conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, hypomethylating agents, checkpoints inhibitors, peptide vaccine and the like, epitopes or neoepitopes from tumor antigens, as well as combinations of one or more of these agents.

In a further aspect, the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell are for use as a medicament.

In a further aspect, the present disclosure provides a use of the antibody or antigen-binding fragment thereof as described herein, the pharmaceutical composition as described herein, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules as described herein, the vector as described herein, or the host cell as described herein in the manufacture of a medicament for the prevention or treatment of cancer.

In yet another aspect, the present disclosure provides a use of the antibody or antigen-binding fragment thereof as described herein, the pharmaceutical composition as described herein, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules as described herein, the vector according as described herein, or the host cell as described herein in the manufacture of a medicament for use in combinatorial therapy for treating or preventing cancer, wherein said medicament is to be administered in combination with radiotherapy or an additional therapeutic agent, preferably selected in the group consisting of alkylating agents, angiogenesis inhibitors, antibodies, in particular anti-tumor targeting antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-2 family inhibitors), activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat

shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, hypomethylating agents, checkpoints inhibitors, peptide vaccine and the like, epitopes or neoepitopes from tumor antigens, as well as combinations of one or more of these agents.

Optionally, the antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell are for use in combination with radiotherapy or an additional therapeutic agent, preferably selected in the group consisting of alkylating agents, angiogenesis inhibitors, antibodies, in particular anti-tumor targeting antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-2 family inhibitors), activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors,

CLAIMS

1. A humanized monoclonal anti-human-PD-1 antibody or an antigen-binding fragment thereof comprising: (a) a VH comprising or consisting of an amino acid sequence of SEQ ID NO: 21; and (b) a VL comprising or consisting of an amino acid sequence of SEQ ID NO: 24, wherein the antibody or antigen binding fragment thereof is an antagonist of the binding of human PD-L1 and/or PD-L2 to human PD-1.

2. The antibody or antigen-binding fragment thereof of ~~any one of~~ claim~~s~~ 1, wherein it comprises: (a) a heavy chain comprising or consisting of an amino acid sequence of SEQ ID NO: 31, and (b) a light chain comprising or consisting of an amino acid sequence of SEQ ID NO: 34.

3. The antibody or antigen-binding fragment thereof of any one of claims 1-2, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant domain derived from a human kappa light chain constant domain and a heavy chain constant domain derived from a human IgG1, IgG2, IgG3 or IgG4 heavy chain constant domain.

4. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant domain derived from a human kappa light chain constant domain and a heavy chain constant domain derived from a human IgG1 heavy chain constant domain, optionally with a substitution or a combination of substitutions selected from the group consisting of T250Q/M428L; M252Y/S254T/T256E + H433K/N434F; E233P/L234V/L235A/G236A + A327G/A330S/P331S; E333A; S239D/A330L/I332E; P257I/Q311; K326W/E333S; S239D/I332E/G236A; N297A; L234A/L235A; N297A + M252Y/S254T/T256E; K322A and K444A, preferably selected from the group consisting of N297A optionally in combination with M252Y/S254T/T256E, and L234A/L235A.

5. The antibody or antigen-binding fragment thereof of any one of claims 1-3, wherein the antibody or antigen-binding fragment thereof comprises a light chain constant domain derived from a human kappa light chain constant domain and a heavy chain constant domain derived from a human IgG4 heavy chain constant domain, optionally with a substitution or a combination of substitutions selected from the group consisting of S228P; L234A/L235A, S228P + M252Y/S254T/T256E and K444A.

6. The antibody or antigen-binding fragment thereof according to any one of claims 1-5, which specifically binds to human PD-1 with a binding affinity constant (KD) for a human PD-1 equal or lower than 10^{-7} M measured by surface plasmon resonance.

7. An isolated nucleic acid molecule or a group of isolated nucleic acid molecules encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 6.

8. A vector comprising the isolated nucleic acid molecule or the group of isolated nucleic acid molecules of claim 7.

9. A host cell comprising the isolated nucleic acid molecule and/or the group of isolated nucleic acid molecules of claim 7 and/or the vector according to claim 8.

10. A method for producing the antibody or antigen-binding fragment thereof of any one of claims 1-6, comprising a step of culturing a host cell according to claim 9 and optionally a step of isolating the antibody or antigen-binding fragment.

11. A pharmaceutical composition comprising an antibody or an antigen-binding fragment thereof according to any one of claims 1-6 and/or the isolated nucleic acid molecule and/or a group of isolated nucleic acid molecules according to claim 7 and/or the vector according to claim 8 and/or the host cell according to claim 9 and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition according to claim 11, wherein it further comprises an additional therapeutic agent, preferably selected in the group consisting of alkylating agents, angiogenesis inhibitors, antibodies, in particular anti-tumor targeting antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-2 family inhibitors), activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase

(PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, hypomethylating agents, checkpoints inhibitors, peptide vaccine and the like, epitopes or neoepitopes from tumor antigens, as well as combinations of one or more of these agents.

13. The antibody or antigen-binding fragment thereof according to any one of claims 1-6, the pharmaceutical composition of claim 11 or 12, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules of claim 7, the vector according to claim 8, or the host cell according to claim 9 for use as a medicament.

