

number of preclinical and clinical studies. Two antibodies against CTLA-4 are in clinical development. Ipilimumab (MDX-010, BMS-734016), a fully human anti-CTLA-4 monoclonal antibody of IgG1-kappa isotype, is an immunomodulatory agent that has been approved as monotherapy for treatment of advanced melanoma. The proposed mechanism of action for Ipilimumab is interference of the interaction of CTLA-4, expressed on a subset of activated T cells, with CD80/CD86 molecules on professional antigen presenting cells. This results in T-cell potentiation due to blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4 and CD80/CD86 interaction. The resulting T-cell activation, proliferation and lymphocyte infiltration into tumors, leads to tumor cell death. The commercial dosage form is a 5 mg/mL concentrate for solution for infusion. Ipilimumab is also under clinical investigation of other tumor types, including prostate and lung cancers. Another anti-CTLA-4 antibody Tremelimumab was evaluated as monotherapy in melanoma and malignant mesothelioma.

Summary

The present disclosure provides isolated antibodies, in particular monoclonal antibodies or humanized monoclonal antibodies. In one aspect, the present disclosure refers to an antibody or antigen binding fragment thereof, comprising a heavy chain variable region comprising CDR1, CDR2, and CDR sequences; and a light chain variable region comprising a light chain complementary-determining region 1 (LCDR1) defined by SEQ ID NO: 41, LCDR2 defined by defined by SEQ ID NO: 32, and LCDR3 defined by SEQ ID NO: 22, and a heavy chain variable region comprising a heavy chain complementary determining region 1 (HCDR1) defined by SEQ ID NO: 36, HCDR2 defined by defined by SEQ ID NO: 28, and HCDR3 defined by SEQ ID NO: 18; and wherein the antibody or the antigen binding fragment specifically binds to CTLA-4.

In another aspect, the present disclosure refers to an antibody or an antigen binding-fragment thereof, wherein the antibody or the antigen binding-fragment binds to human, monkey and mouse CTLA-4.

The aforesaid antibody or the antigen binding-fragment inhibits CTLA-4 binding to CD80 or CD86.

In the aforesaid antibody or the antigen binding-fragment, binding

epitope of the antibody or antigen binding-fragment comprises N145 or polysaccharide on N145 of CTLA-4.

5 In one example, the present disclosure provides an antibody or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to human, monkey CTLA-4, wherein binding epitope of the antibody or antigen binding-fragment comprises P138 of CTLA-4.

10 In one example, the present disclosure provides an antibody or an antigen binding fragment thereof, wherein the antibody or the antigen binding-fragment

- a) binds to human CTLA-4 with a K_D of $4.77E-10$ M or less; and
- b) binds to mouse CTLA-4 with a K_D of $1.39E-09$ M or less.

15 The aforesaid antibody, wherein the antibody or the antigen binding-fragment exhibits at least one of the following properties:

- a) binds to human CTLA-4 with a K_D of between $4.77E-10$ M and $2.08E-10$ M and to mouse CTLA-4 with a K_D of between $1.39E-09$ M and $9.06E-10$ M;
- b) enhances interleukin-2 release from stimulated PBMCs.
- 20 c) does not substantially bind to any protein selected from a group consisting of Factor VIII, FGFR, PD-1, CD22, VEGF, CD3, HER3, OX40, and 4-1BB.

25 The present disclosure provides an antibody or an antigen binding fragment thereof, comprising an amino acid sequence that is at least 70%, 80%, 90% or 95% homologous to a sequence selected from a group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, wherein the antibody or the antigen binding-fragment specifically binds to

CTLA-4.

The present disclosure provides an antibody or an antigen binding fragment thereof, comprising an amino acid sequence selected from a group consisting of SEQ
5 ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14,
wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4.

