

Claims

1. An antibody against human CD147 or an antigen-binding fragment thereof, comprising:

(i) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 75, the CDRH2 comprises SEQ ID NO: 76, and the CDRH3 comprises SEQ ID NO: 77, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 72, the CDRL2 comprises SEQ ID NO: 73, and the CDRL3 comprises SEQ ID NO: 74:

(ii) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 55, the CDRH2 comprises SEQ ID NO: 56, and the CDRH3 comprises SEQ ID NO: 57, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 52, the CDRL2 comprises SEQ ID NO: 53, and the CDRL3 comprises SEQ ID NO: 54;

(iii) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 65, the CDRH2 comprises SEQ ID NO: 66, and the CDRH3 comprises consists of an amino acid sequence represented by SEQ ID NO: 67, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 62, the CDRL2 comprises SEQ ID NO: 63, and the CDRL3 comprises SEQ ID NO: 64; or

(iv) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 85, the CDRH2 comprises SEQ ID NO: 86, and the CDRH3 comprises SEQ ID NO: 87, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 82, the CDRL2 comprises SEQ ID NO: 83, and the CDRL3 comprises SEQ ID NO: 84:

wherein the antibody or antigen-binding fragment thereof competes with at least one antibody selected from the group consisting of the following (A) to (F) for binding to human CD 147 and which activates signal transduction through CD147:

(A) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 71 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 69;

(B) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 51 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 49;

(C) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 61 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 59;

(D) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 81 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 79;

(E) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 10 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 8; and

(F) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 20 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 18.

2. An antibody against human CD147 or an antigen-binding fragment thereof, comprising:

(i) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 75, the CDRH2 comprises SEQ ID NO: 76, and the CDRH3 comprises SEQ ID NO: 77, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 72, the CDRL2 comprises SEQ ID NO: 73, and the CDRL3 comprises SEQ ID NO: 74:

(ii) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 55, the CDRH2 comprises SEQ ID NO: 56, and the CDRH3 comprises SEQ ID NO: 57, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 52, the CDRL2 comprises SEQ ID NO: 53, and the CDRL3 comprises SEQ ID NO: 54,

(iii) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 65, the CDRH2 comprises SEQ ID NO: 66, and the CDRH3 comprises SEQ ID NO: 67, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 62, the CDRL2 comprises SEQ ID NO: 63, and the CDRL3 comprises SEQ ID NO: 64, or

(iv) a heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 85, the CDRH2 comprises SEQ ID NO: 86, and the CDRH3 comprises SEQ ID NO: 87, and a light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the

CDRL1 comprises SEQ ID NO: 82, the CDRL2 comprises SEQ ID NO: 83, and the CDRL3 comprises SEQ ID NO: 84:

wherein the antibody or antigen-binding fragment thereof binds to an epitope to which at least one antibody selected from the group consisting of the following (A) to (F) binds, and which activates signal transduction through CD147:

(A) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 71 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 69;

(B) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 51 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 49;

(C) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 61 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 59;

(D) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 81 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 79;

(E) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 10 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 8; and

(F) an antibody comprising a heavy chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 20 and a light chain variable region consisting of an amino acid sequence comprises SEQ ID NO: 18.

3. The antibody against human CD147 or the antigen-binding fragment thereof according to claim 1, which has decreased ADCC activity or lacks ADCC activity.

4. The antibody against human CD147 or the antigen-binding fragment thereof according to claim 1, which has decreased CDC activity or lacks CDC activity.

5. The antibody against human CD147 or the antigen-binding fragment thereof according to claim 1, which has decreased ADCP activity or lacks ADCP activity.

6. The antibody or the antigen-binding fragment thereof according to claim 1, which binds to an epitope comprising residues of arginine (Arg) at position 106 to glycine (Gly) at position 165 in SEQ ID NO: 3.

