

Claims

It is claimed:

1. An isolated antibody that specifically binds to CD47 and comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises (i) a VH complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 13, 14, 15, 22, 23, 25, 26, 27, 31, 32, 33, 37, 38, or 39; (ii) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 16, 17, 28, 29, 34, or 35; (iii) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 18, 24, 30, 36, or 40; (iv) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 19 or 53; (v) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 20 or 54; and (vi) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 21 or 55.
2. The antibody of claim 1, wherein the VH comprises the amino acid sequence of SEQ ID NO: 1, 3, 7, 8, or 9.
3. The antibody of any one of claims 1-2, wherein the VL comprises the amino acid sequence of SEQ ID NO: 2 or 6.
4. An isolated antibody which specifically binds to CD47, wherein the antibody comprises: a heavy chain variable region (VH) comprising the amino acid sequence as shown in SEQ ID NO: 1 and a light chain variable region (VL) comprising the amino acid sequence as shown in SEQ ID NO: 2.
5. An isolated antibody that specifically binds to PD-L1 and comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises (i) a VH complementarity determining region (CDR) 1 comprising the amino acid sequence of SEQ ID NO: 41, 42, 43, 47, 48, or 49; (ii) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, 45, 50, 51, 58, or 59; and (iii) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 46, 52, 56, 57, or 60; (iv) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 19 or 53; (v) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 20 or 54; and (vi) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 21 or 55.
6. The antibody of claim 5, wherein the VH comprises the sequence of SEQ ID NO: 4, 5, 10, 11, or 12.
7. The antibody of any one of claims 5-6, wherein the VL comprises the sequence of SEQ ID NO: 2 or 6.

8. An isolated antibody which specifically binds to PD-L1, wherein the antibody comprises: a heavy chain variable region (VH) comprising the amino acid sequence as shown in SEQ ID NO: 4 and a light chain variable region (VL) comprising the amino acid sequence as shown in SEQ ID NO: 2.
- 5 9. The antibody of any one of claims 1-8, wherein the antibody is a bispecific antibody.
10. The antibody of claim 9, wherein the bispecific antibody specifically binds to CD47 and PD-L1.
- 10 11. The antibody of claim 10, wherein the antibody comprises a first antigen binding portion and a second antigen binding portion, wherein the first antigen binding portion specifically binds to CD47 and the second antigen binding portion specifically binds to PD-L1, wherein the first antigen binding portion comprises a VH and a VL, wherein the second antigen binding portion comprises a VH and a VL, and wherein the amino acid sequence of the VL of the first antigen binding portion and the amino acid sequence of the VL of the second antigen binding portion have the same amino acid sequence.
- 15 12. The antibody of claim 11, wherein the amino acid sequence of the VL of the first antigen binding portion and the amino acid sequence of the VL of the second antigen binding portion comprise the amino acid sequence as shown in SEQ ID NO: 2
- 20 13. An isolated bispecific antibody comprising a first antigen binding portion that specifically binds to CD47 and a second antigen binding portion that specifically binds to PD-L1, wherein the first antigen binding portion comprises a VH and a VL, wherein the second antigen binding portion comprises a VH and a VL, and wherein one, two, three, or all four of:
- 25 a) the first antigen binding portion VH comprises (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 13, 14, 15, 22, 23, 25, 26, 27, 31, 32, 33, 37, 38, or 39; (ii) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 16, 17, 28, 29, 34, or 35; and (iii)
- 30 a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 18, 24, 30, 36, or 40;
- b) the first antigen binding portion VL comprises (i) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 19 or 53; (ii) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 20 or 54;

and (iii) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 21 or 55;

5 c) the second antigen binding portion VH comprises (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 41, 42, 43, 47, 48, or 49; (ii) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44, 45, 50, 51, 58, or 59; and (iii) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 46, 52, 56, 57, or 60; and

10 d) the second antigen binding portion VL comprises (i) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 19 or 53; (ii) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 20 or 54; and (iii) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 21 or 55.

14. The bispecific antibody of claim 13, wherein one, two, three, or all four of:

15 a) the first antigen binding portion VH comprises (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 13, 14, or 15; (ii) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 16 or 17; and (iii) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 18;

20 b) the first antigen binding portion VL comprises (i) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 19; (ii) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 20; and (iii) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 21;

25 c) the second antigen binding portion VH comprises (i) a VH CDR1 comprising the amino acid sequence of SEQ ID NO: 41, 42, or 43; (ii) a VH CDR2 comprising the amino acid sequence of SEQ ID NO: 44 or 45; and (iii) a VH CDR3 comprising the amino acid sequence of SEQ ID NO: 46; and

30 d) the second antigen binding portion VL comprises (i) a VL CDR1 comprising the amino acid sequence of SEQ ID NO: 19; (ii) a VL CDR2 comprising the amino acid sequence of SEQ ID NO: 20; and (iii) a VL CDR3 comprising the amino acid sequence of SEQ ID NO: 21.

