for the manufacture of a medicament for increasing activation of a T cell in a mammal with cancer. In some examples, a method of increasing activation of a T cell in a mammal is provided, comprising administering an effective amount of an anti-PD-1 antibody provided herein, or a pharmaceutical composition comprising an anti-PD-1 antibody provided herein and a pharmaceutically acceptable carrier.

[0027] In one aspect, there is provided use of the anti-PD-1 antibody provided herein or the pharmaceutical composition provided herein for the manufacture of a medicament for reducing tumor size in a mammal with cancer. In some examples, a method of reducing tumor size in a in a mammal with cancer is provided, comprising administering an effective amount of an anti-PD-1 antibody provided herein, or a pharmaceutical composition comprising an anti-PD-1 antibody provided herein and a pharmaceutically acceptable carrier.

[0028] In any of the examples provided herein, the mammal may be a human.

[0029] In some examples, the mammal is administered at least one additional therapeutic agent. In some such examples, the additional therapeutic agent is administered concurrently or sequentially with the anti-PD-1 antibody. In some examples, the additional therapeutic

agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some examples, the additional therapeutic agent is an anti-ICOS antibody. In some examples, the additional therapeutic agent is a cancer vaccine. In some examples, the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

[0030] In some examples, use of an antibody provided herein is provided for the manufacture of a medicament to treat cancer. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC). In some examples, the medicament is for administration with at least one additional therapeutic agent. In some examples, the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some examples, the additional therapeutic agent is an anti-ICOS antibody. In some examples, the additional therapeutic agent is a cancer vaccine. In some examples, the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

[0031] In some examples, the present disclosure provides uses of an antibody provided herein or a pharmaceutical composition comprising an antibody provided herein and a pharmaceutically acceptable carrier for treating cancer. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0032] In one example, there is provided use of an antibody provided herein or the pharmaceutical composition provided herein and at least one additional therapeutic agent for the manufacture of a medicament for treating cancer. In one aspect, there is provided use of an antibody provided herein or the pharmaceutical composition provided herein and at least one additional therapeutic agent for the manufacture of a medicament for combination therapy for treating cancer. In some examples, the present disclosure provides uses of an antibody provided herein or a pharmaceutical composition comprising an antibody provided herein and a pharmaceutically acceptable carrier, and at least one additional therapeutic agent, for treating cancer. In some examples, the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some examples, the additional therapeutic agent is an anti-ICOS antibody. In some examples, the additional therapeutic agent is a cancer vaccine. In some examples, the cancer vaccine is selected from a DNA vaccine, an

engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0033] In some examples, an antibody provided herein or a pharmaceutical composition comprising an antibody provided herein and a pharmaceutically acceptable carrier for use in treating cancer is provided. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0034] In one example, there is provided use of an antibody provided herein for the manufacture of a medicament for increasing the level of at least one cytokine selected from IFNγ and IL-2 in a mammal. In some examples, a method of increasing the level of at least one cytokine selected from IFNγ and IL-2 in a mammal is provided, comprising administering to the mammal an antibody provided herein. In some examples, the level of the cytokine is measured 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 8 hours, 10 hours, 12 hours, 14 hours, 16 hours, 18 hours, 20 hours, 22 hours, 24 hours, 36 hours, or 48 hours after administration of the antibody. In some examples, at least one cytokine is IFNγ. In some examples, at least one cytokine is IL-2. In some examples, the level of the cytokine is measured 24 hours after administration of the antibody. In some examples, the mammal is a human. In some examples, the human has cancer. In some examples, the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC). In some examples, the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

[0035] In some examples, an immune response is enhanced following administration of the anti-PD-1 antibody. In some examples, activation of T cells is increased following

administration of the anti-PD-1 antibody. In some examples, tumor size is decreased following administration of the anti-PD-1 antibody.

