

determines if there are too many copies of the HER2 gene in the cancer cells, and the Inform Dual In Situ Hybridization test which also determines if there are too many copies of the HER2 gene in the cancer cells.

[0006] The present invention aims at providing anti-HER2 antibodies or antibody fragments with reduced or minimal side effects suitable for therapeutic and diagnostic use, especially for diagnosis and treatment of cancers. Some of these anti-HER2 antibodies or antibody fragments may have a higher binding affinity to HER2 protein in a tumor microenvironment in comparison with HER2 protein present in normal tissues. These anti-HER2 antibodies or antibody fragments typically have at least comparable efficacy to known anti-HER2 antibodies. In addition, the present anti-HER2 antibodies or antibody fragments may exhibit reduced side effects in comparison with monoclonal anti-HER2 antibodies including those that may be known in the art by having a relatively low binding affinity to HER2 protein in normal tissues. These advantages may provide a more selective targeting of the HER2 protein and may permit use of higher dosages of these anti-HER2 antibodies or antibody fragments because of the selectivity of the antibodies for HER2 protein present in a tumor microenvironment, whereby more effective therapeutic treatments may be realized without a corresponding increase in undesirable side effects.

SUMMARY OF THE DISCLOSURE

[0007] In one aspect, the present invention provides an antibody or antigen-binding antibody fragment thereof, that specifically binds to HER2 protein, wherein the binding affinity to HER2 protein at a pH of 5.0 to 6.8 is greater in comparison with the binding affinity to HER2 protein at a pH of 7.0 to 7.6, said antibody or antigen-binding antibody fragment thereof, comprising a heavy chain variable region including three complementarity determining regions, said regions having amino acid sequences H1, H2, and H3, wherein:

the H1 sequence is GFX₁IKDTYIH (SEQ ID NO: 1);

the H2 sequence is X₂IX₃PTX₄X₅YX₆X₇YADSVKG (SEQ ID NO: 2); and

the H3 sequence is WGGDGFYX₈MDY (SEQ ID NO: 3);

wherein X₁ is N or W, X₂ is R or K, X₃ is Y or K or D, X₄ is N or A, X₅ is G or K, X₆ is T or D, X₇ is R or E and X₈ is A or E; and

a light chain variable region including three complementarity determining regions having amino acid sequences L1, L2, and L3, wherein:

the L1 sequence is RASQDVNTX₉VA (SEQ ID NO: 4);

the L2 sequence is SASFLYS (SEQ ID NO: 5); and

the L3 sequence is QQX₁₀YTTPT (SEQ ID NO: 6),

wherein X₉ is A or D and X₁₀ is H or D or E;

provided that when X₁-X₈ are N, R, Y, N, G, T, R and A, respectively, X₉ is not A and X₁₀ is not H; when X₁ is W, X₂-X₁₀ are not R, Y, N, G, T, R, A, A and H, respectively; when X₃ is K or D, X₁-X₂ and X₄-X₁₀ are not N, R, N, G, T, R, A, A and H, respectively; when X₄ is A, X₁-X₃ and X₅-X₁₀ are not N, R, Y, G, T, R, A, A and H, respectively; when X₇ is E, X₁-X₆ and X₈-X₁₀ are not N, R, Y, N, G, T, A, A and H, respectively; and when X₈ is E, X₁-X₆ and X₈-X₁₀ are not N, R, Y, N, G, T, R, A and H, respectively; and wherein the antibody or antigen-binding antibody fragment thereof, up to one point mutation in the H1, H2, and H3, sequences of the heavy chain variable region in comparison with a parent antibody in which X₁-X₈ are N, R, Y, N, G, T, R and A, respectively.