In another aspect, the present disclosure refers to an antibody, or an antigen-
10 binding fragment thereof, comprising:

a) a variable region of a heavy chain having an amino acid sequence that is at least 70%, 80%, 90% or 95% homologous to a sequence selected from a group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, and 7; and

b) a variable region of a light chain having an amino acid sequence that
15 is at least 70%, 80%, 90% or 95% homologous to a sequence selected from a group consisting of SEQ ID NOs: 8, 9, 10, 11, 12, 13, and 14, wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4.

The present disclosure provides an antibody or an antigen binding fragment thereof, comprising:
20

a) a variable region of a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, and 7; and

b) a variable region of a light chain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 9, 10, 11, 12, 13, and 14,

25 wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4.

In various examples, the antibody or an antigen binding fragment thereof comprises:

a) a variable region of a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 1; and

5 b) a variable region of a light chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8,

wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4;

or the antibody or an antigen binding fragment thereof comprises:

10 a) a variable region of a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 2; and

b) a variable region of a light chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 9,

15 wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4;

or the antibody or an antigen binding fragment thereof comprises:

a) a variable region of a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 3; and

20 b) a variable region of a light chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 10,

wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4;

or the antibody or an antigen binding fragment thereof comprises:

25 a) a variable region of a heavy chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4; and

b) a variable region of a light chain having an amino acid sequence selected from the group consisting of SEQ ID NO: 11, wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4;

or the antibody or an antigen binding fragment thereof comprises:

145.10			S
	Light chain	9	DIQMTQSPSSMSASLGDRVTISQCASQDIGSNLIWFQQKPGKSPRPMI YYATHLADGVPSRFSGRSGSDYSLTISSLESEDVADYHCLQYKQYP RTFGGGTKLELK
W3162-1.1 46.19	Heavychain	3	EVQLQESGPGLVKPSQSLTCSVTYHTITSGYDWTWIRKFPGNQME WMGYISYSGNTNYPNPSLKSRSITRDTSKNQFFLHLNSVTSEDTATYY CASMMVPHYYVMDAWGOGASVTVSS
	Light chain	10	DVVLVTQTPPTSSATIGQSVSISCRSSQSLNSDGNTYLYWYLQRPSQS PQLLIYLVSKLGSQVGNRFSGSGSGTDFTLKISGVEAEDLGLYYCVQ GTHDPWTFGGGTKELEK
W3162-1.1 54.8	Heavychain	4	EVQLQESGPGELVAPGSSVKISCKASGYFTFTNYFMNWVKQSPGQGLE WIGRVDPENGRADYAEKFKKATLTADTSTNTAYIHLSSLTSEDTAT YFCARRAMDNYGEAYWGOGTLTVSS
	Light chain	11	EIMLTQSPPTMAASLGKQITITCSANSSLSYMYWFQQKSGASPKLWV HGTSNLASGVDPDRFSGSGSGTSSYYLTINTMEAEDAATYFCHHWSNT QWTFGGGTKELEK
W3162-1.1 45.10-z7	Heavychain	5	EVQLVESGGGLVQPGGSLRLSCAASDLTFSNYDMAWVRQAPGKGL EWVASISPSGGNTYYRDSVKGRFTISRDNAKNSLYLQMNSLRAEDT AVYYCARHLWFAAYWGOGTLTVSS
	Light chain	12	DIQMTQSPSSLSASVGDRTITCQASQDIGSNLIWFQQKPGKAPKPMI YYATHLADGVPSRFSGRSGTDYTLTISSLQPEDFATYYCLQYKQYP RTFGGGTKVEIK
W3162.1.14 6.-z12	Heavychain	6	QVQLQESGPGLVKPSSETLSLTCSVTYHTITSGYDWTWIRKPPGKGM WIGYISYSGNTNYPNPSLKSRTVTISRDTSKNQFFLKLSSVTAADTAVY YCASMMVPHYYVMDAWGOGTLTVSS
	Light chain	13	DIVMTQTPLSLSTPGQPASISCRSSQSLNSDGNTYLYWYLQKPGQ SPQLLIYLVSKLGSQVGNRFSGSGSGTDFTLKISRVEAEDVGVYYCV OGTHDPWTFGGGTKELEK
W3162.1.15 4.8-z35	Heavychain	7	QVQLVQSGAEVKKPGSSVKVSKASGYFTFTNYFMNWVRQAPGQGL EWMGRVDPEQGRADYAEKFKKRVTTADKSTSTAYMELSSLRSEDT AVYYCARRAMDNYGEAYWGOGTLTVSS
	Light chain	14	EIVLTQSPDFQSVTPKEKVTITCSANSSLSYMYWYQQKPDQSPKLW VHGTSNLASGVPSRFSGSGSGTDFTLTINSLEAEDAATYCHHWSNT QWTFGGGTKELEK