[0036] In some examples, the mammal is administered at least one additional therapeutic agent. In some examples, the additional therapeutic agent is administered concurrently or sequentially with the anti-PD-1 antibody. In some examples, the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some examples, the additional therapeutic is an anti-ICOS antibody. In some examples, the additional therapeutic agent is a cancer vaccine. In some examples, the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

[0037] In some examples, a sample of the cancer from the mammal has been determined to express PD-1. In some examples, the sample shows 1+, 2+, or 3+ staining of PD-1 by immunohistochemistry (IHC). In some examples, the sample has been determined to have an elevated level of PD-L1. In some examples, PD-L1 levels are determined using IHC.

BRIEF DESCRIPTION OF THE DRAWINGS

[0038] **Figure 1** shows IFNγ concentrations after mouse splenocyte T cells activated with anti-CD3 and anti-CD28 antibodies are contacted with anti-PD-1 antibodies. Mouse IgG1 and rat IgG2a were used as controls. RMP1-14 was used as a positive control anti-PD-1 antibody.

[0039] **Figure 2** shows the EC_{50} of increase in IL-2 in whole blood samples activated with Staphylococcal enterotoxin B (SEB) after being incubated with anti-PD1 antibodies. nivolumab (Nivo) and pembrolizumab (Pembro) were used as control anti-PD1 antibodies. Effects from antibodies 12228 (28), 13406 (6), 13407 (7), 13408 (8), and 13409 (9) are shown.

[0040] **Figure 3A-3B** show the ability of anti-PD-1 antibodies disclosed herein to block binding of mouse ligands to mouse PD-1. Octet analysis on a Forte-Bio instrument was used to assess the effect of the antibodies on the interaction between mouse PD-L1 and mouse PD-L2 with mouse PD-1.

[0041] **Figure 4A-1, 4A-2, 4B-1, 4B-2, and 4C** show the ability of anti-PD-1 antibodies disclosed herein to block the binding of human ligands to human PD-1. Octet analysis on a Forte-Bio instrument was used to assess the effect of the antibodies on the interaction between human PD-L1 and human PD-L2 with human PD-1.

[0042] **Figure 5** shows the reduction in tumor sizes in mouse tumor models upon administration of an anti-PD-1 antibody disclosed herein. C57BL6/J mice were injected subcutaneously in their flanks with MC38 cells. Mouse IgG1 (MOPC-21) and rat IgG2a (2A3) were used as controls. RMP1-14 was used as a positive control anti-PD1 antibody.

acid residues in a candidate sequence that are identical with the amino acid residues in the specific peptide or polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or MEGALIGN™ (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared.

[00102] An amino acid substitution may include but are not limited to the replacement of one amino acid in a polypeptide with another amino acid. Exemplary substitutions are shown in Table 1A. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, for example, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE 1A

Original Residue	Exemplary Substitutions
Ala (A)	Val; Leu; Ile
Arg (R)	Lys; Gln; Asn
Asn (N)	Gln; His; Asp, Lys; Arg
Asp (D)	Glu; Asn
Cys (C)	Ser; Ala
Gln (Q)	Asn; Glu
Glu (E)	Asp; Gln
Gly (G)	Ala
His (H)	Asn; Gln; Lys; Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe
Lys (K)	Arg; Gln; Asn
Met (M)	Leu; Phe; Ile
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr
Pro (P)	Ala
Ser (S)	Thr
Thr (T)	Val; Ser
Trp (W)	Tyr; Phe

assay buffer for 30 min and then monitored on-line for 60 seconds for baseline establishment. Sensors with loaded IgGs were exposed to 100 nM antigen for 5 minutes, afterwards they were transferred to assay buffer for 5 min for off-rate measurement. Kinetics were analyzed using the 1:1 binding model.