[0008] The isolated polypeptide of the present invention, wherein the H1 sequence is GFWIKDTYIH (SEQ ID NO: 7) or GFNIKDTYIH (SEQ ID NO: 50); the H2 sequence is any one of KIYPTNGYTRYADSVKG (SEQ ID NO: 8), RIKPTNGYTRYADSVKG (SEQ ID NO: 9), RIDPTNGYTRYADSVKG (SEQ ID NO: 10), RIYPTAGYTRYADSVKG (SEQ ID NO: 11), RIYPTNKYTRYADSVKG (SEQ ID NO: 12), RIYPTNGYDRYADSVKG (SEQ ID NO: 13), RIYPTNGYTEYADSVKG (SEQ ID NO: 14), and RIYPTNGYTRYADSVKG (SEQ ID NO: 49); the H3 sequence is WGGDGFYEMDY (SEQ ID NO: 15) or WGGDGFYAMDY (SEQ ID NO: 51); the L1 sequence is RASQDVNTDVA (SEQ ID NO: 16) or RASQDVNTAVA (SEQ ID NO: 52); the L2 sequence is SASFLYS (SEQ ID NO: 5); and the L3 sequence is QQDYTTTPPT (SEQ ID NO: 17), QQEYTTTPPT (SEQ ID NO: 18), or QQHYTTTPPT (SEQ ID NO: 53).

[0008a] In another aspect, the present disclosure provides a bispecific antibody or antigen-binding antibody fragment thereof, that binds to HER2 protein and CD3 protein, comprising the antibody or antigen-binding antibody fragment as claimed in claim 1, and six anti-CD3 complementarity determining regions having amino acid sequences L4, L5, L6, L7, L8, and L9 wherein:

the L4 sequence is GFTFNTYAMN (SEQ ID NO: 54);

the L5 sequence is RIRSKYNNYATYYADSVKD (SEQ ID NO: 55);

the L6 sequence is HX₁₁NFX₁₂NSKVSX₁₃Y (SEQ ID NO: 70);

the L7 sequence is RSSX₁₄GAVTTSNYDN (SEQ ID NO: 71);

the L8 sequence is GTNKRAP (SEQ ID NO: 58); and

the L9 sequence is ALWYSNLWV (SEQ ID NO: 59),

wherein X₁₁ is G, S, A or T, X₁₂ is G or P, X₁₃ is A or Q, and X₁₄ is T or A,

the binding affinity to CD3 at a pH of 5.0 to 6.8 is greater than the binding affinity to CD3 at a pH of 7.0 to 7.6, and the antibody or antibody fragment has up to a total of three point mutations in the L1, L3-L4, and L6-L7, sequences of the light chain variable region, in comparison with the parent antibody or antibody fragment in which X₉-X₁₄ are A, H, G, G, A, and T, respectively.

[0009] In another example, the present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region and a light chain variable region, the heavy chain variable region having an amino acid sequence selected from SEQ ID NOS: 19-28; and a light chain variable region having an amino acid sequence selected from SEQ ID NOS: 29-32.

[0010] In still another example, the present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region and a light chain variable region, the heavy chain variable region having an amino acid sequence selected from SEQ ID NOS: 33 and 19-28; and a light chain variable region having an amino acid sequence selected from SEQ ID NOS: 30-32.

[0011] In still another example, the present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region and a light chain variable region, the heavy chain variable region having an amino acid sequence selected from SEQ ID NOS: 35-39; and a light chain variable region having an amino acid sequence selected from SEQ ID NOS: 41-48.

[0012] In a certain example, present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region having an amino acid sequence of SEQ ID NO: 35; and a light chain variable region having an amino acid sequence selected from any one of SEQ ID NOS: 41-48.

[0013] In another certain example, present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region

having an amino acid sequence of SEQ ID NO: 36; and a light chain variable region having an amino acid sequence selected from any one of SEQ ID NOS: 41-48.

[0014] In another example, present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region having an amino acid sequence of SEQ ID NO: 37; and a light chain variable region having an amino acid sequence selected from any one of SEQ ID NOS: 41-48.

[0015] In still another example, present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region having an amino acid sequence of SEQ ID NO: 38; and a light chain variable region having an amino acid sequence selected from any one of SEQ ID NOS: 41-48.

[0016] In still another example, present invention provides an isolated polypeptide that specifically binds to HER2 protein, said polypeptide comprising a heavy chain variable region having an amino acid sequence of SEQ ID NO: 39; and a light chain variable region having an amino acid sequence selected from any one of SEQ ID NOS: 41-48.

