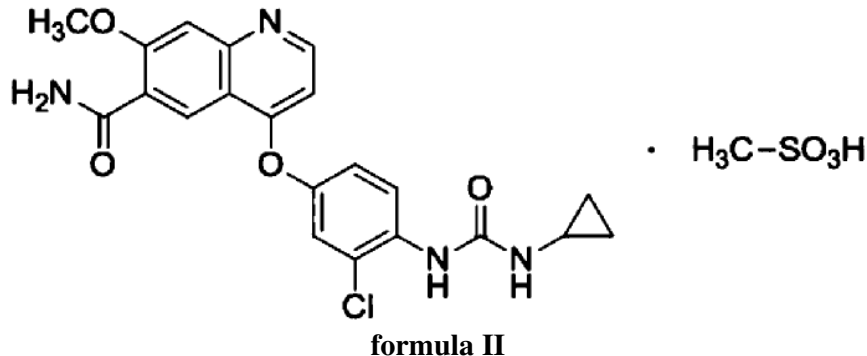


mesylate), named 4-[3-chloro-4-(cyclopropylureido)phenoxy]-7-methoxyquinoline-6-carboxamide mesylate, the chemical structure of which is provided below (formula II):



However, for a variety of tumors, the disease is still uncontrollable for a long term after chemotherapy, and the 5-year survival rate is still very low. Therefore, developing a medication or combination therapy with lower toxicity and higher efficacy is of great meaning.

SUMMARY

By intensive research and creative efforts, the inventor correspondingly modified the Fc fragment of the anti-PD-1 antibody structure to reduce the binding capacity of the Fc region to Fc receptors, thereby reducing ADCC, ADCP and/or CDC effects on T cells and increasing the efficacy of the anti-PD-1 antibody. The present [inventiondisclosure](#) is detailed below.

One aspect of the present [inventiondisclosure](#) relates to an antibody, wherein a heavy chain variable region of the antibody comprises HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NOs: 19–21, respectively, and a light chain variable region of the antibody comprises LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NOs: 22–24, respectively; the antibody is of human IgG1 subtype; wherein, according to the EU numbering system, a heavy chain constant region of the antibody comprises mutations at any 2 or 3 of positions 234, 235 and 237, and an affinity constant of the antibody to FcγRIIIa and/or C1q is reduced after the mutation as compared to that before the mutation; preferably, the affinity constant is measured by a Fortebio Octet system.

In one [embodimentexample](#) of the present [inventiondisclosure](#), the antibody is a monoclonal antibody.

In one [embodimentexample](#) of the present [inventiondisclosure](#), the antibody is an anti-PD-1 antibody, preferably an anti-PD-1 monoclonal antibody.

In some [embodimentexamples](#) of the present [inventiondisclosure](#), for the antibody, according to the EU numbering system, the heavy chain constant region of the antibody comprises the following mutations at positions 234, 235 and/or 237:

L234A and L235A;

L234A and G237A;

L235A and G237A;

or

L234A, L235A and G237A.

In the present [inventiondisclosure](#), letters before the position number represent amino acids before mutation, and letters after the position number represent amino acids after mutation, unless otherwise specified.

The present [inventiondisclosure](#) also relates to an antibody, wherein a heavy chain variable region of the antibody comprises HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NOs: 19–21, respectively, and a light chain variable region of the antibody comprises LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NOs: 22–24, respectively;

the antibody is of human IgG1 subtype;

wherein according to the EU numbering system, a heavy chain constant region of the antibody comprises the following mutations at positions 234, 235 and/or 237:

L234A and L235A;

L234A and G237A;

L235A and G237A;

or

L234A, L235A and G237A.

[Another aspect of the present disclosure relates to an antibody, wherein](#)

[a heavy chain variable region of the antibody comprises HCDR1-HCDR3 with amino acid sequences set forth in SEQ ID NOs: 19–21, respectively, and a light chain variable region of the antibody comprises LCDR1-LCDR3 with amino acid sequences set forth in SEQ ID NOs: 22–24, respectively;](#)

[the antibody is of human IgG1 subtype;](#)

[wherein according to the EU numbering system, a heavy chain constant region of the antibody comprises the following mutations:](#)

[L234A and L235A;](#)

[L234A and G237A;](#)

[L235A and G237A;](#)

[or](#)

[L234A, L235A and G237A.](#)

In some [embodimentexamples](#) of the present [inventiondisclosure](#), according to the EU numbering system, the heavy chain constant region of the antibody further comprises one or more mutations

selected from:

N297A, D265A, D270A, P238D, L328E, E233D, H268D, P271G, A330R, C226S, C229S, E233P, P331S, S267E, L328F, A330L, M252Y, S254T, T256E, N297Q, P238S, P238A, A327Q, A327G, P329A, K322A, T394D, G236R, G236A, L328R, A330S, P331S, H268A, E318A and K320A.

