Claims

1. An isolated antagonist antibody that specifically binds to PD-1 and comprises:

a heavy chain variable region (VH) comprising a VH complementarity determining region one (CDR1), VH CDR2, and VH CDR3 of the VH having an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 4; SEQ ID NO: 5; and SEQ ID NO: 6; and

a light chain variable region (VL) comprising a VL CDR1, VL CDR2, and VL CDR3 of the VL having an amino acid sequence selected from the group consisting of SEQ ID NO: 2; SEQ ID NO:7; SEQ ID NO: 8; and SEQ ID NO: 9.

2. The isolated antagonist antibody of claim 1, wherein the antibody comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 13, 14, or 15, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 16, 17, 24, 25, 27, 28, 35, or 36, a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 18, 23, 26, or 37, a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO:10, 22, 30, or 32, a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 11, 20, or 33 and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 12, 21, 31, or 34.

3. The isolated antagonist antibody of claim 1 or 2, wherein the antibody comprises a VH comprising the amino acid sequence shown in SEQ ID NO: 3, 4, 5, or 6, or a variant thereof with one or several conservative amino acid substitutions in residues that are not within a CDR**.**

4. The isolated antagonist antibody of claim 3, wherein the antibody comprises a VL comprising the amino acid sequence shown in SEQ ID NO: 2, 7, 8, or 9, or a variant thereof with one or several amino acid substitutions in amino acids that are not within a CDR.

5. The isolated antagonist antibody of any one of claims 1 to 4, wherein the antibody comprises a VH comprising the amino acid sequence shown in SEQ ID NO: 3,

4, 5, or 6, and a VL comprising the amino acid sequence shown in SEQ ID NO: 2, 7, 8, or 9**.**

6. The isolated antagonist antibody of any one of claims 1 to 5, wherein the antibody comprises a heavy chain comprising the amino acid sequence shown in SEQ ID NO: 29 or 38 and a light chain comprising the amino acid sequence shown in SEQ ID NO: 39.

7. The isolated antagonist antibody any one of claims 1 to 5, wherein the antibody comprises a constant region.

8. The isolated antagonist antibody of claim 7, wherein the antibody has an isotype that is selected from the group consisting of IgG_2, $IgG_{2\Delta a}$, IgG_4, $IgG_{4\Delta b}$, $IgG_{4\Delta c}$, IgG_4 S228P, $IgG_{4\Delta b}$ S228P and $IgG_{4\Delta c}$ S228P.

9. The isolated antagonist antibody of claim 7, wherein the constant region is IgG_4 S228P.

10. The isolated antagonist antibody of claim 1, wherein each CDR of the antibody is defined in accordance with the Kabat definition, the Chothia definition, the combination of the Kabat definition and the Chothia definition, the AbM definition, or the contact definition of CDR.

11. An isolated anti-PD-1 antibody, wherein the antibody comprises a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 13, a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 17, a VH CDR3 comprising the amino acid sequence shown in SEQ ID NO: 23, a VL CDR1 comprising the amino acid sequence shown in SEQ ID NO: 10, a VL CDR2 comprising the amino acid sequence shown in SEQ ID NO: 20, and a VL CDR3 comprising the amino acid sequence shown in SEQ ID NO: 21.

12. The isolated antibody of any one of the preceding claims, wherein the antibody promotes IFNγ and/or TNF secretion from T cells.

13. The isolated antibody of any one of the preceding claims, wherein the antibody promotes proliferation of T cells.

14. The isolated antibody of any one of the preceding claims, wherein the antibody inhibits tumor growth.

15. The isolated antibody of any one of the preceding claims, wherein the antibody binds human PD-1 and mouse PD-1.

16. The isolated antibody of claim 15, wherein the antibody binds human PD-1 with an affinity of about 0.73 nM at 25ºC as measured by surface plasmon resonance.