[0017] In a yet another example the isolated polypeptide comprises a heavy chain variable region and a light chain variable region, said heavy chain variable region including three anti-HER2 complementarity determining regions, H1, H2, and H3, wherein:

the H1 sequence is SEQ ID NO: 50,

the H2 sequence is SEQ ID NO: 49, SEQ ID NO: 9, SEQ ID NO: 12, or SEQ ID NO: 13, and

the H3 sequence is SEQ ID NO: 51; and

said light chain variable region including three anti-HER2 complementarity determining regions, L1, L2, and L3, and six anti-CD3 complementarity determining regions L4, L5, L6, L7, L8, and L9 wherein:

the L4 sequence is GFTFNTYAMN (SEQ ID NO: 54),

the L5 sequence is RIRSKYNNYATYYADSVKD (SEQ ID NO: 55),

the L6 sequence is $HX_{11}NFX_{12}NSKVSWFX_{13}Y$ (SEQ ID NO: 70),

the L7 sequence is $RSSX_{14}GAVTTSNYDN$ (SEQ ID NO: 71),

the L8 sequence is GTNKRAP (SEQ ID NO: 58), and

the L9 sequence is ALWYSNLWV (SEQ ID NO: 59),

wherein X_{11} is G, S, A or T, X_{12} is G or P, X_{13} is A or Q, and X_{14} is T or A.

[0018] In another example of the isolated polypeptide with nine CDRs, the L6 sequence is any one of SEQ ID NOS: 56 and 60-67, and the L7 sequence is SEQ ID NO: 57, 68 or 69.

[0019] In another certain examples of the isolated polypeptide, the L4 sequence is selected from SEQ ID NO: 57, 68 and 69.

[0020] In another example, the present invention relates to an anti-HER2 antibody or antibody fragment comprising the isolated polypeptide of each of the foregoing embodiments.

[0021] In the foregoing embodiments, the antibody or antibody fragment may have a higher binding affinity to HER2 protein at a pH in a tumor microenvironment in comparison with a pH that occurs in a non-tumor microenvironment. The pH in the tumor microenvironment may range of from 5.0 to 7.0 and the pH in the non-tumor microenvironment may range from 7.2 to 7.8.

[0022] In another example, the invention relates to an antibody or antibody fragment comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region includes three anti-HER2 complementarity determining regions, said regions having sequences H1, H2, and H3, wherein:

the H1 sequence is GFX₁IKDTYIH (SEQ ID NO: 1);

the H2 sequence is X₂IX₃PTX₄X₅YX₆X₇YADSVKG (SEQ ID NO: 2); and

the H3 sequence is WGGDGFYX₈MDY (SEQ ID NO: 3);

wherein X₁ is N or W, X₂ is R or K, X₃ is Y or K or D, X₄ is N or A, X₅ is G or K, X₆ is T or D, X₇ is R or E and X₈ is A or E; and

a light chain variable region including three anti-HER2 complementarity determining regions having sequences L1, L2, and L3, wherein:

the L1 sequence is RASQDVNTX₉VA (SEQ ID NO: 4);

the L2 sequence is SASFLYS (SEQ ID NO: 5); and

the L3 sequence is QQX₁₀YTTTPPT (SEQ ID NO: 6),

wherein X₉ is A or D and X₁₀ is H or D or E; and

provided that when X₁-X₈ are N, R, Y, N, G, T, R and A, respectively, X₉ is not A and X₁₀ is not H.

[0023] In certain examples of the antibody or antibody fragment, the H1 sequence may be GFWIKDTYIH (SEQ ID NO: 7) or GFNIKDTYIH (SEQ ID NO: 50); the H2 sequence may be KIYPTNGYTRYADSVKG (SEQ ID NO: 8), RIKPTNGYTRYADSVKG (SEQ ID NO: 9), RIDPTNGYTRYADSVKG (SEQ ID NO: 10), RIYPTAGYTRYADSVKG (SEQ ID NO: 11), RIYPTNKYTRYADSVKG (SEQ ID NO: 12), RIYPTNGYDRYADSVKG (SEQ ID NO: 13), RIYPTNGYTEYADSVKG (SEQ ID NO: 14) or RIYPTNGYTRYADSVKG (SEQ ID NO: 49); and the H3 sequence may be WGGDGFYEMDY (SEQ ID NO: 15) or WGGDGFYAMDY (SEQ ID NO: 51).