In some [embodimentexamples](#) of the present [inventiondisclosure](#), for the antibody, the heavy chain variable region of the antibody comprises an amino acid sequence selected from SEQ ID NO: 2 and SEQ ID NO: 6; and the light chain variable region of the antibody comprises an amino acid sequence selected from SEQ ID NO: 4 and SEQ ID NO: 8.

In some [embodimentexamples](#) of the present [inventiondisclosure](#), for the antibody, the heavy chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 2, and the light chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 4;

the heavy chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 2, and the light chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 8;

the heavy chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 6, and the light chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 4; or

the heavy chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 6, and the light chain variable region of the antibody comprises an amino acid sequence set forth in SEQ ID NO: 8.

In one [embodimentexample](#) of the present [inventiondisclosure](#), for the antibody, the heavy chain is set forth in SEQ ID NO: 16, and the light chain is set forth in SEQ ID NO: 12;

or

the heavy chain is set forth in SEQ ID NO: 18, and the light chain is set forth in SEQ ID NO: 12.

The variable regions of the light chain and the heavy chain determine the binding of the antigen; the variable region of each chain comprises three hypervariable regions, i.e., complementarity determining regions (CDRs) (the CDRs of the heavy chain (H) include HCDR1, HCDR2, HCDR3, and the CDRs of the light chain (L) include LCDR1, LCDR2, LCDR3; defined by Kabat et al., see *Sequences of Proteins of Immunological Interest*, Fifth Edition (1991), Volumes 1–3, NIH Publication 91-3242, Bethesda MD).

The amino acid sequences of the CDR regions of the monoclonal antibody in (1) to (3) above are analyzed by technical means well known to those skilled in the art, for example, by a VBASE2 database:

The antibodies 14C12, 14C12H1L1(hG1WT), 14C12H1L1(hG1DM) and 14C12H1L1(hG1TM) involved in the present [inventiondisclosure](#) have the same CDRs.

The amino acid sequences of the 3 CDR regions of the heavy chain variable region are as follows:

HCDR1: GFAFSSYD (SEQ ID NO: 19),

HCDR2: ISGGGRYT (SEQ ID NO: 20), and

HCDR3: ANRYGEAWFAY (SEQ ID NO: 21).

The amino acid sequences of the 3 CDR regions of the light chain variable region are as follows:

LCDR1: QDINTY (SEQ ID NO: 22),

LCDR2: RAN (SEQ ID NO: 23), and

LCDR3: LQYDEFPLT (SEQ ID NO: 24).

In some [embodimentexamples](#) of the present [inventiondisclosure](#), the antibody binds to FcγRIIIa_F158, FcγRI, FcγRIIa_H131, FcγRIIIa_V158 and/or FcγRIIb with an affinity constant greater than about 10^{-7} M, for example, greater than about 10^{-6} M, 10^{-5} M, 10^{-4} M, or 10^{-3} M or greater; preferably, the affinity constant is measured by a Fortebio Octet system;

preferably, the antibody has no binding signal or a binding signal of less than 0.1 nm to FcγRIIIa_F158, FcγRI, FcγRIIa_H131, FcγRIIIa_V158 and/or FcγRIIb; preferably, the binding signal refers to a response measured by a Fortebio Octet system.

In some [embodimentexamples](#) of the present [inventiondisclosure](#), the antibody binds to C1q with an affinity constant greater than about 10^{-9} M, for example, greater than about 10^{-8} M, 10^{-7} M, 10^{-6} M, or 10^{-5} M or greater; preferably, the affinity constant is measured by a Fortebio Octet system;

preferably, the antibody has no binding signal or a binding signal of less than 0.1 nm to C1q; preferably, the binding signal refers to a response measured by a Fortebio Octet system.

In some [embodimentexamples](#) of the present [inventiondisclosure](#), the antibody is a monoclonal antibody.

In some [embodimentexamples](#) of the present [inventiondisclosure](#), the antibody is a humanized antibody.

Another [aspectexample](#) of the present [inventiondisclosure](#) relates to an isolated nucleic acid molecule encoding the antibody according to any [embodimentexample](#) of the present [inventiondisclosure](#).

Another aspect of the present disclosure relates to an isolated nucleic acid molecule, encoding the antibody disclosed herein.

Yet another [inventiondisclosure](#) relates to a vector, comprising the isolated nucleic acid molecule disclosed herein.