In another example, the disclosure provides an antibody or an antigen binding fragment thereof, comprising a complementarity-determining region (CDR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 15-41, wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4.

In another example, the disclosure provides an antibody, or an antigen binding fragment thereof, comprising: a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences; and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences,

wherein the heavy chain variable region CDR3 sequence comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 15, 16, 17, and 18, and conservative modifications thereof,

wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4.

Preferably, wherein the light chain variable region CDR3 sequence of the aforesaid antibody or antigen binding fragment thereof comprises an amino acid sequence selected from a group consisting of SEQ ID NOs: 19, 20, 21, and 22, and conservative modifications thereof.

Preferably, wherein the heavy chain variable region CDR2 sequence of the aforesaid antibody or antigen binding fragment thereof comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 23, 24, 25, 26, 27, and 28, and conservative modifications thereof.

Preferably, wherein the light chain variable region CDR2 sequence of the aforesaid antibody or antigen binding fragment thereof comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 29, 30, 31, and 32, and conservative modifications thereof.

Preferably, wherein the heavy chain variable region CDR1 sequence of the aforesaid antibody or antigen binding fragment thereof comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 33, 34, 35, and 36, and conservative modifications thereof.

Preferably, the antibody of this disclosure, wherein the light chain

variable region CDR1 sequence of the aforesaid antibody or antigen binding fragment thereof comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 37, 38, 39, 40, and 41, and conservative modifications thereof.

5

In more preferred example, the disclosure provides an antibody, or an antigen binding fragment thereof, wherein the antibody or antigen binding fragment specifically binds to CTLA-4 and comprises: a heavy chain variable region that comprises CDR1, CDR2, and CDR3 sequences; and a light chain variable region that

10 comprises CDR1, CDR2, and CDR3 sequences, wherein:

15

a) the heavy chain variable region CDR1 sequence comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 33, 34, 35, and 36, and CDR2 sequence comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 23, 24, 25, 26, 27, and 28, CDR3 sequence comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 15, 16, 17, and 18;

20

b) and the light chain variable region CDR1 sequence comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 37, 38, 39, 40, and 41, and CDR2 sequence comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 29, 30, 31, and 32, CDR3 sequence comprises an amino acid sequence selected from a group consisting of amino acid sequences of SEQ ID NOs: 19, 20, 21, and 22,

25

wherein the antibody or the antigen binding-fragment specifically binds to CTLA-4.

A preferred antibody or an antigen binding fragment thereof comprises:

	Light chain	41	SANSALS MY	32	GTSNLAS	22	HHWSNTQWT
--	----------------	----	---------------	----	---------	----	-----------

The antibodies of the disclosure can be chimeric antibody.

The antibodies of the disclosure can be humanized antibody.

The antibodies of the disclosure can be fully human antibody.

5 The antibodies of the disclosure can be rat antibody.

The antibodies or the antigen binding fragment thereof of the disclosure can exhibit at least one of the following properties:

a) binds to human CTLA-4 with a KD of 2.08E-09 M or less and/or to mouse CTLA-4 with a KD of 1.39E-09 M or less;

10 b) enhances interleukin-2 release from the stimulated PBMCs;

In a further aspect, the present disclosure refers to a nucleic acid molecule encoding the antibody or the antigen binding fragment thereof as disclosed herein.