[0024] In each of the foregoing embodiments of this example of the antibody or antibody fragment, the L1 sequence may be RASQDVNTDVA (SEQ ID NO: 16) or RASQDVNTAVA

(SEQ ID NO: 52), the L2 sequence is SASFLYS (SEQ ID NO: 5); and the L3 sequence may be QQDYTTTPPT (SEQ ID NO: 17), QQEYTTTPPT (SEQ ID NO: 18), or QQHYTTTPPT (SEQ ID NO: 53).

[0025] In certain of the foregoing embodiments of this example of the antibody or antibody fragment, the H1 sequence is SEQ ID NO: 50; the H2 sequence is SEQ ID NO: 49, and the H3 sequence is SEQ ID NO: 51.

[0026] In certain of the foregoing embodiments of this example of the antibody or antibody fragment, the L1 sequence is RASQDVNTAVA (SEQ ID NO: 52), and the L3 sequence is QQHYTTTPPT (SEQ ID NO: 53).

[0027] In certain examples of the antibody or antibody fragment, the H1 sequence is SEQ ID NO: 50; the H2 sequence is RIKPTNGYTRYADSVKG (SEQ ID NO: 9), RIYPTNKYTRYADSVKG (SEQ ID NO: 12), RIYPTNGYDRYADSVKG (SEQ ID NO: 13) or RIYPTNGYTRYADSVKG (SEQ ID NO: 49), and the H3 sequence is WGGDGFYEMDY (SEQ ID NO: 15) or WGGDGFYAMDY (SEQ ID NO: 51).

[0028] In each of the foregoing embodiments of this example of the antibody or antibody fragment, the heavy chain variable region may be any one of SEQ ID NOS: 19-28 and the light chain variable region may be any one of SEQ ID NOS: 29-32.

[0029] In each of the foregoing embodiments of this example of the antibody or antibody fragment, the heavy chain variable region may be any one of SEQ ID NOS: 33 and 19-28 and the light chain variable region may be any one of SEQ ID NOS: 30-32.

[0030] In each of the foregoing embodiments of this example of the antibody or antibody fragment, the heavy chain variable region may be any one of SEQ ID NOS: 35-39 and the light chain variable region may be any one of SEQ ID NOS: 41-48.

[0031] In certain embodiments, the antibody or antibody fragment has a heavy chain variable region of SEQ ID NO: 19 or 20 and a light chain variable region of SEQ ID NO: 29.

[0032] In other embodiments, the antibody or antibody fragment has a heavy chain variable is SEQ ID NO: 33 and the light chain variable regions is one of SEQ ID NOS: 30-32.

[0033] In other embodiments, the antibody or antibody fragment has a light chain variable region of SEQ ID NO: 30 and a heavy chain variable region of any one of SEQ ID NOS: 33 and 19-28.

[0034] In certain embodiments, the antibody or antibody fragment has a heavy chain variable region of SEQ ID NO: 35 and a light chain variable region selected from any one of SEQ ID NOS: 41-48.

the L9 sequence is ALWYSNLWV (SEQ ID NO: 59),

wherein X₁₁ is G, S, A or T, X₁₂ is G or P, X₁₃ is A or Q, and X₁₄ is T or A.

