

CLAIMS

1. An isolated antibody or antigen-binding fragment of an antibody having a stronger binding reactivity to HER2 expressed on a cancer cell than to HER2 expressed on a non-cancer cell, wherein the isolated antibody or antigen-binding fragment comprises:

- 5 (i) a heavy chain variable region comprising
 a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 18,
 a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 19, and
 a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 20, as
 well as
- 10 a light chain variable region comprising
 a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 21,
 a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 22, and
 a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 23;
 (ii) a heavy chain variable region comprising
- 15 a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 24,
 a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 25, and
 a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 26, as
 well as
- 20 a light chain variable region comprising
 a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 27,
 a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 28, and
 a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 29; or
 (i) or (ii) above in which one or more of the CDRs have at least one substitution,
 addition, or deletion.

25 2. The antibody or antigen-binding fragment thereof according to claim 1, wherein the
 antibody or antigen-binding fragment thereof (iii) ~~binding-binds~~ to a peptide that comprises
 any amino acid sequence selected from the group consisting of the amino acid sequences of
 SEQ ID NOs: 31 to 37.

30 3. The antibody or antigen-binding fragment thereof according to claim 1 or 2,
 wherein the antibody or antigen-binding fragment thereof (iv) ~~having-has~~ a stronger binding
 affinity (or reactivity) to a peptide consisting of an extracellular domain of HER2 set forth in
 SEQ ID NO: 3 than to a variant of an extracellular domain of HER2 having one or more
 amino acid mutations selected from the group consisting of W614A, K615A, and F616A in a

peptide consisting of a part (a region of amino acid numbers 603 to 622) of the extracellular domain of HER2 set forth in SEQ ID NO: 2.

~~4. The antibody or antigen binding fragment thereof according to any one of claims 1 to 3, comprising:~~

~~(iii) a heavy chain variable region comprising~~
~~a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 18,~~
~~a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 19, and~~
~~a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 20, as well as~~

~~a light chain variable region comprising~~
~~a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 21,~~
~~a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 22, and~~
~~a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 23;~~
~~(iv) a heavy chain variable region comprising~~

~~a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 24,~~
~~a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 25, and~~
~~a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 26, as well as~~

~~a light chain variable region comprising~~
~~a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 27,~~
~~a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 28, and~~
~~a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 29; or~~
~~(iii) or (iv) above in which one or more of the CDRs have at least one substitution, addition, or deletion.~~

54. The antibody or antigen-binding fragment thereof according to any one of claims 1 to 43, comprising:

(vii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 14, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 15;

(viii) a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 16, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 17; or

(vii) or (viii) above in which each of the variable regions has at least one substitution, addition, or deletion.

~~65.~~ The antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~54~~, wherein the antibody or antigen-binding fragment ~~binding~~ binds to a peptide that is produced by LN229 cells of a glioblastoma cell line and consists of the extracellular domain of HER2 set forth in SEQ ID NO: 3.

~~76.~~ The antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~65~~, wherein the cancer cell is an SK-BR-3 cell of a breast cancer cell line, and the non-cancer cell is an HaCaT cell of a normal human epidermal keratinocyte cell line.

~~87.~~ A pharmaceutical composition comprising, as an active ingredient, an HER2-targeting agent comprising the antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~76~~.

~~98.~~ The antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~76~~, conjugated with a cytotoxic agent.

~~109.~~ A pharmaceutical composition comprising, as an active ingredient, the antibody or antigen-binding fragment thereof according to claim ~~98~~.

~~110.~~ The Use of the pharmaceutical composition according to claim ~~8-7~~ or ~~109~~, in the manufacture of a medicament for ~~use in~~ treating cancer.

~~1211.~~ A cancer treating agent comprising, as an active ingredient, the antibody or antigen-binding fragment thereof according to any one of claims 1 to ~~76~~.

~~1312.~~ A nucleic acid molecule encoding the antibody or antigen-binding fragment thereof according to any one of claims ~~2-1~~ to ~~54~~.

~~14.~~ ~~A method for producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody, the method comprising:~~

~~producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody that does not significantly react to HER2 expressed on a non-cancer cell, but can specifically react to HER2 expressed on a cancer cell, from a group of antibodies or antigen-binding fragments of an antibody that bind to HER2 or a fragment thereof.~~

~~1513.~~ A method for producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody, the method comprising:

producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody that satisfies at least one selected from the group consisting of (i) to (iii) below, from

a group of antibodies or antigen-binding fragments of antibodies that bind to HER2 or a fragment thereof:

(i) binding to a peptide that comprises any amino acid sequence selected from the group consisting of the amino acid sequences of SEQ ID NOs: 31 to 37;

(ii) having a stronger reactivity to a peptide consisting of an extracellular domain of HER2 set forth in SEQ ID NO: 3 than to a peptide having one or more amino acid mutations selected from the group consisting of W614A, K615A, and F616A in a peptide consisting of a part (a region of amino acid numbers 603 to 622) of an extracellular domain of HER2 set forth in SEQ ID NO: 2; and

(iii) having a stronger binding reactivity to HER2 expressed on a cancer cell than to HER2 expressed on a non-cancer cell.

~~46~~14. A method for producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody, the method comprising:

producing, selecting or identifying an antibody or antigen-binding fragment thereof that binds to HER2 or a fragment thereof, from a group of antibodies or antigen-binding fragments of antibodies that satisfy at least one selected from the group consisting of (i) to (ii) below:

(i) binding to a peptide that comprises any amino acid sequence selected from the group consisting of the amino acid sequences of SEQ ID NOs: 31 to 37; and

(ii) having a stronger reactivity to a peptide consisting of an extracellular domain of HER2 set forth in SEQ ID NO: 3 than to a peptide having one or more amino acid mutations selected from the group consisting of W614A, K615A, and F616A in a peptide consisting of a part (a region of amino acid numbers 603 to 622) of an extracellular domain of HER2 set forth in SEQ ID NO: 2.

~~47~~15. The method according to claim ~~45~~13 or ~~46~~14, further comprising producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody that does not significantly react to HER2 expressed on a non-cancer cell, but can specifically react to HER2 expressed on a cancer cell, from a group of obtained antibodies or a group of antigen-binding fragments of the obtained antibodies.

~~48~~16. A method for producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody, the method comprising:

producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody that does not significantly react to HER2 expressed on a non-cancer cell, but can

specifically react to HER2 expressed on a cancer cell, from a group of antibodies or antigen-binding fragments of antibodies that have at least one or more amino acid mutations selected from the group consisting of substitutions, additions, insertions, and deletions in at least one CDR of any of the above (iii) or (iv) [as defined in claim 1](#).