

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 embodiments, 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 embodiments, amino acids 126 to 136 are numbered according to SEQ ID NO: 1. In some embodiments, 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 aspect, 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 embodiments, 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 embodiments, the antibody binds to mouse PD-1 ECD-Fc of SEQ ID NO: 403. In some embodiments, 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 ID NO: 394). In some embodiments, 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 embodiments, affinity is determined by biolayer interferometry.

[0011] In some embodiments, 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 embodiments, 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 embodiments, 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 aspect, 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

- 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 aspect, 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.

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

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

[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 embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 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. In some embodiments, 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 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. In some embodiments, 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 embodiments, a method of reducing tumor size 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 embodiments provided herein, the mammal may be a human.

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

agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some embodiments, the additional therapeutic agent is an anti-ICOS antibody. In some embodiments, the additional therapeutic agent is a cancer vaccine. In some embodiments, 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 aspects, use of an antibody provided herein is provided for the manufacture of a medicament to treat cancer. In some embodiments, 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 embodiments, 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 embodiments, the medicament is for administration with at least one additional therapeutic agent. In some embodiments, the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some embodiments, the additional therapeutic agent is an anti-ICOS antibody. In some embodiments, the additional therapeutic agent is a cancer vaccine. In some embodiments, 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 embodiments, 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 embodiments, 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 embodiments, 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 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 treating cancer. In some embodiments, 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 embodiments, the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody. In some embodiments, the additional therapeutic agent is an anti-ICOS antibody. In some embodiments, the additional therapeutic agent is a cancer vaccine. In some embodiments, 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 embodiments, 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 embodiments, 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 aspects, 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 embodiments, 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 embodiments, 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 aspect, 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 IFN γ and IL-2 in a mammal. In some embodiments, a method of increasing the level of at least one cytokine selected from IFN γ and IL-2 in a mammal is provided, comprising administering to the mammal an antibody provided herein. In some embodiments, 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 embodiments, at least one cytokine is IFN γ . In some embodiments, at least one cytokine is IL-2. In some embodiments, the level of the cytokine is measured 24 hours after administration of the antibody. In some embodiments, the mammal is a human. In some embodiments, the human has cancer. In some embodiments, 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 embodiments, 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 embodiments, an immune response is enhanced following administration of the anti-PD-1 antibody. In some embodiments, activation of T cells is increased following

36. The antibody of any one of claims 31 to 35, wherein the level of the chemokine is measured 24 hours after administration of the antibody.
37. The antibody of any one of the preceding claims, wherein administration of the antibody to a mammal enhances an immune response in the mammal.
38. 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.
39. 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.
40. The antibody of any one of claims 31 to 39, wherein the mammal is a human.
41. The antibody of claim 40, wherein the human has cancer.
42. The antibody of claim 41, 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).
43. The antibody of claim 42, 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).
44. An isolated nucleic acid encoding the antibody of any one of the preceding claims.
45. A vector comprising the nucleic acid of claim 44.
46. A host cell comprising the vector of claim 45.
47. A host cell that produces the antibody of any one of claims 1 to 43.
48. A method for making an anti-PD-1 antibody, comprising culturing the host cell of claim 47 under conditions suitable for expression of the antibody.
49. The method of claim 48, further comprising recovering the antibody produced by the host cell.
50. A pharmaceutical composition comprising the anti-PD-1 antibody of any one of claims 1 to 43 and a pharmaceutically acceptable carrier.
51. Use of the anti-PD-1 antibody of any one of claims 1 to 43 or the pharmaceutical composition of claim 50 for the manufacture of a medicament for treating cancer in a mammal.
52. The use of claim 51, 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).

