Claims

[Claim 1]

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

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

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

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

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

consisting of an amino acid sequence represented by SEQ ID NO: 79;

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

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

[Claim 2]

An antibody against human CD147 or an antigen-binding fragment thereof, which 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 represented by SEQ ID NO: 71 and a light chain variable region consisting of an amino acid sequence represented by SEQ ID NO: 69;

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

consisting of an amino acid sequence represented by SEQ ID NO: 49;

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

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

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

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

[Claim 3]

The antibody against human CD147 or the antigen-binding fragment thereof according to claim 1 or 2, which has decreased ADCC activity or lacks ADCC activity.

[Claim 4]

The antibody against human CD147 or the antigen-binding fragment thereof according to any one of claims 1 to 3, which has decreased CDC activity or lacks CDC activity.

[Claim 5]

The antibody against human CD147 or the antigen-binding fragment thereof according to any one of claims 1 to 4, which has decreased ADCP activity or lacks ADCP activity.

[Claim 6]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 5, which binds to an epitope comprising residues of arginine (Arg) at position 106 to glycine (Gly) at position 165 in SEQ ID NO: 3.

[Claim 7]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 6, 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.

[Claim 8]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 7, wherein:

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

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 consists of an amino acid sequence represented by SEQ ID NO: 72, the CDRL2 consists of an amino acid sequence represented by SEQ ID NO: 73, and the CDRL3 consists of an amino acid sequence represented by SEQ ID NO: 74.

[Claim 9]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 5, 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.

[Claim 10]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 5 or 9, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1

consists of an amino acid sequence represented by SEQ ID NO: 55, the CDRH2 consists of an amino acid sequence represented by SEQ ID NO: 56, and the CDRH3 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 consists of an amino acid sequence represented by SEQ ID NO: 52, the CDRL2 consists of an amino acid sequence represented by SEQ ID NO: 53, and the CDRL3 consists of an amino acid sequence represented by SEQ ID NO: 54.

[Claim 11]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 5 or 9, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 consists of an amino acid sequence represented by SEQ ID NO: 65, the CDRH2 consists of an amino acid sequence represented by SEQ ID NO: 66, and the CDRH3 consists of an amino acid sequence represented by SEQ ID NO: 67; and

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 consists of an amino acid sequence represented by SEQ ID NO: 62, the CDRL2 consists of an amino acid sequence represented by SEQ ID NO: 63, and the CDRL3 consists of an amino acid sequence represented by SEQ ID NO: 64.

[Claim 12]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 5 or 9, wherein:

in the heavy chain sequence, which comprises a variable region having CDRH1, CDRH2 and CDRH3, the CDRH1 consists of an amino acid sequence represented by SEQ ID NO: 85, the CDRH2 consists of an amino acid sequence represented by SEQ ID NO: 86, and the CDRH3 consists of an amino acid sequence represented by SEQ ID NO: 87; and

in the light chain sequence, which comprises a variable region having CDRL1, CDRL2 and CDRL3, the CDRL1 consists of an amino acid sequence represented by SEQ ID NO: 82, the CDRL2 consists of an amino acid sequence represented by SEQ ID NO: 83, and the CDRL3 consists of an amino acid sequence represented by SEQ ID NO: 84.

[Claim 13]

The antigen-binding fragment of the antibody according to any one of claims 1 to 12, which is selected from the group consisting of Fab, F(ab')2, Fab' and Fv.

[Claim 14]

The antibody according to any one of claims 1 to 12, which is scFv.

[Claim 15]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 12, which is a chimeric antibody.

[Claim 16]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 12, which is humanized.

[Claim 17]

The antibody according to any one of claims 1 to 16, 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.

[Claim 18]

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

[Claim 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).

[Claim 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).

[Claim 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).

[Claim 22]

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

[Claim 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 represented by 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 represented by 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 represented by 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 represented by 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 represented by 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).

[Claim 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 represented by 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 represented by SEQ ID NO: 137.

[Claim 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 represented by SEQ ID NO: 135; and

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

[Claim 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 represented by 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 represented by SEQ ID NO: 149.