[00349] Equilibrium affinity measurements performed as previously described (Estep *et al.*, 2013). Solution equilibrium titrations (SET) were performed in PBS + 0.1% IgG-Free BSA (PBSF) with antigen held constant at 50 pM and incubated with 3-to 5-fold serial dilutions of antibody starting at 10 nM. Antibodies (20 nM in PBS) were coated onto standard bind MSD-ECL plates overnight at 4°C or at room temperature for 30 min. Plates were then blocked for 30 min with shaking at 700 rpm, followed by three washes with wash buffer (PBSF + 0.05% Tween 20). SET samples were applied and incubated on the plates for 150 seconds with shaking at 700 rpm followed by one wash. Antigen captured on a plate was detected with 250ng/mL sulfotag-labeled streptavidin in PBSF by incubation on the plate for 3 min. The plates were washed three times with wash buffer and then read on the MSD Sector Imager 2400 instrument using 1x Read Buffer T with surfactant. The percent free antigen was plotted as a function of titrated antibody in Prism and fit to a quadratic equation to extract the K_D. To improve throughput, liquid handling robots were used throughout MSD-SET experiments, including SET sample preparation. Table 1B shows the results for the ForteBio affinity measurements.

Table 1B

Antibody	Human PD-1 Monovalent Affinity (K_D)	Mouse PD-1 Monovalent Affinity (K_D)
mAb 1 (12228)	49 nM	6.3 nM
mAb 2 (13405)	73 nM	7.2 nM
mAb 3 (13406)	3.2 nM	3.5 nM
mAb 4 (13407)	3.9 nM	3.2 nM
mAb 5 (13408)	1.2 nM	5.3 nM

Example 2: Mouse activated splenocytes response to anti-PD-1 antibodies

[00350] When mouse T cells derived from splenocytes are activated with anti-CD3 and anti-CD28 antibodies, they express the cell-surface molecule and secrete the soluble molecule interferon- gamma (IFNγ). Blocking antibodies to PD-1 cause the production of IFNγ to be increased. Mouse splenocytes were obtained and incubated with soluble anti-CD3 and anti-CD28 antibodies. After 5 days, they were mixed with equal numbers of T cells purified from freshly prepared splenocytes and anti-PD-1 antibodies in different concentrations. Positive and negative control antibodies RMP1-14, 2A3, and C1.18.4 were purchased from BioXCell. After

WHAT IS CLAIMED IS:

1. An antibody that binds to Programmed Death 1 (PD-1), wherein the antibody comprises:

i) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 5; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 6; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 7; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 9; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 10; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 11; or

ii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 13; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 14; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 15; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 17; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 18; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 19; or

iii) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 21; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 23; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 25; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 27; or

iv) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 29; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 30; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 31; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 33; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 34; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 35; or

v) (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 37; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 38; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 39; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 41; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 42; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 43; or

vi) (a) HCDR1 comprising an amino acid sequence selected from SEQ ID NOs: 45, 53, 61, 101, and 109; (b) HCDR2 comprising an amino acid sequence selected

from SEQ ID NOs: 46, 54, 62, 102, and 110; (c) HCDR3 comprising an amino acid sequence selected from SEQ ID NOs: 47, 55, 63, 103, and 111; (d) LCDR1 comprising an amino acid sequence selected from SEQ ID NOs: 49, 57, 65, 105, and 113; (e) LCDR2 comprising an amino acid sequence selected from SEQ ID NOs: 50, 58, 66, 106, and 114; and (f) LCDR3 comprising an amino acid sequence selected from SEQ ID NOs: 51, 59, 67, 107, and 115.

2. The antibody of claim 1, which comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein:

i) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 4 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 8; or

ii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 12 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 16; or

iii) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 24; or

iv) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 28 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 32; or

v) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 36 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 40; or

vi) the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 44, 52, 60, 100, and 108; and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence selected from SEQ ID NOs: 48, 56, 64, 104, and 112.