7. The antibody or the antigen-binding fragment thereof according to claim 1, which binds to an epitope comprising residues of arginine (Arg) at position 106, lysine (Lys) at position 108, alanine (Ala) at position 109, valine (Val) at position 110, lysine (Lys) at position 127, serine (Ser) at position 128, glutamic acid (Glu) at position 129, serine (Ser) at position 130, valine (Val) at position 131, proline (Pro) at position 132, proline (Pro) at position 133, valine (Val) at position 134, glutamine (Gln) at position 164 and glycine (Gly) at position 165 in the amino acid sequence set forth in SEQ ID NO: 3.

8. The antibody or the antigen-binding fragment thereof according to claim 1, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises by SEQ ID NO: 75, the CDRH2 comprises SEQ ID NO: 76, and the CDRH3 comprises SEQ ID NO: 77; and

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 72, the CDRL2 comprises SEQ ID NO: 73, and the CDRL3 comprises SEQ ID NO: 74.

9. The antibody or the antigen-binding fragment thereof according to claim 1, which binds to an epitope comprising an amino acid sequence set forth in SEQ ID NO: 143 or an amino acid sequence in which one or several amino acids are deleted, substituted or added in the sequence of SEQ ID NO: 143.

10. The antibody or the antigen-binding fragment thereof according to claim 1, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises by SEQ ID NO: 55, the CDRH2 comprises consists of an amino acid sequence represented by SEQ ID NO: 56, and the CDRH3 comprises consists of an amino acid sequence represented by SEQ ID NO: 57; and

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 52, the CDRL2 comprises SEQ ID NO: 53, and the CDRL3 comprises SEQ ID NO: 54.

11. The antibody or the antigen-binding fragment thereof according to claim 1, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 65, the CDRH2 comprises SEQ ID NO: 66, and the CDRH3 comprises SEQ ID NO: 67; and

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 62, the CDRL2 comprises SEQ ID NO: 63, and the CDRL3 comprises SEQ ID NO: 64.

12. The antibody or the antigen-binding fragment thereof according to claim 1, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 comprises SEQ ID NO: 85, the CDRH2 comprises SEQ ID NO: 86, and the CDRH3 comprises SEQ ID NO: 87; and

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 comprises SEQ ID NO: 82, the CDRL2 comprises SEQ ID NO: 83, and the CDRL3 comprises SEQ ID NO: 84.

13. The antigen-binding fragment of the antibody according to claim 1, which is selected from the group consisting of Fab, F(ab')₂, Fab' and Fv.

14. The antibody according to claim 1, which is scFv.

15. The antibody or the antigen-binding fragment thereof according to claim 1, which is a chimeric antibody.

16. The antibody or the antigen-binding fragment thereof according to claim 1, which is humanized.

17. The antibody according to claim 1, wherein the heavy chain comprises a human immunoglobulin G1 heavy chain constant region, a human immunoglobulin G2 heavy chain constant region or a human immunoglobulin G4 heavy chain constant region, and the light chain comprises a human immunoglobulin κ light chain constant region.

18. The antibody according to claim 17, wherein the heavy chain comprises the human immunoglobulin G4 heavy chain constant region.

19. The antibody according to claim 18, wherein within the human immunoglobulin G4 heavy chain constant region, the serine (Ser) at position 228 as indicated by the EU index is substituted with a proline (Pro).

20. The antibody according to claim 18, wherein within the human immunoglobulin G4 heavy chain constant region, the phenylalanine (Phe) at position 234 as indicated by the EU index is substituted with an alanine (Ala), and the leucine (Leu) at position 235 as indicated by the EU index is substituted with an alanine (Ala).

21. The antibody according to claim 18, wherein within the human immunoglobulin G4 heavy chain constant region, the serine (Ser) at position 228 as indicated by the EU index is substituted with a proline (Pro), the phenylalanine (Phe) at position 234 as indicated by the EU index is substituted with an alanine (Ala), and the leucine (Leu) at position 235 as indicated by the EU index is substituted with an alanine (Ala).

22. The antibody according to claim 17, wherein the heavy chain comprises the human immunoglobulin G2 heavy chain constant region.