[Claim 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 represented by SEQ ID NO: 147; and

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

[Claim 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 represented by 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 represented by SEQ ID NO: 151.

[Claim 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 represented by SEQ ID NO: 147; and

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

[Claim 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 represented by 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 represented by 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 represented by 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).

[Claim 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 represented by 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 represented by 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 represented by SEQ ID NO: 127.

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

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

[Claim 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 represented by 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 represented by 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 (e2); 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 represented by 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).

[Claim 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 represented by 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 represented by 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 represented by SEQ ID NO: 133.

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

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

[Claim 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 represented by 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 represented by 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).

[Claim 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 represented by 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 represented by SEQ ID NO: 141.

[Claim 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 represented by SEQ ID NO: 139; and

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

[Claim 39]

The antibody against human CD147 or the antigen-binding fragment thereof according to any one of claims 23 to 38, which has decreased ADCC activity or lacks ADCC activity.

[Claim 40]

The antibody against human CD147 or the antigen-binding fragment thereof according to any one of claims 23 to 39, which has decreased CDC activity or lacks CDC activity.

[Claim 41]

The antibody against human CD147 or the antigen-binding fragment thereof according to any one of claims 23 to 40, which has decreased ADCP activity or lacks ADCP activity.

[Claim 42]

A pharmaceutical composition comprising at least one of the antibodies or antigen-binding fragments thereof according to any one of claims 1 to 41.

[Claim 43]

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

[Claim 44]

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

[Claim 45]

The pharmaceutical composition according to claim 43 or 44, 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).

[Claim 46]

The pharmaceutical composition according to any one of claims 43 to 45, 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).

[Claim 47]

The pharmaceutical composition according to any one of claims 43 to 46, wherein the tumor is a SMAD4-positive tumor or a tumor having a decreased expression level of or lacking the expression of KLF5.

[Claim 48]

The pharmaceutical composition according to any one of claims 42 to 47, further comprising another antitumor agent.

[Claim 49]

A method for treating a tumor, comprising administering the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41 or the pharmaceutical composition according to any one of claims 42 to 48 to a patient.

[Claim 50]

The method according to claim 49, wherein the tumor is a tumor expressing CD147.

[Claim 51]

The method according to claim 49 or 50, 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).

[Claim 52]

The method according to any one of claims 49 to 51, 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).

[Claim 53]

The method according to any one of claims 49 to 52, wherein the tumor is a SMAD4-positive tumor or a tumor having a decreased expression level of or lacking the expression of KLF5.

[Claim 54]

The method according to any one of claims 49 to 53, wherein the antibody or the antigen-binding fragment thereof, or the pharmaceutical composition is administered in combination with another antitumor agent.

[Claim 55]

A polynucleotide which encodes the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41.

[Claim 56]

The polynucleotide according to claim 55, which comprises a polynucleotide selected from the group consisting of the following (j1) to (j3):

(j1) a polynucleotide encoding CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 75, CDRH2 consisting of an amino acid sequence represented by SEQ ID NO: 76 and CDRH3 consisting of an amino acid sequence represented by SEQ ID NO: 77, and a polynucleotide encoding CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 72, CDRL2 consisting of an amino acid sequence represented by SEQ ID NO: 73 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 74;

(j2) a polynucleotide having at least 95% sequence identity with the nucleotide sequence according to (j1); and

(j3) a polynucleotide in which one to several nucleotides are substituted, deleted or added in the polynucleotide according to (j1) or (j2).

[Claim 57]

The polynucleotide according to claim 55, which comprises a polynucleotide selected from the group consisting of the following (i1) to (i3):

(i1) a polynucleotide encoding CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 55, CDRH2 consisting of an amino acid sequence represented by SEQ ID NO: 56 and CDRH3 consisting of an amino acid sequence represented by SEQ ID NO: 57, and a polynucleotide encoding CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 52, CDRL2 consisting of an amino acid sequence represented by SEQ ID NO: 53 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 54;

(i2) a polynucleotide having at least 95% sequence identity with the nucleotide sequence according to (i1); and

(i3) a polynucleotide in which one to several nucleotides are substituted, deleted or added in the polynucleotide according to (i1) or (i2).

