

~~1. An antibody or an antigen binding portion thereof that specifically binds to and inhibits Programmed Death 1 (PD-1) ("anti PD-1 antibody") for use in a method of treating a human subject afflicted with a cancer in combination with an antibody or an antigen binding portion thereof that specifically binds to and inhibits Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) ("anti CTLA-4 antibody"), comprising administering to the subject 1 mg/kg of the anti PD-1 antibody and 3 mg/kg of the anti CTLA-4 antibody every 3 weeks for 4 doses, followed by subsequently administering the anti PD-1 antibody alone at a dosing frequency of once every 2 weeks.~~

~~2. The anti PD-1 antibody for use of claim 1, wherein the anti PD-1 antibody subsequently administered alone is administered at a dosage of 3 mg/kg.~~

~~3. The anti PD-1 antibody for use of claim 1 or 2, wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.~~

~~4. The anti PD-1 antibody for use of any one of claims 1 to 3, wherein the cancer is selected from liver cancer, hepatocellular carcinoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, melanoma, renal cancer, renal cell carcinoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, colorectal cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, castration resistant prostate cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, gastric cancer, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the CNS, primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, asbestos-induced cancers, and a hematologic malignancy.~~

~~5. The anti PD-1 antibody for use of any one of claims 1 to 4, wherein the cancer is melanoma.~~

~~6. The anti PD-1 antibody for use of any one of claims 1 to 5, wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.~~

~~7. The anti PD-1 antibody for use of any one of claims 1 to 6, wherein the treatment is further combined with one of more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti PD-L1 antibody or antigen binding portion thereof.~~

18. An anti-PD-1 antibody for use in a method of treating a human subject afflicted with a cancer in combination with an anti-CTLA-4 antibody;

comprising:

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

(ii) a maintenance dosing schedule comprising administration of the anti-PD-1 antibody and the anti-CTLA-4 antibody at a dosing frequency of once every 8, 2 to 12 or 16 weeks, or once a quarter, for 4, 6, 8, 10, 12 or 16 doses;

wherein the anti-PD-1 antibody and anti-CTLA-4 antibody are to be administered at dosages of: (a) 1 mg/kg of anti-PD-1 antibody and 3 mg/kg of anti-CTLA-4 antibody or (b) 3 mg/kg of anti-PD-1 antibody and 1 mg/kg of anti-CTLA-4 antibody.

2. The anti-PD-1 antibody for use of claim 1, wherein the anti-PD-1 antibody is to be administered at a dosage of 1 mg/kg and the anti-CTLA-4 antibody is to be administered at a dosage of 3 mg/kg.

3. The anti-PD-1 antibody for use of claim 1, wherein the anti-PD-1 antibody is to be administered at a dosage of 3 mg/kg and the anti-CTLA-4 antibody is to be administered at a dosage of 1 mg/kg.

4. The anti-PD-1 antibody for use of any one of claims 1 to 3, wherein the treatment provides a reduction in tumor size, reduction in tumor growth, elimination of the tumor, reduction in number of metastatic lesions over time, complete response, partial response, or stable disease.

5. The anti-PD-1 antibody for use of any one of claims 1 to 4, wherein the cancer is selected from liver cancer, hepatocellular carcinoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, breast cancer, lung cancer, squamous non-small cell lung cancer (NSCLC), non-squamous NSCLC, melanoma, renal cancer, renal cell carcinoma, uterine cancer, ovarian cancer, colorectal cancer, colon cancer, colorectal cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, castration-resistant prostate cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, gastric cancer, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the CNS, primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, asbestos-induced cancers, and a hematologic malignancy.

6. The anti-PD-1 antibody for use of any one of claims 1 to 5, wherein the cancer is melanoma.

7. The anti-PD-1 antibody for use of any one of claims 1 to 6, wherein the cancer is an advanced, recurring, metastatic, and/or refractory cancer.

8. The anti-PD-1 antibody for use of any one of claims 1 to 7, wherein the treatment is further combined with one or more of chemotherapy, radiation, surgery, hormone deprivation, angiogenesis inhibitors, and an anti-PD-L1 antibody or antigen-binding portion thereof.