3. The antibody of claim 1, which comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein:

i) the V_H comprises the amino acid sequence of SEQ ID NO: 4 and the V_L comprises the amino acid sequence of SEQ ID NO: 8; or

ii) the V_H comprises the amino acid sequence of SEQ ID NO: 12 and the V_L comprises the amino acid sequence of SEQ ID NO: 16; or

iii) the V_H comprises the amino acid sequence of SEQ ID NO: 20 and the V_L comprises the amino acid sequence of SEQ ID NO: 24; or

iv) the V_H comprises the amino acid sequence of SEQ ID NO: 28 and the V_L comprises the amino acid sequence of SEQ ID NO: 32; or

v) the V_H comprises the amino acid sequence of SEQ ID NO: 36 and the V_L comprises the amino acid sequence of SEQ ID NO: 40; or

vi) the V_H comprises the amino acid sequence of SEQ ID NO: 44 and the V_L comprises the amino acid sequence of SEQ ID NO: 48; or

vii) the V_H comprises the amino acid sequence of SEQ ID NO: 52 and the V_L comprises the amino acid sequence of SEQ ID NO: 56; or

viii) the V_H comprises the amino acid sequence of SEQ ID NO: 60 and the V_L comprises the amino acid sequence of SEQ ID NO: 64; or

ix) the V_H comprises the amino acid sequence of SEQ ID NO: 100 and the V_L comprises the amino acid sequence of SEQ ID NO: 104; or

x) the V_H comprises the amino acid sequence of SEQ ID NO: 108 and the V_L comprises the amino acid sequence of SEQ ID NO: 112.

4. The antibody of claim 1, wherein the antibody comprises: (a) HCDR1 comprising the amino acid sequence of SEQ ID NO: 21; (b) HCDR2 comprising the amino acid sequence of SEQ ID NO: 22; (c) HCDR3 comprising the amino acid sequence of SEQ ID NO: 23; (d) LCDR1 comprising the amino acid sequence of SEQ ID NO: 25; (e) LCDR2 comprising the amino acid sequence of SEQ ID NO: 26; and (f) LCDR3 comprising the amino acid sequence of SEQ ID NO: 27.

5. The antibody of claim 4, wherein the antibody comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein: the V_H is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 20 and the V_L is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to the amino acid sequence of SEQ ID NO: 24.

6. The antibody of claim 4, wherein the antibody comprises a heavy chain variable region (V_H) and a light chain variable region (V_L), wherein: the V_H comprises the amino acid sequence of SEQ ID NO: 20 and the V_L comprises the amino acid sequence of SEQ ID NO: 24.

7. An antibody that competes for binding to human PD-1 with an antibody of any one of the preceding claims, wherein the antibody binds to human PD-1 and mouse PD-1, and wherein the antibody inhibits binding of human PD-1 to human PD-L1, inhibits binding of human PD-1 to human PD-L2, inhibits binding of mouse PD-1 to mouse PD-L1, and inhibits binding of mouse PD-1 to mouse PD-L2.

8. The antibody of any one of the preceding claims, wherein the antibody binds to human PD-1 with an affinity (K_D) of less than 5 nM.

9. The antibody of any one of the preceding claims, wherein the antibody binds to mouse PD-1 with an affinity (K_D) of less than 10 nM.

10. The antibody of claim 8 or claim 9, wherein affinity is determined using biolayer interferometry.

11. The antibody of any one of the preceding claims, wherein the antibody is a monoclonal antibody.

12. The antibody of any one of the preceding claims, wherein the antibody is a human antibody, chimeric antibody, or a humanized antibody.

13. The antibody of any one of the preceding claims, wherein the antibody is an antibody fragment selected from a Fab, Fab', Fv, scFv or $(Fab')_2$ fragment.

14. The antibody of any one of the preceding claims, wherein the antibody is a full length antibody.

15. The antibody of any one of the preceding claims, wherein the antibody binds human PD-1 comprising the amino acid sequence of SEQ ID NO: 382.

16. The antibody of any one of the preceding claims, wherein the antibody binds mouse PD-1 comprising the amino acid sequence of SEQ ID NO: 383.

17. The antibody of any one of the preceding claims, wherein the antibody binds cynomolgus monkey PD-1 comprising the amino acid sequence of SEQ ID NO: 384.