Yet another [aspectexample](#) of the present [inventiondisclosure](#) relates to a host cell comprising the isolated nucleic acid molecule or the vector disclosed herein.

Another aspect of the present disclosure relates to a host cell, comprising the isolated nucleic acid molecule disclosed herein or the vector disclosed herein.

Yet another [aspectexample](#) of the present [inventiondisclosure](#) relates to a conjugate, comprising an antibody and a conjugated moiety, wherein the antibody is the antibody according to any [embodimentexample](#) of the present [inventiondisclosure](#), and the conjugated moiety is a detectable label; preferably, the conjugated moiety is a radioisotope, a fluorescent substance, a luminescent substance, a colored substance, or an enzyme.

Another aspect of the present disclosure relates to a conjugate, comprising the antibody disclosed herein and a conjugated moiety, wherein the conjugated moiety is a detectable label; preferably, the conjugated moiety is a radioisotope, a fluorescent substance, a luminescent substance, a colored substance, or an enzyme.

Yet another [aspectexample](#) of the present [inventiondisclosure](#) relates to a kit comprising the antibody according to any [embodimentexample](#) of the present [inventiondisclosure](#) or comprising the conjugate disclosed herein;

preferably, the kit further comprises a second antibody specifically recognizing the antibody; optionally, the second antibody further comprises a detectable label, for example, a radioisotope, a fluorescent substance, a luminescent substance, a colored substance, or an enzyme.

Another aspect of the present disclosure relates to a kit, comprising the antibody disclosed herein or the conjugate disclosed herein;

wherein preferably, the kit further comprises a second antibody specifically recognizing the antibody; optionally, the second antibody further comprises a detectable label, for example, a radioisotope, a fluorescent substance, a luminescent substance, a colored substance, or an enzyme.

Yet another [aspectexample](#) of the present [inventiondisclosure](#) relates to use of the antibody or the conjugate according to any [embodimentexample](#) of the present [inventiondisclosure](#) in preparing a kit for detecting the presence or level of PD-1 in a sample.

Another aspect of the present disclosure relates to use of the antibody disclosed herein or the conjugate disclosed herein in preparing a kit for detecting the presence or level of PD-1 in a sample.

Yet another aspect-example of the present inventiondisclosure relates to a pharmaceutical composition comprising the antibody or the conjugate according to any embodimentexample of the present inventiondisclosure; optionally, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or excipient.

Another aspect of the present disclosure relates to a pharmaceutical composition, comprising the antibody disclosed herein or the conjugate disclosed herein, wherein, optionally, the pharmaceutical composition further comprises a pharmaceutically acceptable carrier and/or excipient.

In one or more embodimentexamples of the present inventiondisclosure, the pharmaceutical composition further comprises one or more anti-tumor chemotherapeutics; preferably, the anti-tumor chemotherapeutic is a tyrosine kinase inhibitor; more preferably, the anti-tumor chemotherapeutic is anlotinib or a pharmaceutically acceptable salt thereof (e.g., hydrochloride salt), or lenvatinib or a pharmaceutically acceptable salt thereof (e.g., mesylate salt).

In one or more embodimentexamples of the present inventiondisclosure, the unit dose of the pharmaceutical composition is 100–1000 mg, 200–800 mg, 200–500 mg, 300–600 mg, 400–500 mg, or 450 mg, based on the mass of the antibody.

Yet another aspect-example of the present inventiondisclosure relates to a therapeutic combination comprising: the antibody according to any embodimentexample of the present inventiondisclosure, and at least one (e.g., 1, 2 or 3) anti-tumor chemotherapeutic.

Another aspect of the present disclosure relates to a therapeutic combination, comprising the antibody disclosed herein, and at least one (e.g., 1, 2 or 3) anti-tumor chemotherapeutic.

In one or more embodimentexamples of the present inventiondisclosure, for the therapeutic combination, the anti-tumor chemotherapeutic is a tyrosine kinase inhibitor; preferably, the anti-tumor chemotherapeutic is anlotinib or a pharmaceutically acceptable salt thereof (e.g., hydrochloride salt), or lenvatinib or a pharmaceutically acceptable salt thereof (e.g., mesylate salt).

In one or more embodimentexamples of the present inventiondisclosure, for the therapeutic combination, the unit dose of the antibody is 100–1000 mg, 200–800 mg, 200–500 mg, 300–600 mg, 400–500 mg, or 450 mg.

In one or more embodimentexamples of the present inventiondisclosure, for the therapeutic combination, the unit dose of the anti-tumor chemotherapeutic is 0.1–100 mg, 0.5–50 mg, 0.5–10 mg, 1–10 mg, 2–8 mg, or 1–5 mg.