[0040] In another example of the antibody or antibody fragment, said antibody or antibody fragment is multi-specific and comprises a heavy chain variable region including three anti-HER2 complementarity determining regions, H1, H2, and H3, wherein:

the H1 sequence is SEQ ID NO: 50,

the H2 sequence is selected from SEQ ID NO: 49, SEQ ID NO: 9, SEQ ID NO: 12, or SEQ ID NO: 13, and

the H3 sequence is SEQ ID NO: 51 and a light chain variable region including three anti-HER2 complementarity determining regions L1, L2, and L3, and six anti-CD3 complementarity determining regions L4, L5, L6, L7, L8, and L9 wherein:

the L1 sequence is SEQ ID NO: 52 or SEQ ID NO: 16,

the L2 sequence is SEQ ID NO: 5,

the L3 sequence is SEQ ID NO: 53,

the L4 sequence is GFTFNTYAMN (SEQ ID NO: 54),

the L5 sequence is RIRSKYNNYATYYADSVKD (SEQ ID NO: 55),

the L6 sequence is HX₁₁NFX₁₂NSKVSWFX₁₃Y (SEQ ID NO: 70),

the L7 sequence is RSSX₁₄GAVTTSNYDN (SEQ ID NO: 71),

the L8 sequence is GTNKRAP (SEQ ID NO: 58), and

the L9 sequence is ALWYSNLWV (SEQ ID NO: 59),

wherein X₁₁ is G, S, A or T, X₁₂ is G or P, X₁₃ is A or Q, and X₁₄ is T or A.

[0041] In another example of the multi-specific antibody or antibody fragment, the L6 sequence is any one of SEQ ID NOs: 56 and 60-67, and the L7 sequence is SEQ ID NO: 57, 68 or 69.

[0042] Each of the foregoing embodiments of the antibody or antibody fragment of this example may have a higher binding affinity to HER2 protein at a pH in a tumor microenvironment in comparison with a different pH that occurs in a non-tumor microenvironment. The pH in the tumor microenvironment may be in a range of from 5.0 to 7.0 and the pH in the non-tumor microenvironment may be in a range of from 7.2 to 7.8.

[0043] Each of the foregoing embodiments of the antibody or antibody fragment of this example may have a ratio of binding affinity to the HER2 protein at a pH in a tumor microenvironment to a binding affinity to the HER2 protein at a different pH in a non-tumor microenvironment of at least about 1.5:1, at least about 2:1, at least about 3:1, at least about 4:1, at least about 5:1, at least about 6:1, at least about 7:1, at least about 8:1, at least about 9:1, at least about 10:1, at least about 20:1, at least about 30:1, at least about 50:1, at least about 70:1, or at least about 100:1.

[0044] In a further aspect, the present invention relates to an immunoconjugate comprising the antibody or antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of the invention, conjugated to at least one agent.. This immunoconjugate may include at least one agent selected from a chemotherapeutic agent, a radioactive atom, a cytostatic agent and a cytotoxic agent, or at least two said agents.

[0045] In each of the foregoing embodiments of the immunoconjugate, the at least one agent may be a radioactive agent and the radioactive agent may be selected from an alpha emitter, a beta emitter and a gamma emitter.

[0046] In each of the foregoing embodiments of the immunoconjugate, the at least one agent may be covalently bonded to a linker molecule. In each of the foregoing embodiments of the immunoconjugate, the at least one agent may be selected from maytansinoids, auristatins, dolastatins, calicheamicin, pyrrolobenzodiazepines, and anthracyclines.

[0047] In yet another aspect, the present invention relates to a pharmaceutical composition comprising the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of the invention, or the immunoconjugate of the invention;; and a pharmaceutically acceptable carrier.

[0048] The foregoing embodiment of the pharmaceutical may include a tonicity agent.

[0049] Each of the foregoing embodiments of the pharmaceutical composition may further include an immune checkpoint inhibitor molecule. The immune checkpoint inhibitor molecule may be an antibody or antibody fragment against an immune checkpoint. The immune checkpoint may be selected from CTLA4, LAG3, TIM3, TIGIT, VISTA, BTLA, OX40, CD40, 4-1BB, PD-1, PD-L1, GITR, B7-H3, B7-H4, KIR, A2aR, CD27, CD70, DR3, and ICOS. Alternatively, the immune checkpoint may be one of CTLA4, PD-1 or PD-L1.

[0050] Each of the foregoing embodiments of the pharmaceutical composition may further include an antibody or antibody fragment against an antigen selected from CTLA4, PD1, PD-L1, AXL, ROR2, CD3, EpCAM, B7-H3, ROR1, SFRP4 and a WNT protein.