23. An antibody against human CD147 or an antigen-binding fragment thereof, which comprises the following (c) and (d), and activates signal transduction through CD147:

(c) a heavy chain variable region selected from the group consisting of the following (c1) to (c4):

(c1) a heavy chain variable region consisting of amino acid residues at positions 20 to 136 in an amino acid sequence comprising SEQ ID NO: 135;

(c2) a heavy chain variable region consisting of amino acid residues at positions 20 to 136 in an amino acid sequence comprising SEQ ID NO: 147;

(c3) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (c1) or (c2); and

(c4) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence according to any one of (c1) to (c3); and

(d) a light chain variable region selected from the group consisting of the following (d1) to (d5):

(d1) a light chain variable region consisting of amino acid residues at positions 21 to 128 in an amino acid sequence comprising SEQ ID NO: 137;

(d2) a light chain variable region consisting of amino acid residues at positions 21 to 128 in an amino acid sequence comprising SEQ ID NO: 149;

(d3) a light chain variable region consisting of amino acid residues at positions 21 to 128 in an amino acid sequence comprising SEQ ID NO: 151;

(d4) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence according to any one of (d1) to (d3); and

(d5) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence according to any one of (d1) to (d4).

24. The antibody or the antigen-binding fragment thereof according to claim 23, which comprises:

the heavy chain variable region consisting of amino acid residues at positions 20 to 136 in the amino acid sequence comprising SEQ ID NO: 135; and

the light chain variable region consisting of amino acid residues at positions 21 to 128 in the amino acid sequence comprising SEQ ID NO: 137.

25. The antibody or the antigen-binding fragment thereof according to claim 23, which comprises:

the heavy chain consisting of amino acid residues at positions 20 to 463 in the amino acid sequence comprising SEQ ID NO: 135; and

the light chain consisting of amino acid residues at positions 21 to 234 in the amino acid sequence comprising SEQ ID NO: 137.

26. The antibody or the antigen-binding fragment thereof according to claim 23, which comprises:

the heavy chain variable region consisting of amino acid residues at positions 20 to 136 in the amino acid sequence comprising SEQ ID NO: 147; and

the light chain variable region consisting of amino acid residues at positions 21 to 128 in the amino acid sequence comprising SEQ ID NO: 149.

27. The antibody or the antigen-binding fragment thereof according to claim 23, which comprises:

the heavy chain consisting of amino acid residues at positions 20 to 463 in the amino acid sequence comprising SEQ ID NO: 147; and

the light chain consisting of amino acid residues at positions 21 to 234 in the amino acid sequence comprising SEQ ID NO: 149.

28. The antibody or the antigen-binding fragment thereof according to claim 23, which comprises:

the heavy chain variable region consisting of amino acid residues at positions 20 to 136 in the amino acid sequence comprising SEQ ID NO: 147; and

the light chain variable region consisting of amino acid residues at positions 21 to 128 in the amino acid sequence comprising SEQ ID NO: 151.

29. The antibody or the antigen-binding fragment thereof according to claim 23, which comprises:

the heavy chain consisting of amino acid residues at positions 20 to 463 in the amino acid sequence comprising SEQ ID NO: 147; and

the light chain consisting of amino acid residues at positions 21 to 234 in the amino acid sequence comprising SEQ ID NO: 151.

30. An antibody against human CD147 or an antigen-binding fragment thereof, which comprises the following (a) and (b), and activates signal transduction through CD147:

(a) a heavy chain variable region selected from the group consisting of the following (a1) to (a4):

(a1) a heavy chain variable region consisting of amino acid residues at positions 20 to 140 in an amino acid sequence comprising SEQ ID NO: 123;

(a2) a heavy chain variable region consisting of amino acid residues at positions 20 to 140 in an amino acid sequence comprising SEQ ID NO: 125;

(a3) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (a1) or (a2); and

(a4) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence according to any one of (a1) to (a3); and

(b) a light chain variable region selected from the group consisting of the following (b1) to (b3):

(b1) a light chain variable region consisting of amino acid residues at positions 21 to 128 in an amino acid sequence comprising SEQ ID NO: 127;

(b2) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (b1); and

(b3) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence of (b1) or (b2).