15 The disclosure provides a cloning or expression vector comprising the nucleic acid molecule encoding the antibody, or antigen binding fragment thereof.

In another aspect, the present disclosure refers to a cloning or expression vector comprising the nucleic acid molecule as disclosed herein.

20 The disclosure also provides a host cell comprising one or more cloning or expression vectors.

In another aspect, the present disclosure refers to a host cell comprising one or more expression vectors as disclosed herein.

25 In yet another example, the disclosure provides a process, comprising culturing the host cell of the disclosure and isolating the antibody, wherein the antibody is prepared through immunization in a SD rat with human CTLA-4 extracellular domain and mouse CTLA-4 extracellular domain.

30 In another aspect, the present disclosure refers to a process for the production of the antibody as disclosed herein, comprising culturing the host cell as disclosed herein and isolating the antibody.

The disclosure provides a transgenic animal such as rat comprising human immunoglobulin heavy and light chain transgenes, wherein the rat expresses the antibody of this disclosure.

In another aspect, the present disclosure refers to a transgenic rat comprising human immunoglobulin heavy and light chain transgenes, wherein the rat expresses the antibody as disclosed herein.

The disclosure provides hybridoma prepared from the rat of this disclosure, wherein the hybridoma produces said antibody.

In a further example, the disclosure provides pharmaceutical composition comprising the antibody, or the antigen binding fragment of said antibody in the disclosure, and one or more of a pharmaceutically acceptable excipient, a diluent or a carrier.

In another aspect, the present disclosure refers to a pharmaceutical composition comprising the antibody or the antigen binding fragment thereof as disclosed herein, and one or more of a pharmaceutically acceptable excipient, a diluent and a carrier.

The disclosure provides an immunoconjugate comprising said antibody, or antigen-binding fragment thereof in this disclosure, linked to a therapeutic agent.

In another aspect, the present disclosure refers to an immunoconjugate comprising the antibody or the antigen binding fragment thereof as disclosed herein, linked to a therapeutic agent.

Wherein, the disclosure provides a pharmaceutical composition comprising said immunoconjugate and one or more of a pharmaceutically acceptable excipient, a diluent or a carrier.

In another aspect, the present disclosure refers to a method for preparing an anti-CTLA-4 antibody or an antigen-binding fragment thereof comprising:

(a) providing:

(i) a heavy chain variable region antibody sequence comprising a CDR1 sequence that is selected from a group consisting of SEQ ID NOs: 33-36, a CDR2 sequence that is selected from a group consisting of SEQ ID NOs: 23-28; and a CDR3 sequence that is selected from the group consisting of SEQ ID NOs: 15-18; and/or

(ii) a light chain variable region antibody sequence comprising a CDR1 sequence that is selected from the group consisting of SEQ ID NOs: 37-41, a

CDR2 sequence that is selected from the group consisting of SEQ ID NOs: 29-32, and a CDR3 sequence that is selected from the group consisting of SEQ ID NOs: 19-22; and

(b) expressing the altered antibody sequence as a protein.

5

In another aspect, the present disclosure refers to the antibody or antigen binding fragment thereof as disclosed herein for use as a medicament.

10

The disclosure also provides a method of modulating an immune response in a subject comprising administering to the subject the antibody, or antigen binding fragment of any one of said antibodies in this disclosure.

In another aspect, the present disclosure refers to use of the antibody or antigen binding fragment thereof as disclosed herein in the manufacture of a medicament for modulating an immune response in a subject.

15

In another aspect, the present disclosure refers to use of the antibody or the antigen binding fragment thereof as disclosed herein in the manufacture of a medicament for the treatment or prophylaxis of an immune disorder or cancer.