~~9. The anti PD-1 antibody for use of claim 8, wherein the anti PD-1 antibody and the anti CTLA-4 antibody are administered in the induction dosing schedule at the following dosage:~~

- ~~(a) 0.1 mg/kg anti PD-1 antibody and 3 mg/kg of anti CTLA-4 antibody;~~
- ~~(b) 5 mg/kg anti PD-1 antibody and 3 mg/kg of anti CTLA-4 antibody;~~
- ~~(c) 10 mg/kg anti PD-1 antibody and 3 mg/kg of anti CTLA-4 antibody;~~
- ~~(d) 0.1 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(e) 0.3 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(f) 1 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(g) 3 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(h) 5 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(i) 10 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(j) 0.1 mg/kg anti PD-1 antibody and 0.1 mg/kg of anti CTLA-4 antibody;~~
- ~~(k) 0.3 mg/kg anti PD-1 antibody and 0.3 mg/kg of anti CTLA-4 antibody;~~
- ~~(l) 0.5 mg/kg anti PD-1 antibody and 0.5 mg/kg of anti CTLA-4 antibody; or~~
- ~~(m) 5 mg/kg anti PD-1 antibody and 5 mg/kg of anti CTLA-4 antibody.~~

~~940.~~ The anti-PD-1 antibody for use of any one of claims 1 to ~~89~~, wherein the anti-PD-1 antibody is nivolumab.

~~4410.~~ The anti-PD-1 antibody for use of any one of claims 1 to ~~940~~, wherein the anti-CTLA-4 antibody is ipilimumab.

11. The anti-PD-1 antibody for use of any one of claims 1 to 10, further comprising assessing the proportion of cells that express PD-L1 on the cell surface in a test tissue sample obtained from the subject.

12. The anti-PD-1 antibody for use of claim 11, wherein the proportion of cells that express PD-L1 on the cell surface is determined by immunohistochemistry using an anti-PD-L1 antibody.

13. The anti-PD-1 antibody for use of claim 12, wherein the anti-PD-L1 antibody 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.

14. The anti-PD-1 antibody for use of claim 12 or 13, wherein the anti-PD-L1 antibody 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.

~~12. The anti PD-1 antibody for use of any one of claims 9 to 11, wherein the anti-CTLA-4 antibody is administered during the induction dosing schedule once every 3 weeks for a total of 4 doses.~~

~~13. The anti PD-1 antibody for use of any one of claims 9 to 12, wherein the anti PD-1 antibody and the anti CTLA-4 antibody are administered in the maintenance dosing schedule at the following dosages:~~

- ~~(a) 0.1 mg/kg anti PD-1 antibody and 3 mg/kg of anti CTLA-4 antibody;~~
- ~~(b) 5 mg/kg anti PD-1 antibody and 3 mg/kg of anti CTLA-4 antibody;~~
- ~~(c) 10 mg/kg anti PD-1 antibody and 3 mg/kg of anti CTLA-4 antibody;~~
- ~~(d) 0.1 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(e) 0.3 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(f) 1 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(g) 3 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(h) 5 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(i) 10 mg/kg anti PD-1 antibody and 1 mg/kg of anti CTLA-4 antibody;~~
- ~~(j) 0.1 mg/kg anti PD-1 antibody and 0.1 mg/kg of anti CTLA-4 antibody;~~
- ~~(k) 0.3 mg/kg anti PD-1 antibody and 0.3 mg/kg of anti CTLA-4 antibody;~~
- ~~(l) 0.5 mg/kg anti PD-1 antibody and 0.5 mg/kg of anti CTLA-4 antibody; or~~
- ~~(m) 5 mg/kg anti PD-1 antibody and 5 mg/kg of anti CTLA-4 antibody.~~

~~14. The anti PD-1 antibody for use of any one of claims 9 to 13, wherein:~~

- ~~(a) 5 mg/kg of the anti PD 1 antibody and 3 mg/kg of the anti CTLA 4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule;~~
- ~~(b) 1 mg/kg of the anti PD 1 antibody and 1 mg/kg of the anti CTLA 4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule;~~
- ~~(c) 3 mg/kg of the anti PD 1 antibody and 1 mg/kg of the anti CTLA 4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule; or~~
- ~~(d) 5 mg/kg of the anti PD 1 antibody and 1 mg/kg of the anti CTLA 4 antibody are administered to a human subject every 3 weeks for 4 doses in the induction dosing schedule.~~

~~15. — The anti PD 1 antibody for use of any one of claims 9 to 14, wherein:~~

- ~~(i) the induction dosing schedule comprises administration of the anti PD 1 antibody and the anti CTLA 4 antibody at a dosing frequency of once every 3 weeks for 4 doses, followed by administration of the anti PD 1 antibody alone at a dosing frequency of once every 3 weeks for 4 doses; and~~
- ~~(ii) the maintenance dosing schedule comprises administration of the anti PD 1 antibody and the anti CTLA 4 antibody at a dosing frequency of once every 2 to 12 weeks for up to 8 doses.~~