15. The bispecific antibody of any one of claims 13 to 14, wherein one, two, three, or all four of:

- a) the first antigen binding portion VH comprises the amino acid sequence of SEQ ID NO: 1 or 3;
- b) the first antigen binding portion VL comprises the amino acid sequence of SEQ ID NO: 2;
- 5 c) the second antigen binding portion VH comprises the amino acid sequence of SEQ ID NO: 4; and
- d) the second antigen binding portion VL comprises the amino acid sequence of SEQ ID NO: 2.
- 10 16. An isolated bispecific antibody comprising a first antigen binding portion that specifically binds to CD47 and a second antigen binding portion that specifically binds to PD-L1, wherein the antibody comprises a first antigen binding portion VH comprising the amino acid sequence as shown in SEQ ID NO: 1, a first antigen binding portion VL comprising the amino acid sequence as shown in SEQ ID NO: 2, a second antigen binding portion VH comprising the amino acid sequence as shown in SEQ ID NO: 4, and a second antigen binding portion VL comprising the amino acid sequence as shown in SEQ ID NO: 2.
- 15 17. The bispecific antibody of any one of claims 9 to 16, wherein the bispecific antibody comprises a Fc domain.
18. The bispecific antibody of claim 17, wherein the Fc domain is an IgG1 Fc domain, IgG2 Fc domain, or an IgG4 Fc domain.
- 20 19. The bispecific antibody of any of claims 17 to 18, wherein the first Fc chain and the second Fc chain of the Fc domain contain one or more modifications promoting the association of the first Fc chain with the second Fc chain.
20. The bispecific antibody of any one of claims 17 to 19, wherein the antibody comprises an anti-CD47 heavy chain comprising the amino acid sequence of SEQ ID NO: 61 or 63 and the antibody comprises an anti-PD-L1 heavy chain comprising the amino acid sequence of SEQ ID NO: 64.
- 25 21. The bispecific antibody of any one of claims 17 to 20, wherein the antibody further comprises an anti-CD47 light chain comprising the amino acid sequence of SEQ ID NO: 62 and an anti-PD-L1 light chain comprising the amino acid sequence of SEQ ID NO: 62.
- 30 22. An isolated bispecific antibody that specifically binds to CD47 and PD-L1, wherein the antibody comprises a first antibody heavy chain, a second antibody heavy chain, a first antibody light chain, and a second antibody light chain;

wherein the first antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 61 and the second antibody heavy chain comprises the amino acid sequence of SEQ ID NO: 64; and

wherein both the first antibody light chain and the second antibody light chain
5 comprise the amino acid sequence of SEQ ID NO: 62.

23. The bispecific antibody of any one of claims 9-22, wherein the affinity of the anti-PD-L1 antigen binding portion for PD-L1 is greater than the affinity of the anti-CD47 antigen binding portion for CD47.

10 24. A pharmaceutical composition comprising a therapeutically effective amount of the antibody of any one of claims 1-8 or the bispecific antibody of any one of claims 9-23, and a pharmaceutically acceptable carrier.

25. An isolated polynucleotide comprising a nucleotide sequence encoding an amino acid sequence as provided in any one of claims 1-22.

26. A vector comprising the polynucleotide of claim 25.

15 27. A host cell that comprises a recombinant polynucleotide comprising a nucleotide sequence encoding an amino acid sequence as provided in any one of claims 1-22.

20 28. A method of producing an antibody or a bispecific antibody, comprising culturing the host cell of claim 27 under conditions that result in the production of the antibody of any one of claims 1-8 or the bispecific antibody of any one of claims 9-23, and purifying the produced antibody or bispecific antibody.

25 29. Use of the antibody of any one of claims 1-8, the bispecific of any one of claims 9-23, the pharmaceutical composition of claim 24, the polynucleotide of claim 25, the vector of claim 26, or the host cell of claim 27 in the manufacture of a medicament for use in the treatment of cancer.

30. The antibody of any one of claims 1-8, the bispecific antibody of any one of claims 9-23, or the pharmaceutical composition of claim 24, for use as a medicament.

31. The antibody, bispecific antibody, or pharmaceutical composition for use of claim 30, wherein the medicament is for use in the treatment of cancer.

30 ~~32. A method of treating a disease in a subject in need thereof, the method comprising administering to the subject an effective amount of the antibody of any one of claims 1-8, the bispecific antibody of any one of claims 9-23, or the pharmaceutical composition of claim 24.~~

33.32. _____ The ~~method-use~~ of claim 3229, wherein the ~~method-use~~ further comprises ~~administering~~ a second therapeutic agent to be administered to the subject.

5 34.33. _____ The ~~method-use~~ of claim 3229, or the antibody, bispecific antibody, or pharmaceutical composition for use of claim 31, wherein the cancer is gastric cancer, sarcoma, lymphoma, Hodgkin's lymphoma, leukemia, head and neck cancer, thymic cancer, epithelial cancer, salivary cancer, liver cancer, stomach cancer, thyroid cancer, lung cancer (including, for example, non-small-cell lung carcinoma), ovarian cancer, breast cancer, prostate cancer, esophageal cancer,
10 pancreatic cancer, glioma, leukemia, multiple myeloma, renal cell carcinoma, bladder cancer, cervical cancer, choriocarcinoma, colon cancer, oral cancer, glioblastoma, skin cancer, or melanoma.