

WHAT IS CLAIMED IS:

1. Use of a PD-1 x CTLA-4 bispecific molecule in the manufacture of a medicament for a method of treating a cancer ~~comprising administering a PD-1 x CTLA-4 bispecific molecule to~~ a subject in need thereof, wherein said PD-1 x CTLA-4 bispecific molecule comprises a PD-1 Binding Domain and a CTLA-4 Binding Domain, and wherein ~~said method comprises administering~~ said PD-1 x CTLA-4 bispecific molecule is to be administered to a subject at a dose of about 3 mg/kg to about 10 mg/kg once every 3 weeks.
2. Use of a PD-1 x CTLA-4 bispecific molecule in the manufacture of a medicament for a method of stimulating immune cells ~~comprising administering a PD-1 x CTLA-4 bispecific molecule to~~ a subject in need thereof, wherein said PD-1 x CTLA-4 bispecific molecule comprises a PD-1 Binding Domain and a CTLA-4 Binding Domain, and wherein ~~said method comprises administering~~ said PD-1 x CTLA-4 bispecific molecule is to be administered to a subject at a dose of about 3 mg/kg to about 10 mg/kg once every 3 weeks.
3. The ~~use method~~ of claim 1 or 2, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered to said subject at a dose of about 3 mg/kg to about 10 mg/kg once every 3 weeks during an induction period.
4. The ~~use method~~ of claim 2 or 3, wherein said immune cells are T cells.
5. The ~~use method~~ of any one of claims 1-4, wherein:
 - (I) said PD-1 Binding Domain comprises a Light Chain Variable Domain (VL_{PD-1}) that comprises the CDR_{L1}, CDR_{L2} and CDR_{L3} of **SEQ ID NO:1**, and a Heavy Chain Variable Domain (VH_{PD-1}) that comprises the PD-1-specific CDR_{H1}, CDR_{H2} and CDR_{H3} of **SEQ ID NO:5**; and
 - (II) said CTLA-4 Binding Domain comprises a Light Chain Variable Domain (VL_{CTLA-4}) that comprises the CDR_{L1}, CDR_{L2} and CDR_{L3} of **SEQ ID NO:9**, and a Heavy Chain Variable Domain (VH_{CTLA-4}) that comprises the CTLA-4-specific CDR_{H1}, CDR_{H2} and CDR_{H3} of **SEQ ID NO:13**.

6. The ~~usemethod~~ of any one of claims 1-5, wherein said PD-1 x CTLA-4 bispecific molecule comprises:
 - (I) two of said PD-1 Binding Domains; and
 - (II) two of said CTLA-4 Binding Domains.
7. The ~~usemethod~~ of any one of claims 1-6, wherein:
 - (a) said PD-1 Binding Domain comprises the VL Domain of **SEQ ID NO:1** and the VH Domain of **SEQ ID NO:5**; and
 - (b) said CTLA-4 Binding Domain comprises the VL Domain of **SEQ ID NO:9** and the VH Domain of **SEQ ID NO:13**.
8. The ~~usemethod~~ of any one of claims 1-7, wherein said PD-1 x CTLA-4 bispecific molecule comprises a Hinge Domain and an Fc Region of an IgG1, IgG2, IgG3, or IgG4 isotype.
9. The ~~usemethod~~ of claim 8, wherein said Fc Region and said Hinge Domain are of the IgG4 isotype, and wherein said Hinge Domain comprises a stabilizing mutation.
10. The ~~usemethod~~ of any one of claims 8-9, wherein said Fc Region is a variant Fc Region that comprises:
 - (a) one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR; and/or
 - (b) one or more amino acid modifications that enhances the serum half-life of the variant Fc Region.
11. The ~~usemethod~~ of claim 10, wherein:
 - (a) said one or more amino acid modifications that reduces the affinity of the variant Fc Region for an FcγR comprise the substitution of L234A or L235A, or L234A and L235A; and/or
 - (b) said one or more amino acid modifications that enhances the serum half-life of the variant Fc Region comprise the substitution of M252Y; or M252Y and S254T; or M252Y and T256E; or M252Y, S254T and T256E; or K288D and H435K,wherein said numbering is that of the EU index as in Kabat.