14. Use of t~~T~~he antibody or antigen-binding fragment thereof according to any one of claims 1-6, the pharmaceutical composition of claim 11 or 12, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules of claim 7, the vector according to claim 8, or the host cell according to claim 9 in the manufacture of a medicament for ~~use according to claim 13 in~~ the prevention or treatment of cancer.

15. The ~~antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for~~ use according to claim 14, wherein the cancer is selected from the group consisting of a hematologic malignancy or a solid tumor with expression of PD-1 and/or PD-L1 such as a cancer selected from the group consisting of hematolymphoid neoplasms, angioimmunoblastic T cell lymphoma, myelodysplasic syndrome, and acute myeloid leukemia, a cancer induced by virus or associated with immunodeficiency such as a cancer selected from the group consisting of Kaposi sarcoma (e.g., associated with Kaposi sarcoma herpes virus); cervical, anal, penile and vulvar squamous cell cancer and oropharyngeal cancers (e.g., associated with human papilloma virus); B cell non-Hodgkin lymphomas (NHL) including diffuse large B-cell lymphoma, Burkitt lymphoma, plasmablastic lymphoma, primary central nervous system lymphoma, HHV-8 primary effusion lymphoma, classic Hodgkin lymphoma, and lymphoproliferative disorders (e.g., associated with Epstein-Barr virus (EBV) and/or Kaposi sarcoma herpes virus); hepatocellular carcinoma (e.g., associated with hepatitis B and/or C viruses); Merkel cell carcinoma (e.g., associated with Merkel cell polyoma virus (MPV)); and cancer associated with human immunodeficiency virus infection (HIV) infection, and a cancer selected from the group consisting of metastatic or not metastatic, Melanoma, malignant mesothelioma, Non-Small Cell Lung Cancer, Renal Cell Carcinoma, Hodgkin's Lymphoma, Head and Neck Cancer, Urothelial

Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Small Cell Lung Cancer, Metastatic Merkel Cell Carcinoma, Gastric or Gastroesophageal cancers and Cervical Cancer.

16. The ~~antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for~~ use according to claim 14, wherein the cancer has tumor cells which are PD-L1 negative.

17. Use of t~~T~~he antibody or antigen-binding fragment thereof according to any one of claims 1-6, the pharmaceutical composition of claim 11 or 12, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules of claim 7, the vector according to claim 8, or the host cell according to claim 9 in the manufacture of a medicament for use in combinatorial therapy for treating or preventing cancer ~~according to any one of claims 10-16~~, ~~for use~~ wherein said medicament is to be administered in combination with radiotherapy or an additional therapeutic agent, preferably selected in the group consisting of alkylating agents, angiogenesis inhibitors, antibodies, in particular anti-tumor targeting antibodies, antimetabolites, antimitotics, antiproliferatives, antivirals, aurora kinase inhibitors, apoptosis promoters (for example, Bcl-2 family inhibitors), activators of death receptor pathway, Bcr-Abl kinase inhibitors, BiTE (Bi-Specific T cell Engager) antibodies, antibody drug conjugates, biologic response modifiers, Bruton's tyrosine kinase (BTK) inhibitors, cyclin-dependent kinase inhibitors, cell cycle inhibitors, cyclooxygenase-2 inhibitors, DVDs, leukemia viral oncogene homolog (ErbB2) receptor inhibitors, growth factor inhibitors, heat shock protein (HSP)-90 inhibitors, histone deacetylase (HDAC) inhibitors, hormonal therapies, immunologicals, inhibitors of inhibitors of apoptosis proteins (IAPs), intercalating antibiotics, kinase inhibitors, kinesin inhibitors, Jak2 inhibitors, mammalian target of rapamycin inhibitors, microRNAs, mitogen-activated extracellular signal-regulated kinase inhibitors, multivalent binding proteins, non-steroidal anti-inflammatory drugs (NSAIDs), poly ADP (adenosine diphosphate)-ribose polymerase (PARP) inhibitors, platinum chemotherapeutics, polo-like kinase (Plk) inhibitors, phosphoinositide-3 kinase (PI3K) inhibitors, proteasome inhibitors, purine analogs, pyrimidine analogs, receptor tyrosine kinase inhibitors, retinoids/deltoids plant alkaloids, small inhibitory ribonucleic acids (siRNAs), topoisomerase inhibitors, ubiquitin ligase inhibitors, hypomethylating agents, checkpoints inhibitors, peptide vaccine and the like, epitopes or neoepitopes from tumor antigens, as well as combinations of one or more of these agents.

18. The ~~antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for~~ use according to claim 13 in the prevention or treatment of an infectious disease, preferably a chronic infectious disease, even more preferably caused by a virus selected from the group consisting of HIV,

hepatitis virus, herpes virus, adenovirus, influenza virus, flaviviruses, echovirus, rhinovirus, coxsackie virus, coronavirus, respiratory syncytial virus, mumps virus, rotavirus, measles virus, rubella virus, parvovirus, vaccinia virus, HTLV virus, dengue virus, papillomavirus, molluscum virus, poliovirus, rabies virus, JC virus and arboviral encephalitis virus.

~~19. The antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for use according to claim 13 in the prevention or treatment of patients with lymphopenic disorder.~~

19~~20~~. The ~~antibody or antigen-binding fragment thereof, the pharmaceutical composition, the isolated nucleic acid molecule or the group of isolated nucleic acid molecules, the vector, or the host cell for~~ use according to any one of claims 13-18~~9~~, wherein the subject to be treated is immunosuppressed, immunocompromised or immunodepressed.