In one or more embodimentexamples of the present inventiondisclosure, for the therapeutic combination, the unit dose of the anti-tumor chemotherapeutic is 1–20 mg, 2–15 mg, 4–12 mg, or 8–12 mg.

In one or more [embodimentexamples](#) of the present [inventiondisclosure](#), for the therapeutic combination, wherein

the therapeutic combination is a fixed combination, e.g., in the form of a solid pharmaceutical composition or a liquid pharmaceutical composition; or

the therapeutic combination is a non-fixed combination, e.g., the anti-PD-1 antibody and the anti-tumor chemotherapeutic in the non-fixed combination are each in the form of a pharmaceutical composition.

Yet another [aspect-example](#) of the present [inventiondisclosure](#) relates to a kit product comprising the pharmaceutical composition according to any [embodimentexample](#) of the present [inventiondisclosure](#) or the therapeutic combination according to any [embodimentexample](#) of the present [inventiondisclosure](#), and a package insert.

Another aspect of the present disclosure relates to a kit product, comprising: the pharmaceutical composition disclosed herein or the therapeutic combination disclosed herein, and a package insert.

Yet another [aspect-example](#) of the present [inventiondisclosure](#) relates to use of the antibody according to any [embodimentexample](#) of the present [inventiondisclosure](#), the conjugate disclosed herein, the pharmaceutical composition according to any [embodimentexample](#) of the present [inventiondisclosure](#) or the therapeutic combination according to any [embodimentexample](#) of the present [inventiondisclosure](#) in preparing a medicament for treating and/or preventing a tumor or anemia, or in preparing a medicament for diagnosing a tumor or anemia, wherein preferably the tumor is selected from one or more of melanoma, renal cancer, prostate cancer, bladder cancer, colon cancer, rectal cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, leukemia, nasopharyngeal cancer and endometrial cancer;

preferably, the lung cancer is selected from one or more of non-small cell lung cancer, small cell lung cancer and squamous cell lung cancer;

preferably, the gastric cancer is gastric adenocarcinoma or gastroesophageal junction adenocarcinoma;

preferably, the tumor is a solid tumor of MSI-H/dMMR phenotype; preferably, the tumor is selected from one or more of the following tumors of MSI-H/dMMR phenotype:

colon cancer, rectal cancer, endometrial cancer, gastric cancer, mesothelioma, sarcoma, adrenocortical carcinoma, malignant melanoma and ovarian germ cell neoplasm.

Another aspect of the present disclosure provides use of the antibody disclosed herein, the conjugate disclosed herein, the pharmaceutical composition disclosed herein or the therapeutic combination disclosed herein in preparing a medicament for treating and/or preventing a tumor or anemia, or in preparing a medicament for diagnosing a tumor or anemia, wherein preferably the tumor is selected from one or more of melanoma, renal cancer, prostate cancer, bladder cancer, colon cancer, rectal cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, leukemia, nasopharyngeal cancer and endometrial cancer;

preferably, the lung cancer is selected from one or more of non-small cell lung cancer, small cell lung cancer and squamous cell lung cancer;

preferably, the gastric cancer is gastric adenocarcinoma or gastroesophageal junction adenocarcinoma;

preferably, the tumor is a solid tumor of MSI-H/dMMR phenotype; preferably, the tumor is selected from one or more of the following tumors of MSI-H/dMMR phenotype:

colon cancer, rectal cancer, endometrial cancer, gastric cancer, mesothelioma, sarcoma, adrenocortical carcinoma, malignant melanoma and ovarian germ cell neoplasm.

In one or more ~~embodiment~~examples of the present ~~invention~~disclosure, for the use, the tumor is a recurrent, metastatic (e.g., lymphatic metastasis, brain metastasis, and/or bone metastasis) or refractory tumor.

MSI refers to microsatellite instability. Microsatellites are short tandem repeats throughout the human genome, including 10–50 repeats of one, two or more nucleotides. Microsatellites in certain abnormal cells, such as tumors, are altered in length by insertion or deletion of repeat units as compared to normal cells. Such alteration is referred to as MSI. Based on instability and extent, MSI can be classified as microsatellite instability-high (MSI-H), microsatellite instability-low (MSI-L) and microsatellite stable (MSS). The major cause of MSI is DNA mismatch repair (MMR) deficiency. Human mismatch repair genes (MMR genes) can express corresponding mismatch repair proteins through transcription and translation. Absence of any MMR protein may lead to mismatch repair deficiency, and basepair mismatch will accumulate in the process of DNA replication due to such deficiency, ultimately resulting in MSI. About 15% of colorectal cancers are attributed to the MSI pathway. This was first reported in colorectal cancer, and may also occur in gastric cancer, endometrial cancer, adrenocortical carcinoma and the like (Baretti M et al., *Pharmacol Ther.*, 2018; 189:45-62). MSI-H/dMMR characteristics were also found in mesothelioma, sarcoma, adrenocortical carcinoma, malignant melanoma and ovarian germ cell neoplasm in subsequent studies.

