CLAIMS

What is claimed is:

1. ~~A method of treating a subject afflicted with a cancer comprising administering to the subject~~ Use of a therapeutically effective amount of an antibody or an antigen-binding portion thereof that disrupts the interaction between Programmed Death-1 (PD-1) and Programmed Death Ligand-1 (PD-L1) in the manufacture of a medicament for treating a subject afflicted with cancer, wherein the antibody or antigen-binding portion thereof binds specifically to PD-1 or to PD-L1.

2. The ~~method~~ use of claim 1, wherein the cancer is selected from the group consisting of melanoma, renal cell carcinoma, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, colorectal cancer, castration-resistant prostate cancer, ovarian cancer, gastric cancer, hepatocellular carcinoma, pancreatic carcinoma, squamous cell carcinoma of the head and neck, carcinomas of the esophagus, gastrointestinal tract and breast, and a hematological malignancy.

3. The ~~method~~ use of claim 1, wherein the therapeutically effective amount of the antibody or antigen-binding portion thereof comprises a dose ranging from 0.1 to 10.0 mg/kg body weight which is administered at a dosing schedule of once per week, once every two weeks, or once a month.

4. A method for ~~immunotherapy of a subject afflicted with cancer, which method comprises:~~

~~(a)~~ selecting a subject that is a suitable candidate for immunotherapy, the selecting comprising:

   (i) providing a test tissue sample ~~obtained from a patient with cancer of the tissue~~, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells;

   (ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface; and

   (iii) selecting the subject as a suitable candidate based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface exceeds a predetermined threshold level.; ~~and~~

5. ~~(b) administering a composition comprising~~ Use of a therapeutically effective amount of an anti-PD-1 antibody in the manufacture of a medicament for immunotherapy~~to the selected subject~~.

~~5~~6. The method of claim 4, wherein the proportion of cells that express PD-L1 is assessed by performing an assay to determine the presence of PD-L1 polypeptide on the surface of cells in the test tissue sample.

~~6~~7. The method of claim ~~5~~6, wherein the test tissue sample is a formalin-fixed paraffin-embedded (FFPE) tissue sample.

~~7~~8. The method of claim ~~6~~7, wherein the presence of PD-L1 polypeptide is determined using an automated IHC assay.

~~8~~9. The method of claim ~~1~~28, wherein the IHC assay is performed using an anti-PD-L1 monoclonal antibody to bind to the PD-L1 polypeptide, wherein the anti-PD-L1 monoclonal antibody is selected from 28-8, 28-1, 28-12, 29-8, and 5H1.

~~9~~10. The method of claim 4, wherein the predetermined threshold level is 1% of tumor cells or a single tumor-infiltrating inflammatory cell expressing cell surface PD-L1 as determined by automated IHC using mAb 28-8.

~~10~~11. A method for ~~treatment of a subject afflicted with cancer, which method comprises:~~

~~(a)~~ selecting a subject that is not suitable for anti-PD-1 antibody immunotherapy, the selecting comprising:

(i) providing a test tissue sample ~~obtained from a patient with cancer of the tissue~~, the test tissue sample comprising tumor cells and tumor-infiltrating inflammatory cells;

(ii) assessing the proportion of cells in the test tissue sample that express PD-L1 on the cell surface; and

(iii) selecting the subject as not suitable for anti-PD-1 antibody immunotherapy based on an assessment that the proportion of cells in the test tissue sample that express PD-L1 on the cell surface is less than a predetermined threshold level.~~; and~~

12. ~~(b) administering~~ Use of a standard-of-care therapeutic other than an anti-PD-1 antibody in the manufacture of a medicament for treatment of a subject afflicted with cancer ~~to the selected subject~~.

~~11~~13. A monoclonal antibody or an antigen-binding portion thereof that binds specifically to a cell surface-expressed PD-L1 polypeptide in a formalin-fixed, paraffin-embedded (FFPE) tissue sample.

~~12~~14. The monoclonal antibody or antigen-binding portion thereof of claim ~~16~~13, which antibody or portion thereof comprises the CDR1, CDR2 and CDR3 regions in a heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 35, and the CDR1, CDR2 and CDR3 regions in a light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 36.

~~13~~15. The monoclonal antibody or antigen-binding portion thereof of claim ~~16~~13, which antibody or portion thereof comprises a heavy chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 35, and a light chain variable region comprising consecutively linked amino acids having the sequence set forth in SEQ ID NO: 36.

