

WHAT IS CLAIMED IS:

1. An antibody or antigen-binding fragment thereof that binds to cytotoxic T-lymphocyte-associated protein 4 (CTLA4) comprising:

a heavy chain variable region (VH) comprising complementarity determining regions (CDRs) 1, 2, and 3, and

a light chain variable region (VL) comprising CDRs 1, 2, and 3, wherein the VH CDRs 1, 2, and 3 amino acid sequences and the VL CDRs, 1, 2, and 3 amino acid sequences are one of the following:

(1) the selected VH CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID

NOs: 1, 2, 3, respectively, and the selected VL CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 4, 5, 6, respectively;

(2) the selected VH CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 7, 8, 9, respectively, and the selected VL CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 10, 11, 12, respectively;

(3) the selected VH CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 45, 46, 47, respectively, and the selected VL CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 48, 49, 50, respectively;

(4) the selected VH CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 51, 52, 53, respectively, and the selected VL CDRs 1, 2, 3 amino acid sequences are set forth in SEQ ID NOs: 54, 55, 56, respectively.

2. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises CDRs 1, 2, 3 with the amino acid sequences set forth in SEQ ID NOs: 1, 2, and 3 respectively, and the VL comprises CDRs 1, 2, 3 with the amino acid sequences set forth in SEQ ID NOs: 4, 5, and 6, respectively.

3. The antibody or antigen-binding fragment thereof of claim 1, wherein the VH comprises CDRs 1, 2, 3 with the amino acid sequences set forth in SEQ ID NOs: 7, 8, and 9 respectively, and the VL comprises CDRs 1, 2, 3 with the amino acid sequences set forth in SEQ ID NOs: 10, 11, and 12, respectively.

4. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment specifically binds to human CTLA4.

5 5. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment is a humanized antibody or antigen-binding fragment thereof.

6. The antibody or antigen-binding fragment thereof of claim 1, wherein the antibody or antigen-binding fragment is a single-chain variable fragment (scFV).

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7. A nucleic acid comprising a polynucleotide encoding the antibody or antigen-binding fragment thereof of any one of claims 1 to 6.

8. The nucleic acid of claim 7, wherein the immunoglobulin heavy chain or the fragment thereof is a humanized immunoglobulin heavy chain or a fragment thereof, and the immunoglobulin light chain or the fragment thereof is a humanized immunoglobulin light chain or a fragment thereof.

9 The nucleic acid of claim 7, wherein the nucleic acid encodes a single-chain variable fragment (scFv).

10. A vector comprising one or more of the nucleic acids of claim 7-.

11. A vector comprising two of the nucleic acids of claim 7, wherein the vector encodes the VL region and the VH region that together bind to a CTLA4.

12. A pair of vectors, wherein each vector comprises one of the nucleic acids of claim 7, wherein together the pair of vectors encodes the VL region and the VH region that together bind to CTLA4.

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13. A cell comprising the vector of claim 10 or 11, or the pair of vectors of claim 12.

14. The cell of claim 13, wherein the cell is a CHO cell.

5 15. A cell comprising one or more of the nucleic acids of claim 7.

16. A cell comprising two of the nucleic acids of claim 7.

17. A method of producing an antibody or an antigen-binding fragment thereof of any one
10 of claims 1-6, the method comprising

(a) culturing the cell of claim 13 under conditions sufficient for the cell to produce the
antibody or the antigen-binding fragment; and

(b) collecting the antibody or the antigen-binding fragment produced by the cell.

15 18. The antibody or antigen-binding fragment thereof of any one of claims 1-6 comprising
a heavy chain variable region (VH) and a light chain variable region (VL), wherein
the VH sequence and the VL sequence are one of the following:

(1) the selected VH sequence is SEQ ID NO: 13, 14, 15, 16, 17, or 69, and the
selected VL sequence is SEQ ID NO: 18, 19, 20, or 70;

20 (2) the selected VH sequence is SEQ ID NO: 21, 22, 23, 24, or 71, and the selected
VL sequence is SEQ ID NO: 25, 26, 27, 28, or 72;

(3) the selected VH sequence is SEQ ID NO: 73, and the selected VL sequence is
SEQ ID NO: 74;

25 (4) the selected VH sequence is SEQ ID NO: 75, and the selected VL sequence is
SEQ ID NO: 76.

19. The antibody or antigen-binding fragment thereof of claim 18, wherein the VH
comprises the sequence of SEQ ID NO: 13 and the VL comprises the sequence of SEQ ID
NO: 19.

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20. The antibody or antigen-binding fragment thereof of claim 18, wherein the VH comprises the sequence of SEQ ID NO: 14 and the VL comprises the sequence of SEQ ID NO: 19.

5 21. The antibody or antigen-binding fragment thereof of claim 18, wherein the VH comprises the sequence of SEQ ID NO: 21 and the VL comprises the sequence of SEQ ID NO: 25.

10 22. The antibody or antigen-binding fragment thereof of claim 18, wherein the VH comprises the sequence of SEQ ID NO: 22 and the VL comprises the sequence of SEQ ID NO: 25.

15 23. The antibody or antigen-binding fragment thereof of claim 18, wherein the antibody or antigen-binding fragment is a humanized antibody or antigen-binding fragment thereof.

24. The antibody or antigen-binding fragment thereof of claim 18, wherein the antibody or antigen-binding fragment is a single-chain variable fragment (scFV).

20 25. An antibody-drug conjugate comprising the antibody or antigen-binding fragment thereof of any one of claims 1-6 and 18 covalently bound to a therapeutic agent.

26. The antibody drug conjugate of claim 25, wherein the therapeutic agent is a cytotoxic or cytostatic agent.

25 27. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-6 and 18, or the antibody-drug conjugate of claim 25 in the manufacture of a medicament for the treatment of a cancer.

30 28. The use of claim 27, wherein the cancer is melanoma.

29. The method of claim 27, wherein the cancer is unresectable melanoma or metastatic melanoma.

30. The method of claim 27, wherein the cancer is non-small cell lung carcinoma (NSCLC), small cell lung cancer (SCLC), bladder cancer, or metastatic hormone-refractory prostate cancer.

31. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-6 and 18, or the antibody-drug conjugate of claim 25 in the manufacture of a medicament for decreasing the rate of tumor growth.

32. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-6 and 18, or the antibody-drug conjugate of claim 25 in the manufacture of a medicament for killing a tumor cell.

33. A pharmaceutical composition comprising the antibody or antigen-binding fragment thereof of any one of claims 1-6 and 18, and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising the antibody drug conjugate of claim 25 or 26, and a pharmaceutically acceptable carrier.