MSI-H and dMMR represent the results of two different assays and are biologically consistent, called MSI-H/dMMR or MSI-high/dMMR, while MSI-L and MSS are phenotypes of proficient MMR (pMMR). The detection of dMMR is to perform an immunohistochemical assay of protein expression for four mismatch genes of MSH2, MLH1, MSH6 and PMS2 based on tumor specimens (including surgical specimens and aspiration specimens). Absence of any of the four proteins confirms the dMMR; positive results of all the four proteins indicate pMMR, i.e., a complete mismatch repair function. The detection of MSI is to match the length of the repeated DNA sequences (microsatellite sequences) in tumor cells and somatic cells, and to compare the lengths. When 5 standard loci are detected using PCR based on the American NCI standard, inconsistencies in two or more loci indicate instability, defined as MSI-H, one inconsistent locus indicates MSI-L, and 5 consistent loci

indicate MSS. High-throughput sequencing (also referred to as next-generation sequencing, or NGS) can also be used as a method for detecting microsatellite instability. When more microsatellite loci are selected, such as more than 5 loci or additional microsatellite loci, for PCR assay, inconsistency in $\geq 30\%$ loci is defined as MSI-H, consistency in all loci is defined as MSS, and inconsistency between 0 and 30 % is defined as MSI-L.

Yet another [aspect/example](#) of the present [invention/disclosure](#) relates to use of the antibody according to any [embodiment/example](#) of the present [invention/disclosure](#), the conjugate described herein, the pharmaceutical composition according to any [embodiment/example](#) of the present [invention/disclosure](#) or the therapeutic combination according to any [embodiment/example](#) of the present [invention/disclosure](#) in preparing:

a medicament for blocking the binding of PD-1 to PD-L1,

a medicament for down-regulating the activity or level of PD-1,

a medicament for relieving the immunosuppression of PD-1 in an organism, or

a medicament for elevating IFN- γ and/or IL-2 expression in T lymphocytes.

Another aspect of the present disclosure relates to use of the antibody disclosed herein, the conjugate disclosed herein, the pharmaceutical composition disclosed herein or the therapeutic combination disclosed herein in preparing:

a medicament for blocking the binding of PD-1 to PD-L1,

a medicament for down-regulating the activity or level of PD-1,

a medicament for relieving the immunosuppression of PD-1 in an organism, or

a medicament for elevating IFN- γ and/or IL-2 expression in T lymphocytes.

Interferon γ (IFN- γ) is produced primarily and innately by natural killer cells (NK) and natural killer T cells (NKT) and is produced by effector T cells such as CD4 Th1 cells and CD8 cytotoxic T lymphocytes stimulated by specific antigens. As an important innate and acquired immune cytokine, IFN- γ plays an important role in fighting or inhibiting viral infection and certain bacterial and protozoal disease infections. Meanwhile, IFN- γ can activate macrophages, induce the expression of type II major histocompatibility complex, and activate the immune response to control tumor progression (Schoenborn JR, Wilson CB., Regulation of Interferon- γ During Innate and Adaptive Immune Responses, *Advances in Immunology*, 2007, 96:41–101). In the *in vitro* experiment of the present [invention/disclosure](#), the antibody disclosed herein can induce the IFN- γ secretion to activate the immune response.

Interleukin 2 (IL-2) is produced by T cells. It is a growth factor that regulates T cell subgroups, and an important factor in regulating immune responses. It promotes the proliferation of activated B cells, and participates in antibody responses, hematopoiesis and tumor surveillance. Recombinant human IL-2 has been approved by the U.S. FDA for treating malignancies, including melanoma and renal tumor (Chavez, A.R., et al.,

Pharmacologic administration of interleukin-2, *Ann. N.Y. Acad. Sci.*, 2009, 1182:p.14–27). *In-vitro* studies demonstrated that the antibody disclosed herein can specifically relieve the immunosuppression of PD-1, activate T cells, and induce IL-2 generation, and is promising in wide applications in therapies against diseases such as tumors and parasite infections.