20

The disclosure also provides a method of inhibiting growth of tumor cells in a subject, comprising administering to the subject a therapeutically effective amount of said antibody, or said antigen-binding fragment to inhibit growth of the tumor cells.

25

In another aspect, the present disclosure refers to use of the antibody or the antigen binding fragment thereof as disclosed herein in the manufacture of a medicament for inhibiting growth of tumor cells.

30

Wherein, the disclosure provides the method, wherein the tumor cells are of a cancer selected from a group consisting of melanoma, renal cancer, prostate cancer, breast cancer, colon cancer, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, and rectal cancer.

35

Wherein, the disclosure provides the method, wherein the antibody is a chimeric antibody, humanized antibody, human antibody or rat antibody.

The features and advantages of this disclosure

The inventors have generated humanized antibodies against CTLA-4

utilizing the proprietary hybridoma technology, wherein the antibodies inhibited CTLA-4 binding to its ligands CD80 and CD86. The antibodies reported in this disclosure have high binding affinity, specifically binding to both human and monkey CTLA-4 protein; and potent modulating immune responses and increasing interleukin-2 production.

One of the antibodies not only bound to human and monkey CTLA-4, but also bound to murine CTLA-4, which could greatly facilitate preclinical validation of its efficacy in mouse tumor models.

Brief Description of the Drawings

Figure 1 shows graphs of chimeric antibodies binding to human CTLA-4 in ELISA.

Figure 2 shows graphs of chimeric antibodies binding to cyno CTLA-4 in ELISA.

Figure 3 shows graphs of chimeric antibodies binding to mouse CTLA-4 in ELISA.

Figure 4 shows graphs of chimeric antibodies binding to human CTLA-4 on cells by FACS.

Figure 5 shows the result of chimeric antibodies binding on human CTLA-4 by SPR.

Figure 6 shows the result of chimeric antibodies blocking ligand binding.

Figure 7 shows graphs of chimeric Abs inhibited CTLA-4 binding on CD80- or CD86- expressing cells.

Figure 8 shows the results of chimeric antibodies enhanced cytokine release from SEB stimulated PBMCs.

Figure 9 shows graphs of humanized antibodies binding to human, cynomolgus monkey and mouse CTLA-4 in ELISA.

Claims

1. An antibody or antigen binding fragment thereof, comprising a heavy chain variable region comprising CDR1, CDR2, and CDR sequences; and
a light chain variable region comprising a light chain complementary-determining region 1 (LCDR1) defined by SEQ ID NO: 41, LCDR2 defined by defined by SEQ ID NO: 32, and LCDR3 defined by SEQ ID NO: 22, and
a heavy chain variable region comprising a heavy chain complementary determining region 1 (HCDR1) defined by SEQ ID NO: 36, HCDR2 defined by defined by SEQ ID NO: 28, and HCDR3 defined by SEQ ID NO: 18; and
wherein the antibody or the antigen binding fragment specifically binds to CTLA-4.
2. The antibody or antigen binding fragment thereof according to claim 1, wherein the light chain variable region has the amino acid sequence of SEQ ID NO: 14.
3. The antibody or antigen binding fragment thereof according to claim 1 or 2, wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 7.
4. The antibody or antigen binding fragment thereof according to claim 3, wherein the light chain variable region has the amino acid sequence of SEQ ID NO: 14 and the heavy chain variable region has the amino acid sequence of SEQ ID NO: 7.
5. An antibody or an antigen binding fragment thereof, wherein the antibody or the antigen binding fragment binds to human, monkey and mouse CTLA-4.
6. The antibody or the antigen binding-fragment thereof according to any one of claims 1-5, wherein the antibody inhibits CTLA-4 binding to CD80 or CD86.
7. The antibody or the antigen binding-fragment thereof according to any one of claims 1-6, wherein binding epitope of antibody or antigen binding-fragment comprises N145, polysaccharide on N145, or P138 of CTLA-4.