[Claim 58]

The polynucleotide according to claim 55, which comprises a polynucleotide selected from the group consisting of the following (k1) to (k3):

(k1) a polynucleotide encoding CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 65, CDRH2 consisting of an amino acid sequence represented by SEQ ID NO: 66 and CDRH3 consisting of an amino acid

sequence represented by SEQ ID NO: 67, and a polynucleotide encoding CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 62, CDRL2 consisting of an amino acid sequence represented by SEQ ID NO: 63 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 64;

(k2) a polynucleotide having at least 95% sequence identity with the nucleotide sequence according to (k1); and

(k3) a polynucleotide in which one to several nucleotides are substituted, deleted or added in the polynucleotide according to (k1) or (k2).

[Claim 59]

The polynucleotide according to claim 53, which comprises a polynucleotide selected from the group consisting of the following (m1) to (m3):

(m1) a polynucleotide encoding CDRH1 consisting of an amino acid sequence represented by SEQ ID NO: 85, CDRH2 consisting of an amino acid sequence represented by SEQ ID NO: 86 and CDRH3 consisting of an amino acid sequence represented by SEQ ID NO: 87, and a polynucleotide encoding CDRL1 consisting of an amino acid sequence represented by SEQ ID NO: 82, CDRL2 consisting of an amino acid sequence represented by SEQ ID NO: 83 and CDRL3 consisting of an amino acid sequence represented by SEQ ID NO: 84;

(m2) a polynucleotide having at least 95% sequence identity with the nucleotide sequence according to (m1); and

(m3) a polynucleotide in which one to several nucleotides are substituted, deleted or added in the polynucleotide according to (m1) or (m2).

[Claim 60]

An expression vector comprising the polynucleotide according to any one of claims 55 to 59.

[Claim 61]

A host cell transformed with the expression vector according to claim 60.

[Claim 62]

A method for producing the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41, comprising a step of culturing the host cell according to claim 61 and collecting a target antibody or an antigen-binding fragment thereof from a culture supernatant.

[Claim 63]

The antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41, wherein the activation of signal transduction through CD147 is an activation of p38MAPK and/or an activation of SMAD4.

[Claim 64]

The antibody or the antigen-binding fragment thereof according to claim 63, 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.

[Claim 65]

A method for treating a tumor, comprising administering the antibody or the antigen-binding fragment thereof according to claim 63 or 64.

[Claim 66]

A method for predicting responsiveness to cancer treatment, comprising:

detecting the expression of SMAD4 or the expression of KLF5 in a biological sample derived from a cancer patient; and

determining a patient's responsiveness to cancer treatment with the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41 or the pharmaceutical composition according to any one of claims 42 to 48 to be positive, when SMAD4 expression is detected in the patient, or a decrease in KLF5 expression level or a lack of KLF5 expression is detected in the patient.

[Claim 67]

A method for selecting subjects for cancer treatment, comprising:

detecting the expression of SMAD4 or the expression of KLF5 in a biological sample derived from a cancer patient; and

selecting a patient as a subject of cancer treatment with the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41 or the pharmaceutical composition according to any one of claims 42 to 48, when SMAD4 expression is detected in the patient or a decrease in KLF5 expression level or a lack of KLF5 expression is detected in the patient.

[Claim 68]

A method for treating cancer, comprising:

using a biological sample derived from a cancer patient to detect the presence or the absence of the expression of SMAD4 or to detect the expression of KLF5 in the biological sample; and

administering the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41 or the pharmaceutical composition according to any one of claims 42 to 48 to a patient in whom SMAD4 expression is detected or to a patient in whom a decrease in KLF5 expression level or a lack of KLF5 expression is detected.

[Claim 69]

A kit for determining responsiveness to cancer treatment with the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41 or the pharmaceutical composition according to any one of

claims 42 to 48, 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.

[Claim 70]

An antibody-drug complex comprising the antibody or the antigen-binding fragment thereof according to any one of claims 1 to 41 conjugated to another drug.

[Claim 71]

A bispecific antibody comprising: the antigen-binding fragment of the antibody according to any one of claims 1 to 41; and an antigen-binding fragment which binds to an antigen other than CD147.

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 □ 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.