binding fragment thereof that can have a stronger binding affinity to HER2 expressed on cancer cells than to HER2 expressed on non-cancer cells. The present invention more preferably provides an antibody or antigen-binding fragment thereof that does not significantly react to HER2 expressed on non-cancer cells, but can specifically react to HER2 expressed on cancer cells. The present invention also provides a method for treating cancer in a patient using the antibody or antigen-binding fragment thereof that binds to HER2. Furthermore, the present invention provides a method for detecting HER2-positive cancer cells, the method including a patient bringing an antibody or antigen-binding fragment thereof that binds to HER2 into contact with a cancer sample obtained from the patient. The present invention also provides a method for determining whether a patient is responsive to a HER2-targeting therapy using the antibody or antigen-binding fragment thereof that binds to HER2.

[0006] The present inventors have created an antibody that specifically recognizes HER2 expressed on cancer cells. The present inventors have also found that HER2 expressed on normal cells and HER2 expressed on cancer cells can be distinguished by an antibody, and have created an antibody capable of distinguishing them. The present invention is based on such findings.

[0007] According to the present invention, the following embodiments are provided.

[0] An isolated antibody or antigen-binding fragment thereof that has a binding reactivity to HER2 expressed on a cancer cell.

[1] An isolated antibody or antigen-binding fragment thereof that has a stronger binding reactivity to HER2 expressed on a cancer cell than to HER2 expressed on a non-cancer cell.

[1-1] 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:

(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

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

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

(i) or (ii) above in which one or more of the CDRs have at least one substitution, addition, or deletion.

[2] The antibody or antigen-binding fragment thereof according to [0] or [1] above that (i) binds to a peptide comprising any amino acid sequence selected from the group consisting of the amino acid sequences of SEQ ID NOs: 31 to 37 (for example, the amino acid sequences of SEQ ID NOs: 31 to 36).

[3] The antibody or antigen-binding fragment thereof according to [0], [1], or [2] above that (ii) 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, for example, a stronger reactivity to the peptide consisting of the extracellular domain of HER2

(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 variable region has at least one substitution, addition, or deletion.

[6] The antibody or antigen-binding fragment thereof according to any one of [0] and [1] to [5] above, binding 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

[7] The antibody or antigen-binding fragment thereof according to any one of [0] and [1] to [6] above, 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.

[8] A pharmaceutical composition containing, as an active ingredient, an HER2-targeting agent containing the antibody or antigen-binding fragment thereof according to any one of [0] and [1] to [7] above.

[9] The antibody or antigen-binding fragment thereof according to any one of [0] and [1] to [7] above, conjugated with a cytotoxic agent.

[10] A pharmaceutical composition containing, as an active ingredient, the antibody or antigen-binding fragment thereof according to [9] above.

[11] The pharmaceutical composition according to [8] or [10] above, for use in treating cancer.

[11-1] Use of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating cancer.

[12] A cancer treating agent containing, as an active ingredient, the antibody or antigen-binding fragment thereof according to any one of [0] and [1] to [7] above.

[13] A nucleic acid molecule encoding the antibody or antigen-binding fragment thereof according to any one of [2] to [6] above.

[0008] [14] An antibody or antigen-binding fragment thereof, specifically binding to an epitope of an extracellular domain of HER2,

including:

(iii) a heavy chain variable region including:

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

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 (for example, one to ten, for example, one, two, three, four, five, or six) amino acid mutations selected from the group consisting of substitutions, additions, insertions, and deletions in at least one CDR of any of (iii), (iv), and (xii).

[0010] [20-1] The method according to any one of [16] to [19] above, the method including causing an antibody producing cell (for example, a CHO cell) to produce the selected or identified antibody or the selected or identified antigen-binding fragment of the antibody.

[21] An antibody obtained by the method according to [20] above.

[22] The method according to any one of [16] to [20] above, wherein the antibody is a monoclonal antibody (for example, an isolated monoclonal antibody).

[23] A pharmaceutical composition containing an HER2-targeting agent that contains the antibody or antigen-binding fragment thereof according to any one of [1] to [7] above.

[24] A pharmaceutical composition containing the antibody or antigen-binding fragment thereof according to [9] above.

[25] The pharmaceutical composition according to [23] or [24] above, for use in treating cancer.

[0011] [101] (xi) The antibody or antigen-binding fragment thereof according to [0] or [1] above that binds to a peptide including ~~any amino acid sequence selected from the group consisting of~~ the amino acid sequence of SEQ ID NO: 37.

[102] (xii)The antibody or antigen-binding fragment thereof according to any one of [0], [1] to [3], and [101] above, including:

a heavy chain variable region including

a heavy chain CDR1 comprising the amino acid sequence according to SEQ ID NO: 81,

a heavy chain CDR2 comprising the amino acid sequence according to SEQ ID NO: 82, and

a heavy chain CDR3 comprising the amino acid sequence according to SEQ ID NO: 83, as well as

a light chain variable region including

(n) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 65, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 66;

(o) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 67, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 68;

(p) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 69, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 70;

(q) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 71, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 72;

(r) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 73, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 74;

(s) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 75, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 76;

(t) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 77, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 78;

(u) An antibody or antigen-binding fragment thereof including a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 79, and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 80; or

(xiv) The antibody or antigen-binding fragment thereof according to any one of [0], [1] to [3], [101] and [102] above, having at least one substitution, addition or deletion in each of at least one or more of variable regions of the antibody or antigen-binding fragment thereof according to any one of (xiii) (a) to (u).

[104] A method for producing, selecting or identifying an antibody or an antigen-binding fragment of an antibody, the method including:

producing, selecting or identifying an antibody or an antigen-binding fragment thereof that satisfies (xi) below, from a group of antibodies or antigen-binding fragments thereof that bind to HER2 or a fragment thereof.