Yet another [aspect-example](#) of the present [invention-disclosure](#) relates to an *in vivo* or *in vitro* method comprising: administering to a subject in need an effective amount of the antibody according to any [embodiment-example](#) of the present [invention-disclosure](#), the conjugate described herein, the pharmaceutical composition according to any [embodiment-example](#) of the present [invention-disclosure](#) or the therapeutic combination according to any [embodiment-example](#) of the present [invention-disclosure](#). The method is selected from:

a method for blocking the binding of PD-1 to PD-L1,
a method for down-regulating the activity or level of PD-1,
a method for relieving the immunosuppression of PD-1 in an organism, or
a method for elevating IFN- γ and/or IL-2 expression in T lymphocytes.

Also related are the antibody according to any [embodiment-example](#) of the present [invention-disclosure](#), the conjugate described herein, the pharmaceutical composition according to any [embodiment-example](#) of the present [invention-disclosure](#) or the therapeutic combination according to any [embodiment-example](#) of the present [invention-disclosure](#) for use in treating and/or preventing a tumor or anemia, or in diagnosing a tumor or anemia, wherein preferably the tumor is selected from one or more of melanoma, renal cancer, prostate cancer, bladder cancer, colon cancer, rectal cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, leukemia, nasopharyngeal cancer and endometrial cancer; preferably, the lung cancer is selected from one or more of non-small cell lung cancer, small cell lung cancer and squamous cell lung cancer; preferably, the gastric cancer is gastric adenocarcinoma or gastroesophageal junction adenocarcinoma; preferably, the tumor is a solid tumor of MSI-H/dMMR phenotype; preferably, the tumor is selected from one or more of the following tumors of MSI-H/dMMR phenotype:

colon cancer, rectal cancer, endometrial cancer, gastric cancer, mesothelioma, sarcoma, adrenocortical carcinoma, malignant melanoma and ovarian germ cell neoplasm.

Another aspect of the present disclosure relates to the antibody disclosed herein, the conjugate disclosed herein, the pharmaceutical composition disclosed herein or the therapeutic combination disclosed herein for use in treating and/or preventing a tumor or anemia, or for use in diagnosing a tumor or anemia, wherein preferably the tumor is selected from one or more of melanoma, renal cancer, prostate cancer, bladder cancer, colon cancer, rectal cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, leukemia, nasopharyngeal cancer and endometrial cancer;

preferably, the lung cancer is selected from one or more of non-small cell lung cancer, small cell lung cancer and squamous cell lung cancer;

preferably, the gastric cancer is gastric adenocarcinoma or gastroesophageal junction adenocarcinoma;

preferably, the tumor is a solid tumor of MSI-H/dMMR phenotype; preferably, the tumor is selected from one or more of the following tumors of MSI-H/dMMR phenotype:

colon cancer, rectal cancer, endometrial cancer, gastric cancer, mesothelioma, sarcoma, adrenocortical carcinoma, malignant melanoma and ovarian germ cell neoplasm.

In one or more embodimentexample of the present inventiondisclosure, for the antibody or the conjugate described herein, the tumor is a recurrent, metastatic (e.g., lymphatic metastasis, brain metastasis, and/or bone metastasis) or refractory tumor.

The antibody according to any embodimentexample of the present inventiondisclosure, the conjugate described herein, the pharmaceutical composition according to any embodimentexample of the present inventiondisclosure or the therapeutic combination according to any embodimentexample of the present inventiondisclosure are used for:

blocking the binding of PD-1 to PD-L1,

down-regulating the activity or level of PD-1,

relieving the immunosuppression of PD-1 in an organism, or

elevating IFN- γ and/or IL-2 expression in T lymphocytes.

Yet another aspect-example of the present inventiondisclosure relates to a method of treating and/or preventing a tumor or anemia, or a method of diagnosing a tumor or anemia, comprising: administering to a subject in need an effective amount of the antibody according to any embodimentexample of the present inventiondisclosure, the conjugate described herein, the pharmaceutical composition according to any embodimentexample of the present inventiondisclosure or the therapeutic combination according to any embodimentexample of the present inventiondisclosure, wherein preferably the tumor is selected from one or more of melanoma, renal cancer, prostate cancer, bladder cancer, colon cancer, rectal cancer, gastric cancer, liver cancer, lung cancer, ovarian cancer, leukemia, nasopharyngeal cancer and endometrial cancer;

preferably, the lung cancer is selected from one or more of non-small cell lung cancer, small cell lung cancer and squamous cell lung cancer;

preferably, the gastric cancer is gastric adenocarcinoma or gastroesophageal junction adenocarcinoma;

preferably, the tumor is a solid tumor of MSI-H/dMMR phenotype; preferably, the tumor is selected from one or more of the following tumors of MSI-H/dMMR phenotype:

colon cancer, rectal cancer, endometrial cancer, gastric cancer, mesothelioma, sarcoma,

adrenocortical carcinoma, malignant melanoma and ovarian germ cell neoplasm.