8. The antibody or an antigen binding fragment thereof according to any one of claims 1-7, wherein the antibody or the antigen binding-fragment
 - a) binds to human CTLA-4 with a K_D of $4.77E-10$ M or less; and
 - b) binds to mouse CTLA-4 with a K_D of $1.39E-09$ M or less.
9. The antibody or an antigen binding fragment thereof according to any one of claims 5-8, comprising an amino acid sequence that is at least 70%, 80%, 90% or 95% homologous to a sequence selected from a group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, wherein the antibody or the antigen binding fragment specifically binds to CTLA-4.
10. An antibody, or an antigen-binding fragment thereof, comprising:
 - a) a variable region of a heavy chain having an amino acid sequence that is at least 70%, 80%, 90% or 95% homologous to a sequence selected from a group consisting of SEQ ID NOs: 1, 2, 3, 4, 5, 6, and 7; and
 - b) a variable region of a light chain having an amino acid sequence that is at least 70%, 80%, 90% or 95% homologous to a sequence selected from a group consisting of SEQ ID NOs: 8, 9, 10, 11, 12, 13, and 14,wherein the antibody or the antigen binding fragment specifically binds to CTLA-4.
11. The antibody or the antigen binding fragment thereof according to any one of claims 1-10, wherein the antibody is chimeric, humanized, fully human, or rat antibody.
12. A nucleic acid molecule encoding the antibody or the antigen binding fragment thereof according to any one of claims 1 to 11.
13. A cloning or expression vector comprising the nucleic acid molecule of claim 12.
14. A host cell comprising one or more expression vectors of claim 13.

15. A process for the production of the antibody of any one of claims 1-11, comprising culturing the host cell of claim 14 and isolating the antibody.
16. A transgenic rat comprising human immunoglobulin heavy and light chain transgenes, wherein the rat expresses the antibody of any one of claims 1-11.
17. A pharmaceutical composition comprising the antibody or the antigen binding fragment thereof according to any one of claims 1 to 11, and one or more of a pharmaceutically acceptable excipient, a diluent and a carrier.
18. An immunoconjugate comprising the antibody or the antigen binding fragment thereof according to any one of claims 1-11, linked to a therapeutic agent.
19. A method for preparing an anti-CTLA-4 antibody or an antigen-binding fragment thereof comprising:
 - (a) providing:
 - (i) a heavy chain variable region antibody sequence comprising a CDR1 sequence that is selected from a group consisting of SEQ ID NOs: 33-36, a CDR2 sequence that is selected from a group consisting of SEQ ID NOs: 23-28; and a CDR3 sequence that is selected from the group consisting of SEQ ID NOs: 15-18; and/or
 - (ii) a light chain variable region antibody sequence comprising a CDR1 sequence that is selected from the group consisting of SEQ ID NOs: 37-41, a CDR2 sequence that is selected from the group consisting of SEQ ID NOs: 29-32, and a CDR3 sequence that is selected from the group consisting of SEQ ID NOs: 19-22; and
 - (b) expressing the altered antibody sequence as a protein.
20. The antibody or antigen binding fragment thereof according to any one of claims 1 to 11 for use as a medicament.

21. Use of the antibody or antigen binding fragment thereof according to any one of claims 1 to 11 in the manufacture of a medicament for modulating an immune response in a subject.
22. Use of the antibody or the antigen binding fragment thereof according to any one of claims 1 to 11 in the manufacture of a medicament for the treatment or prophylaxis of an immune disorder or cancer.
23. Use of the antibody or the antigen binding fragment thereof according to any one of claims 1 to 11 in the manufacture of a medicament for inhibiting growth of tumor cells.
24. The use of claim 23, wherein the tumor cells are of a cancer selected from a group consisting of melanoma, renal cancer, prostate cancer, breast cancer, colon cancer, lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, and rectal cancer.