18. The antibody of any one of the preceding claims, wherein the antibody inhibits binding of PD-1 to PD-L1.

19. The antibody of any one of the preceding claims, wherein the antibody inhibits binding of PD-1 to PD-L2.

20. The antibody of any one of the preceding claims, wherein the antibody inhibits binding of PD-1 to PD-L1 and inhibits the binding of PD-1 to PD-L2.

21. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal increases the level of at least one cytokine selected from IFNγ and IL-2.

22. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal enhances an immune response in the mammal.

23. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal results in activation of T cells in the mammal.

24. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal reduces tumor size in a mammal with cancer.

25. An isolated nucleic acid encoding the antibody of any one of the preceding claims.

26. A vector comprising the nucleic acid of claim 25.

27. A host cell comprising the vector of claim 26.

28. A host cell that produces the antibody of any one of claims 1 to 24.

29. A method for making an anti-PD-1 antibody, comprising culturing the host cell of claim 27 or claim 28 under conditions suitable for expression of the antibody.

30. The method of claim 29, further comprising recovering the antibody produced by the host cell.

31. A pharmaceutical composition comprising the anti-PD-1 antibody of any one of claims 1 to 24 and a pharmaceutically acceptable carrier.

32. Use of the anti-PD-1 antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 31 for the manufacture of a medicament for treating cancer in a mammal.

33. The use of claim 32, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC).

34. The use of claim 32, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

35. Use of the anti-PD-1 antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 31 for the manufacture of a medicament for enhancing an immune response in a mammal with cancer.

36. Use of the anti-PD-1 antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 31 for the manufacture of a medicament for increasing activation of a T cell in a mammal with cancer.

37. Use of the anti-PD-1 antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 31 for the manufacture of a medicament for reducing tumor size in a mammal with cancer.

38. The use of any one of claims 32 to 37, wherein the mammal is a human.

39. The use of any one of claims 32 to 38, wherein the mammal is to be administered at least one additional therapeutic agent.

40. The use of claim 39, wherein the additional therapeutic agent is to be administered concurrently or sequentially with the anti-PD-1 antibody.

41. The use of claim 39 or 40 wherein the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody.

42. The use of claim 41, wherein the additional therapeutic agent is an anti-ICOS antibody.

43. The use of claim 39 or claim 40, wherein the additional therapeutic agent is a cancer vaccine.

44. The use of claim 43, wherein the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

45. Use of an antibody of any one of claims 1 to 24 or the pharmaceutical composition of claim 31 and at least one additional therapeutic agent for the manufacture of a medicament for combination therapy for treating cancer.

46. The use of claim 45, wherein the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody.

47. The use of claim 46, wherein the additional therapeutic agent is an anti-ICOS antibody.

48. The use of claim 45, wherein the additional therapeutic agent is a cancer vaccine.

49. The use of claim 48, wherein the cancer vaccine is selected from a DNA vaccine, an engineered virus vaccine, an engineered tumor cell vaccine, and a cancer vaccine developed using neoantigens.

50. The use of any one of claims 45 to 49, wherein the cancer is selected from melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), gastric cancer, bladder cancer, diffuse large B-cell lymphoma (DLBCL), Hodgkin's lymphoma, ovarian cancer, head & neck squamous cell cancer (HNSCC), mesothelioma, and triple negative breast cancer (TNBC).

51. The use of claim 50, wherein the cancer is selected from melanoma, gastric cancer, head & neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), and triple negative breast cancer (TNBC).

52. The use of any one of claims 32 to 51, wherein a sample of the cancer has been determined to express PD-1.

53. The use of claim 52, wherein the sample shows 1+, 2+, or 3+ staining of PD-1 by immunohistochemistry (IHC).

54. The use of any one of claims 32 to 53, wherein a sample of the cancer has been determined to have an elevated level of PD-L1.

55. The use of claim 54, wherein PD-L1 levels are determined using IHC.