~~14~~16. ~~A method of treating a subject afflicted with a cancer comprising administering to the subject~~Use of:

(a) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Programmed Death-1 (PD-1); and

(b) an antibody or an antigen-binding portion thereof that specifically binds to and inhibits Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4);

in the manufacture of a medicament for treating a subject afflicted with a cancer, each antibody being administered at a dosage ranging from 0.1 to 20.0 mg/kg body weight in a concurrent regimen comprising:

(i) an induction dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of at least once every 2, 3 or 4 weeks, or at least once a month, for at least 2, 4, 6, 8 or 10 doses, followed by administration of the anti-PD-1 alone at a dosing frequency of at least once every 2, 3 or 4 weeks, or at least once a month, for at least 2, 4, 6, 8 or 12 doses; followed by

(ii) a maintenance dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a

dosing frequency of at least once every 8, 12 or 16 weeks, or at least once a quarter, for at least 4, 6, 8, 10, 12 or 16 doses.

~~15~~17. The ~~method~~ use of claim ~~14~~16, wherein the anti-PD-1 and anti-CTLA-4 antibodies are administered at the following dosages:

(a) 0.1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

(b) 0.3 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

(c) 1 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

(d) 3 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

(e) 5 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

(f) 10 mg/kg anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody;

(g) 0.1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;

(h) 0.3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;

(i) 1 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;

(j) 3 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody;

(k) 5 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody; or

(l) 10 mg/kg anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody.

~~16~~18. ~~A method of treating a subject afflicted with a cancer, the subject having previously been treated with an anti-CTLA-4 antibody, which method comprises administering to the subject in a sequenced regimen~~ Use of an antibody or an antigen-binding portion thereof that specifically binds to and inhibits PD-1 at a dosage ranging from 0.1 to 20.0 mg/kg body weight and at a dosing frequency of at least once every week, at least once every 2, 3 or 4 weeks, or at least once a month, for up to 6 to up to 72 doses in the manufacture of a medicament for treating a subject afflicted with cancer in a sequenced regimen, the subject having previously been treated with an anti-CTLA-4 antibody..

~~17~~19. The ~~method~~ use of claim ~~15~~17 or ~~16~~18, wherein the anti-PD-1 antibody is nivolumab.

~~18~~20. The ~~method~~ use of claim ~~15~~17 or ~~16~~18, wherein the anti-CTLA-4 antibody is ipilimumab.

~~19~~21. An anti-PD-1 antibody or an antigen-binding portion thereof for use in treating a subject afflicted with a cancer in a concurrent regimen comprising combined administration with an anti-CTLA-4 antibody or an antigen-binding portion thereof, wherein the anti-PD-1 and anti-CTLA-4 antibodies are each administered

at a dosage ranging from 0.1 to 20.0 mg/kg body weight, and further wherein the concurrent regimen comprises:

(i) an induction dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of at least once every 2, 3 or 4 weeks, or at least once a month, for at least 2, 4, 6, 8 or 12 doses, followed by administration of the anti-PD-1 alone at a dosing frequency of at least once every 2, 3 or 4 weeks, or at least once a month, for at least 2, 4, 6, 8 or 10 doses; followed by

(ii) a maintenance dosing schedule comprising combined administration of the anti-PD-1 and anti-CTLA-4 antibodies at a dosing frequency of at least once every 8, 12 or 16 weeks, or at least once a quarter, for up to 4, 6, 8, 10, 12 or 16 doses.

~~20~~22. A kit for treating a subject afflicted with a cancer, the kit comprising:

(a) a dosage ranging from 0.1 to 20.0 mg/kg body weight of an antibody or an antigen-binding portion thereof that specifically binds to and inhibits PD-1;

(b) a dosage ranging from 0.1 to 20.0 mg/kg body weight of an antibody or an antigen-binding portion thereof that specifically binds to and inhibits CTLA-4; and

(c) instructions for using the anti-PD-1 and anti-CTLA-4 antibodies the concurrent regimen method of claim ~~14~~16.

21. A kit for treating a subject afflicted with a cancer, the kit comprising:

(a) a dosage ranging from 0.1 to 20.0 mg/kg body weight of an antibody or an antigen-binding portion thereof that specifically binds to and inhibits PD-1; and

(b) instructions for using the anti-PD-1 antibody in the sequenced regimen method of claim ~~16~~18.