12. The ~~usemethod~~ of any one of claims 1-11, wherein said PD-1 x CTLA-4 bispecific molecule is a diabody comprising one polypeptide chain that comprises the amino acid sequence of **SEQ ID NO:40** and a second polypeptide chain that comprises the amino acid sequence of **SEQ ID NO:41**.
13. The ~~usemethod~~ of any one of claims 1-12, wherein said PD-1 x CTLA-4 bispecific molecule is a diabody comprising two polypeptide chains each comprising the amino acid sequence of **SEQ ID NO:40** and two polypeptide chains each comprising the amino acid sequence of **SEQ ID NO:41**.
14. The ~~usemethod~~ of any one of claims 1-16, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered at a dose of between about 3 mg/kg and 8 mg/kg.
15. The ~~usemethod~~ of any one of claims 1-14, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered at a dose of about 6 mg/kg.
16. The ~~usemethod~~ of any one of claims 3-15, ~~wherein further comprising administering~~ said PD-1 x CTLA-4 bispecific molecule is to be further administered to said subject at a dose of from about 3 mg/kg to about 10 mg/kg once every 6 weeks during a maintenance period, wherein said maintenance period follows said induction period.
17. The ~~usemethod~~ of any one of claims 3-13 or 16, wherein said induction period has a duration of up to about 24 weeks.
18. The ~~usemethod~~ of any one of claims 3-13, or 16-17, wherein said maintenance period has a duration of up to about 84 weeks.
19. The ~~usemethod~~ of any one of claims 3-13, or 16-18, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered at a dose of between about 3 mg/kg and 8 mg/kg during said induction period.
20. The ~~usemethod~~ of any one of claims 3-13, or 16-19, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered at a dose of about 6 mg/kg during said induction period.

21. The ~~usemethod~~ of any one of claims 16-20, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered at a dose of between about 3 mg/kg and 8 mg/kg during said maintenance period.
22. The ~~usemethod~~ of any one of claims 16-21, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered at a dose of about 6 mg/kg during said maintenance period.
23. The ~~usemethod~~ of any one of claims 16-22, wherein said dose of said PD-1 x CTLA-4 bispecific molecule administered in said maintenance period is the same as said dose administered in said induction period.
24. The ~~usemethod~~ of any one of claims 1-23, wherein said PD-1 x CTLA-4 bispecific molecule is to be administered by intravenous (IV) infusion.
25. The ~~usemethod~~ of any one of claims 1-24, wherein said cancer is selected from the group consisting of: an adrenal gland cancer, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, an anal cancer, a bile duct cancer, a bladder cancer, a bone cancer, a brain cancer, a brain and spinal cord cancer, a breast cancer, a HER2+ breast cancer, a triple negative breast cancer (TNBC), a carotid body tumors, a cervical cancer, an HPV-related cervical cancer, a cervical squamous cell carcinoma, a chondrosarcoma, a chordoma, a clear cell carcinoma, a colon cancer, a colorectal cancer (CRC), a microsatellite instability-high colorectal cancer (MSI-H CRC), a microsatellite-stable colorectal cancer (non-microsatellite-instability-high colorectal cancer, non-MSI-H CRC), a desmoplastic small round cell tumor, an endometrial cancer, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fallopian tube carcinoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, a gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a glioblastoma, a head and neck cancer, an HPV-related head and neck cancer, a hematological malignancy, a hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a non-small-cell lung cancer (NSCLC), a medulloblastoma, a melanoma, a meningioma, Merkel cell carcinoma, a mesothelioma pharyngeal cancer, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a

neuroblastoma, a neuroendocrine tumor, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a pheochromocytoma, a pituitary tumor, a prostate cancer, a metastatic castration resistant prostate cancer (mCRPC), a posterior uveal melanoma, a renal cancer, a renal cell carcinoma (RCC), a rhabdoid tumor, a rhabdomyosarcoma, a sarcoma, a skin cancer, a small round blue cell tumor of childhood(including neuroblastoma and rhabdomyosarcoma), a soft-tissue sarcoma, a pleomorphic undifferentiated sarcoma, a dedifferentiated liposarcoma, a synovial sarcoma, a myxofibrosarcoma, a squamous cell cancer, a squamous cell cancer of the head and neck (SCCHN), a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid cancer, a thyroid metastatic cancer, and a uterine cancer.

26. The ~~use~~method of claim 25, wherein said cancer is selected from the group consisting of: cervical cancer, HPV-related cervical cancer, cervical squamous cell carcinoma, CRC, MSI-H CRC, non-MSI-H CRC, head and neck cancer, HPV-related head and neck cancer, lung cancer, melanoma, NSCLC, prostate cancer, renal cancer, RCC, soft-tissue sarcoma, a pleomorphic undifferentiated sarcoma, a dedifferentiated liposarcoma, a synovial sarcoma, a myxofibrosarcoma, squamous cell cancer, and SCCHN.
27. The ~~use~~method of any one of claims 1-26, ~~wherein further comprising administering~~ a therapeutically or prophylactically effective amount of one or more additional therapeutic agents or chemotherapeutic agents is to be further administered.
28. The ~~use~~method of any one of claims 1-27, wherein said subject in need thereof is a human.
29. A pharmaceutical kit comprising:
 - (a) a container comprising a PD-1 x CTLA-4 bispecific molecule; and
 - (b) an instructional material,
 wherein the instructional material instructs that said PD-1 x CTLA-4 bispecific molecule is to be used according to the ~~use~~method of any one of claims 1-27.
30. ~~Use of t~~The pharmaceutical kit of claim 29 for use in the treatment of cancer or for stimulating immune cells.