31. The antibody or the antigen-binding fragment thereof according to claim 30, which comprises:

the heavy chain variable region consisting of amino acid residues at positions 20 to 140 in the amino acid sequence comprising SEQ ID NO: 123 or the heavy chain variable region consisting of amino acid residues at positions 20 to 140 in the amino acid sequence comprising SEQ ID NO: 125; and

the light chain variable region consisting of amino acid residues at positions 21 to 128 in the amino acid sequence comprising SEQ ID NO: 127.

32. The antibody or the antigen-binding fragment thereof according to claim 30, which comprises:

the heavy chain consisting of amino acid residues at positions 20 to 466 in the amino acid sequence comprising SEQ ID NO: 123 or the heavy chain consisting of amino acid residues at positions 20 to 467 in the amino acid sequence comprising SEQ ID NO: 125; and

the light chain consisting of amino acid residues at positions 21 to 234 in the amino acid sequence comprising SEQ ID NO: 127.

33. An antibody against human CD147 or an antigen-binding fragment thereof, which comprises the following (e) and (f), and activates signal transduction through CD147:

(e) a heavy chain variable region selected from the group consisting of the following (e1) to (e4):

(e1) a heavy chain variable region consisting of amino acid residues at positions 20 to 137 in an amino acid sequence comprising SEQ ID NO: 129;

(e2) a heavy chain variable region consisting of amino acid residues at positions 20 to 137 in an amino acid sequence comprising SEQ ID NO: 131;

(e3) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (e1) or (2); and

(e4) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence according to any one of (e1) to (e3); and

(f) a light chain variable region selected from the group consisting of the following (f1) to (f3):

(f1) a light chain variable region consisting of amino acid residues at positions 21 to 128 in an amino acid sequence comprising SEQ ID NO: 133;

(f2) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (f1); and

(f3) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence of (f1) or (f2).

34. The antibody or the antigen-binding fragment thereof according to claim 33, which comprises:

the heavy chain variable region consisting of amino acid residues at positions 20 to 137 in the amino acid sequence comprising SEQ ID NO: 129 or the heavy chain variable region consisting of amino acid residues at positions 20 to 137 in the amino acid sequence comprising SEQ ID NO: 131; and

the light chain variable region consisting of amino acid residues at positions 21 to 128 in the amino acid sequence comprising SEQ ID NO: 133.

35. The antibody or the antigen-binding fragment thereof according to claim 33, which comprises:

the heavy chain consisting of amino acid residues at positions 20 to 463 in the amino acid sequence comprising SEQ ID NO: 129 or the heavy chain consisting of amino acid residues at positions 20 to 464 in the amino acid sequence comprising SEQ ID NO: 131; and

the light chain consisting of amino acid residues at positions 21 to 234 in the amino acid sequence comprising SEQ ID NO: 133.

36. An antibody against human CD147 or an antigen-binding fragment thereof, which comprises the following (g) and (h), and activates signal transduction through CD147:

(g) a heavy chain variable region selected from the group consisting of the following (g1) to (g3):

(g1) a heavy chain variable region consisting of amino acid residues at positions 20 to 138 in an amino acid sequence comprising SEQ ID NO: 139;

(g2) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (g1); and

(g3) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence of (g1) or (g2); and

(h) a light chain variable region selected from the group consisting of the following (h1) to (h3):

(h1) a light chain variable region consisting of amino acid residues at positions 21 to 128 in an amino acid sequence comprising SEQ ID NO: 141;

(h2) an amino acid sequence having at least 95% or more sequence identity with the sequence of a framework region outside each CDR sequence in the sequence of (h1); and

(h3) an amino acid sequence in which one or several amino acids are deleted, substituted, or added in the sequence of a framework region outside each CDR sequence in the sequence of (h1) or (h2).