53. The use of claim 52, 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).
54. Use of the anti-PD-1 antibody of any one of claims 1 to 43 or the pharmaceutical composition of claim 50 for the manufacture of a medicament for enhancing an immune response in a mammal.
55. Use of the anti-PD-1 antibody of any one of claims 1 to 43 or the pharmaceutical composition of claim 50 for the manufacture of a medicament for increasing activation of a T cell in a mammal.
56. Use of the anti-PD-1 antibody of any one of claims 1 to 43 or the pharmaceutical composition of claim 50 for the manufacture of a medicament for reducing tumor size in a mammal with cancer.
57. The use of any one of claims 51 to 56, wherein the mammal is a human.
58. The use of any one of claims 51 to 57, wherein the mammal is to be administered at least one additional therapeutic agent.
59. The use of claim 58, wherein the additional therapeutic agent is to be administered concurrently or sequentially with the anti-PD-1 antibody.
60. The use of claim 58 or 59 wherein the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody.
61. The use of claim 60, wherein the additional therapeutic agent is an anti-ICOS antibody.
62. The use of claim 58 or claim 59, wherein the additional therapeutic agent is a cancer vaccine.
63. The use of claim 62, 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.
64. Use of an antibody of any one of claims 1 to 43 for the manufacture of a medicament to treat cancer.
65. The use of claim 64, 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).
66. The use of claim 65, 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).

67. The use of any one of claims 64 to 66, wherein the medicament is for administration with at least one additional therapeutic agent.
68. The use of claim 67, wherein the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody.
69. The use of claim 68, wherein the additional therapeutic agent is an anti-ICOS antibody.
70. The use of claim 67, wherein the additional therapeutic agent is a cancer vaccine.
71. The use of claim 70, 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.
72. Use of an antibody of any one of claims 1 to 43 or the pharmaceutical composition of claim 50 and at least one additional therapeutic agent for the manufacture of a medicament for treating cancer.
73. The use of claim 72, wherein the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody.
74. The use of claim 73, wherein the additional therapeutic agent is an anti-ICOS antibody.
75. The use of claim 72, wherein the additional therapeutic agent is a cancer vaccine.
76. The use of claim 75, 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.
77. The use of any one of claims 72 to 76, 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).

78. The use of claim 77, 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).

79. An antibody of any one of claims 1 to 43 or the pharmaceutical composition of claim 50 for use in treating cancer.

80. The antibody of claim 79, 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).

81. The antibody of claim 80, 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).

82. Use of an antibody of any one of claims 1 to 43 for the manufacture of a medicament for increasing the level of at least one cytokine selected from IFN γ and IL-2 in a mammal.

83. The use of claim 82, wherein 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.

84. The use of claim 82 or 83, wherein at least one cytokine is IFN γ .

85. The use of any one of claims 82 to 84, wherein at least one cytokine is IL-2.

86. The use of any one of claims 82 to 85, wherein the level of the cytokine is measured 24 hours after administration of the antibody.

87. The use of any one of claims 82 to 86, wherein the mammal is a human.

88. The use of claim 87, wherein the human has cancer.

89. The use of claim 88, 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).

90. The use of claim 89, 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).

91. The use of any one of claims 82 to 90, wherein an immune response is enhanced following administration of the anti-PD-1 antibody.

92. The use of any one of claims 82 to 91, wherein activation of T cells is increased following administration of the anti-PD-1 antibody.

93. The use of any one of claims 82 to 92, wherein tumor size is decreased following administration of the anti-PD-1 antibody.

94. The use of any one of claims 82 to 93, wherein the mammal is to be administered at least one additional therapeutic agent.

95. The use of claim 94, wherein the additional therapeutic agent is to be administered concurrently or sequentially with the anti-PD-1 antibody.

96. The use of any one of claims 94 or 95, wherein the additional therapeutic agent is selected from an anti-ICOS antibody and an anti-CTLA4 antibody.

97. The use of claim 96, wherein the additional therapeutic is an anti-ICOS antibody.

98. The use of claim 94 or 95, wherein the additional therapeutic agent is a cancer vaccine.

99. The use of claim 98, 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.

100. The use of any one of claims 51 to 78, wherein a sample of the cancer has been determined to express PD-1.

101. The use of claim 100, wherein the sample shows 1+, 2+, or 3+ staining of PD-1 by immunohistochemistry (IHC).

102. The use of any one of claims 51 to 78, 100, or 101, wherein the sample has been determined to have an elevated level of PD-L1.

103. The use of claim 102, wherein PD-L1 levels are determined using IHC.