In one or more [embodimentexamples](#) of the present [inventiondisclosure](#), for the method, the tumor is a recurrent, metastatic (e.g., lymphatic metastasis, brain metastasis, and/or bone metastasis) or refractory tumor.

In one or more [embodimentexamples](#) of the present [inventiondisclosure](#), for the method, the administration is before or after a surgical treatment and/or before or after a radiotherapy.

In one or more [embodimentexamples](#) of the present [inventiondisclosure](#), the method, wherein

the unit dose of the anti-PD-1 antibody is 0.1–100 mg, preferably 1–10 mg (e.g., 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7 mg, 8 mg, 9 mg or 10 mg) per kg body weight; alternatively, the unit dose of the anti-PD-1 antibody is 10–1000 mg (e.g., about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 mg, about 400 mg, about 450 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg or about 1000 mg), preferably 50–500 mg, 100–400 mg, 150–300 mg, 150–250 mg or 200 mg in each subject;

preferably, the dose is given once every 3 days, 4 days, 5 days, 6 days, 10 days, 1 week, 2 weeks or 3 weeks;

preferably, the route of administration is intravenous drip infusion or intravenous injection. In some [embodimentexamples](#), the administration of the anti-PD-1 antibody is performed in cycles of 2 weeks (14 days) or 3 weeks (21 days), and preferably, the anti-PD-1 antibody is administered intravenously on the first day (D1) of each cycle. For example, the anti-PD-1 antibody is administered once every two weeks (q2w) or three weeks (q3w).

In the present [inventiondisclosure](#), unless otherwise defined, the scientific and technical terms used herein have the meanings generally understood by those skilled in the art. In addition, the laboratory operations of cell culture, molecular genetics, nucleic acid chemistry and immunology used herein are the routine procedures widely used in the corresponding fields. Meanwhile, in order to better understand the present [inventiondisclosure](#), the definitions and explanations of the relevant terms are provided below.

As used herein, when referring to the amino acid sequence of PD-1 protein (programmed cell death protein 1, NCBI GenBank: NP_005009.2), it includes the full length of the PD-1 protein, or the extracellular fragment PD-1ECD of PD-1 or a fragment comprising PD-

1ECD, and it also includes a fusion protein of PD-1ECD, such as a fragment fused to an Fc protein fragment of a mouse or human IgG (mFc or hFc). However, those skilled in the art will appreciate that in the amino acid sequence of the PD-1 protein, mutations or variations (including but not limited to, substitutions, deletions and/or additions) can be naturally produced or artificially introduced without affecting biological functions thereof. Therefore, in the present ~~invention~~disclosure, the term "PD-1 protein" should include all such sequences and natural or artificial variants thereof. Moreover, when describing the sequence fragment of the PD-1 protein, it includes not only the sequence fragment but also a corresponding sequence fragment in natural or artificial variants thereof.

As used herein, when referring to the amino acid sequence of PDL1 protein (NCBI Genebank ID: NP_054862.1), it includes the full length of PDL1 protein, or the extracellular fragment PDL1ECD of PDL1 or a fragment comprising PDL1ECD; also included are fusion proteins of PDL1ECD, such as a fragment fused to an Fc protein fragment of a mouse or human IgG (mFc or hFc). However, those skilled in the art will appreciate that in the amino acid sequence of the PDL1 protein, mutations or variations (including but not limited to, substitutions, deletions and/or additions) can be naturally produced or artificially introduced without affecting biological functions thereof. Therefore, in the present ~~invention~~disclosure, the term "PDL1 protein" shall include all such sequences and natural or artificial variants thereof. Moreover, when describing the sequence fragment of the PDL1 protein, it includes not only a PDL1 sequence fragment but also a corresponding sequence fragment in natural or artificial variants thereof.

As used herein, the term EC₅₀ refers to the half maximum effective concentration.

As used herein, the term "antibody" refers to an immunoglobulin molecule that generally consists of two pairs of polypeptide chains (each pair with one "light" (L) chain and one "heavy" (H) chain). Antibody light chains are classified as κ and λ light chains. Heavy chains are classified as μ , δ , γ , α , or ϵ . Isotypes of antibodies are defined as IgM, IgD, IgG, IgA, and IgE. In light chains and heavy chains, the variable region and constant region are linked by a "J" region of about 12 or more amino acids, and the heavy chain also comprises a "D" region of about 3 or more amino acids. Each heavy chain consists of a heavy chain variable region (V_H) and a heavy chain constant region (C_H). The heavy chain constant region consists

sequences, enhancer sequences, selection elements, and reporter genes. In addition, the vector may further comprise a replication initiation site.