37. The antibody or the antigen-binding fragment thereof according to claim 36, which comprises:

the heavy chain variable region consisting of amino acid residues at positions 20 to 138 in the amino acid sequence comprising SEQ ID NO: 139; and

the light chain variable region consisting of amino acid residues at positions 21 to 128 in the amino acid sequence comprising SEQ ID NO: 141.

38. The antibody or the antigen-binding fragment thereof according to claim 36, which comprises:

the heavy chain consisting of amino acid residues at positions 20 to 464 in the amino acid sequence comprising SEQ ID NO: 139; and

the light chain consisting of amino acid residues at positions 21 to 234 in the amino acid sequence comprising SEQ ID NO: 141.

39. The antibody against human CD147 or the antigen-binding fragment thereof according to claim 23, which has decreased ADCC activity or lacks ADCC activity.

40. The antibody against human CD147 or the antigen-binding fragment thereof according to claim 23, which has decreased CDC activity or lacks CDC activity.

41. The antibody against human CD147 or the antigen-binding fragment thereof according to claim 23, which has decreased ADCP activity or lacks ADCP activity.

42. A pharmaceutical composition comprising at least one of the antibodies or antigen-binding fragments thereof according to claim 1.

43. The pharmaceutical composition according to claim 42, which is an antitumor agent.

44. The pharmaceutical composition according to claim 43, wherein the tumor is a tumor expressing CD147.

45. The pharmaceutical composition according to claim 43, wherein the tumor is pancreatic cancer, liver cancer, gastric cancer, colon cancer, renal cancer, breast cancer, uterine cancer, ovarian cancer, lung cancer, lymphoma, thyroid cancer, skin cancer, head and neck cancer, sarcoma, prostate cancer, bladder cancer, brain tumor, gastrointestinal stromal tumor (GIST), leukemia, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), malignant lymphoma, B-cell lymphoma, non-Hodgkin's lymphoma or diffuse large B-cell lymphoma (DLBCL).

46. The pharmaceutical composition according to claim 43, wherein the tumor is pancreatic cancer, liver cancer, gastric cancer, colon cancer, renal cancer, leukemia, acute myeloid leukemia (AML), chronic myeloid leukemia (CML), chronic lymphocytic leukemia (CLL), acute lymphocytic leukemia (ALL), malignant lymphoma, B-cell lymphoma, non-Hodgkin's lymphoma or diffuse large B-cell lymphoma (DLBCL).

47. The pharmaceutical composition according to claim 43, wherein the tumor is a SMAD4-positive tumor or a tumor having a decreased expression level of or lacking the expression of KLF5.

48. The pharmaceutical composition according to claim 42, further comprising another antitumor agent.

49. A method for producing the antibody or the antigen-binding fragment thereof, comprising a step of culturing a host cell with an expression vector comprising a nucleotide that encodes the antibody or antigen-binding fragment thereof according to claim 1 and collecting the target antibody or the antigen-binding fragment thereof from a culture supernatant.

50. The antibody or the antigen-binding fragment thereof according to claim 1, wherein the activation of signal transduction through CD147 is an activation of p38MAPK and/or an activation of SMAD4.

51. The antibody or the antigen-binding fragment thereof according to claim 50, wherein the activation of p38MAPK and/or the activation of SMAD4 is an increase in p38MAPK expression level, the phosphorylation of p38MAPK, the phosphorylation of HSP27, an increase in CXCL8 expression level, an increase in rhoB expression level, a decrease in KLF5 mRNA or a decrease in KLF5 protein expression level.

52. A kit for determining responsiveness to cancer treatment with the antibody or the antigen-binding fragment thereof according to claim 1 or a pharmaceutical composition thereof, the kit comprising at least one means for detecting the expression of SMAD4 or the expression of KLF5 in a biological sample derived from a cancer patient.

53. An antibody-drug complex comprising the antibody or the antigen-binding fragment thereof according to claim 1 conjugated to another drug.

54. A bispecific antibody comprising: the antigen-binding fragment of the antibody according to claim 1; and an antigen-binding fragment which binds to an antigen other than CD147.