17. An isolated cell line that produces the antibody of any one of the preceding claims.

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

19. A recombinant expression vector comprising the nucleic acid of claim 18.

20. A host cell comprising the expression vector of claim 19.

21. A hybridoma capable of producing the antibody of any one of the preceding claims.

22. A method of producing an anti-PD-1 antagonist antibody, the method comprising: culturing a cell line that recombinantly produces the antibody of any one of the preceding claims under conditions wherein the antibody is produced; and recovering the antibody.

23. A method of producing an anti-PD-1 antagonist antibody, the method comprising: culturing a cell line comprising nucleic acid encoding an antibody comprising a heavy chain comprising the amino acid sequence shown in SEQ ID NO: 29 or 38 and a light chain comprising the amino acid sequence shown in SEQ ID NO: 39 under conditions wherein the antibody is produced; and recovering the antibody.

24. The method of claim 23, wherein the heavy and light chains of the antibody are encoded on separate vectors.

25. The method of claim 23, wherein the heavy and light chains of the antibody are encoded on the same vector.

26. A pharmaceutical composition comprising the antibody of any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

27. A kit for the treatment of cancer comprising the pharmaceutical composition of claim 26.

28. The use of the anti-PD-1 antibody of any one of claims 1 to 16 or the pharmaceutical composition of claim 26 in the manufacture of a medicament for the treatment of cancer in an individual.

29. The use of claim 28, wherein the cancer is selected from the group consisting of gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, leukemia, head and neck cancer, squamous cell head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer, ovarian cancer, breast cancer, prostate cancer, esophageal cancer, pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, skin cancer, and melanoma.

30. The use of claim 28 or 29 wherein the individual is a previously treated adult patient with locally advanced or metastatic melanoma, squamous cell head and neck cancer (SCHNC), ovarian carcinoma, sarcoma, or relapsed or refractory classic Hodgkin's Lymphoma (cHL).

31. The use of any one of claims 28 to 30, wherein the anti-PD-1 antibody is to be administered at a dosage of about 0.5 mg/kg, about 1.0 mg/kg, about 3.0 mg/kg, or about 10 mg/kg.

32. The use of any one of claims 28 to 31, wherein the anti-PD-1 antibody is to be administered once every 7, 14, 21, or 28 days.

33. The use of any one of claims 28 to 32, wherein the anti-PD-1 antibody is to be administered intravenously or subcutaneously.

34. The use of any one of claims 28 to 33, wherein the treatment further comprises the administration of an effective amount of a second therapeutic agent.

35. The use of claim 34, wherein the second therapeutic agent is selected from the group consisting of an anti-CTLA4 antibody, an anti-4-1BB antibody, a second PD-1 antagonist, an anti-PD-L1 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, an anti-TIGIT antibody, an anti-OX40 antibody, an anti-GITR antibody, a tyrosine kinase inhibitor, and an ALK inhibitor.
36. The use of claim 35, wherein the tyrosine kinase inhibitor is axitinib or palbociclib.
37. The use of claim 35, wherein the ALK inhibitor is sunitinib or crizotinib.
38. The use of the anti-PD-1 antibody of any one of claims 1 to 16 or the pharmaceutical composition of claim 26 in the manufacture of a medicament for the treatment of cancer in an individual in need, wherein the treatment when carried out comprises the administration of the medicament and a vaccine capable of eliciting an immune response against cells of the cancer.
39. The use of the anti-PD-1 antibody of any one of claims 1 to 16 or the pharmaceutical composition of claim 26 in the manufacture of a medicament for the treatment of cancer in an individual, wherein the treatment when carried out comprises administration of the medicament to the individual, wherein the individual is also administered a vaccine for the treatment of cancer, and wherein the medicament enhances the immunogenicity or therapeutic effect of the vaccine.
40. The use of claim 38 or 39, wherein the cancer is selected from the group consisting of breast cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, and colorectal cancer.
41. The use of claim 38 or 39, wherein the treatment or enhancement further comprises the administration to the individual an effective amount of one or more other immune modulators.
42. The use of claim 41, wherein the other immune modulators are selected from the group consisting of protein kinase receptor inhibitor, a CTLA-4 antagonist, a CD40 agonist, and a TLR9 agonist.