As used herein, the term "host cell" refers to cells to which vectors can be introduced, including, but not limited to, prokaryotic cells such as *E. coli* or *bacillus subtilis*, fungal cells such as yeast cells or *aspergillus*, insect cells such as S2 drosophila cells or Sf9, or animal cells such as fibroblasts, CHO cells, COS cells, NSO cells, HeLa cells, BHK cells, HEK 293 cells, or human cells.

As used herein, the term "specific binding" refers to a non-random binding reaction between two molecules, such as a reaction between an antibody and an antigen it targets. In some [embodiment examples](#), an antibody specifically binding to an antigen (or an antibody specific to an antigen) means that the antibody binds to the antigen with an affinity (K_D) of less than about 10^{-5} M, e.g., less than about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M or 10^{-10} M or less.

As used herein, the term " K_D " refers to a dissociation equilibrium constant for a specific antibody-antigen interaction, which is used to describe the binding affinity between the antibody and the antigen. A smaller equilibrium dissociation constant indicates a stronger antibody-antigen binding and a higher affinity between the antibody and the antigen. Generally, antibodies bind to antigens (e.g., PD-1 protein) with a dissociation equilibrium constant (K_D) of less than about 10^{-5} M, such as less than about 10^{-6} M, 10^{-7} M, 10^{-8} M, 10^{-9} M or 10^{-10} M or less. K_D can be determined using methods known to those skilled in the art, e.g., using a Fortebio system.

As used herein, the terms "monoclonal antibody" and "mAb" have the same meaning and can be used interchangeably; the terms "polyclonal antibody" and "pAb" have the same meaning and can be used interchangeably; the terms "polypeptide" and "protein" have the same meaning and can be used interchangeably. Besides, amino acids are generally represented herein by single-letter and three-letter abbreviations known in the art. For example, alanine can be represented by A or Ala.

As used herein, the term "pharmaceutically acceptable carrier and/or excipient" refers to a carrier and/or excipient that is pharmacologically and/or physiologically compatible with the subject and the active ingredient. Such carriers and/or excipients are well known in the art (see, e.g., *Remington's Pharmaceutical Sciences*, edited by Gennaro AR, 19th Ed.,

Pennsylvania, Mack Publishing Company, 1995), including but not limited to: pH regulators, surfactants, adjuvants, and ionic strength enhancers. For example, the pH regulators include, but are not limited to, phosphate buffer; the surfactants include, but are not limited to, cationic, anionic, or non-ionic surfactants, such as Tween-80; the ionic strength enhancers include, but are not limited to, sodium chloride.

As used herein, the term "adjuvant" refers to a non-specific immune enhancer, which can enhance the immune response of an organism to antigens or change the type of immune response when delivered into the organism together with the antigens or in advance. There are various adjuvants, including, but not limited to, aluminum adjuvant (e.g., aluminum hydroxide), Freund's adjuvant (e.g., complete Freund's adjuvant and incomplete Freund's adjuvant), *Corynebacterium parvum*, lipopolysaccharide, cytokine, etc. The Freund's adjuvant is the most commonly used adjuvant in animal experiments. The aluminum hydroxide adjuvant is used more frequently in clinical trials.

As used herein, the term "effective amount" refers to an amount sufficient to obtain or at least partially obtain desired effects. For example, a prophylactically effective amount against a disease (e.g., RA) refers to an amount sufficient to prevent, stop, or delay the onset of the disease (e.g., RA); a therapeutically effective amount refers to an amount sufficient to cure or at least partially stop a disease and complications thereof in patients suffering from the disease. It is undoubtedly within the ability of those skilled in the art to determine such an effective amount. For example, the amount effective for therapeutic purpose will depend on the severity of the disease to be treated, the overall state of the patient's own immune system, the general condition of the patient such as age, body weight and gender, the route of administration, and other treatments given concurrently, etc.

As used herein, the term "completely eliminated" refers to the absence of binding signal or an extremely weak binding signal as detected by existing instrumentation (e.g., a Fortebio Octet system). In one [embodiment example](#) of the present [invention disclosure](#), the absence of binding signal or the extremely weak binding signal refers to a binding signal (i.e., response) below 0.1 nm.

A "recurrent" cancer is one that regenerates at the original site or a distant site after response to a previous treatment (e.g., surgery). A "locally recurrent" cancer is one that occurs at the same site as the previously treated cancer after treatment.