[0051] In another aspect, the present invention relates to a use of the polypeptide of the invention, the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of the invention, the immunoconjugate of the invention, or the pharmaceutical composition of the invention, in the manufacture of a medicament for treating cancer, wherein the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof is at least 80% identical to the amino acid sequence of the heavy chain variable region of SEQ ID NO: 33 and is at least 80% identical to the amino acid sequence of the light chain variable region of SEQ ID NO: 29..

[0052] In yet another aspect, the present invention provides a kit for diagnosis or treatment comprising the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of the invention, or the immunoconjugate of the invention, or the pharmaceutical composition of the invention, and instructions for using the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, the immunoconjugate and/or the pharmaceutical composition for diagnosis or treatment.

WHAT IS CLAIMED IS:

1. An antibody or antigen-binding antibody fragment thereof, that specifically binds to HER2 protein, wherein the binding affinity to HER2 protein at a pH of 5.0 to 6.8 is greater in comparison with the binding affinity to HER2 protein at a pH of 7.0 to 7.6, said antibody or antigen-binding antibody fragment thereof, comprising a heavy chain variable region including three complementarity determining regions, said regions having amino acid sequences H1, H2, and H3, wherein:

the H1 sequence is GFX₁IKDTYIH (SEQ ID NO: 1);

the H2 sequence is X₂IX₃PTX₄X₅YX₆X₇YADSVKG (SEQ ID NO: 2); and

the H3 sequence is WGGDGFYX₈MDY (SEQ ID NO: 3);

wherein X₁ is N or W, X₂ is R or K, X₃ is Y or K or D, X₄ is N or A, X₅ is G or K, X₆ is T or D, X₇ is R or E and X₈ is A or E; and

a light chain variable region including three complementarity determining regions having amino acid sequences L1, L2, and L3, wherein:

the L1 sequence is RASQDVNTX₉VA (SEQ ID NO: 4);

the L2 sequence is SASFLYS (SEQ ID NO: 5); and

the L3 sequence is QQX₁₀YTTPPT (SEQ ID NO: 6),

wherein X₉ is A or D and X₁₀ is H or D or E;

provided that

when X₁-X₈ are N, R, Y, N, G, T, R and A, respectively, X₉ is not A and X₁₀ is not H;

when X₁ is W, X₂-X₁₀ are not R, Y, N, G, T, R, A, A and H, respectively;

when X₃ is K or D, X₁-X₂ and X₄-X₁₀ are not N, R, N, G, T, R, A, A and H, respectively;

when X₄ is A, X₁-X₃ and X₅-X₁₀ are not N, R, Y, G, T, R, A, A and H, respectively;

when X₇ is E, X₁-X₆ and X₈-X₁₀ are not N, R, Y, N, G, T, A, A and H, respectively; and

when X₈ is E, X₁-X₆ and X₈-X₁₀ are not N, R, Y, N, G, T, R, A and H, respectively; and

wherein the antibody or antigen-binding antibody fragment thereof, up to one point mutation in the H1, H2, and H3, sequences of the heavy chain variable region in comparison with a parent antibody in which X₁-X₈ are N, R, Y, N, G, T, R and A, respectively.

2. A bispecific antibody or antigen-binding antibody fragment thereof, that binds to HER2 protein and CD3 protein, comprising the antibody or antigen-binding antibody fragment as claimed in claim 1, and

six anti-CD3 complementarity determining regions having amino acid sequences L4, L5, L6, L7, L8, and L9 wherein:

the L4 sequence is GFTFNTYAMN (SEQ ID NO: 54);

the L5 sequence is RIRSKYNNYATYYADSVKD (SEQ ID NO: 55);

the L6 sequence is HX₁₁NFX₁₂NSKVSWFX₁₃Y (SEQ ID NO: 70);

the L7 sequence is RSSX₁₄GAVTTSNYDN (SEQ ID NO: 71);

the L8 sequence is GTNKRAP (SEQ ID NO: 58); and

the L9 sequence is ALWYSNLWV (SEQ ID NO: 59),

wherein X₁₁ is G, S, A or T, X₁₂ is G or P, X₁₃ is A or Q, and X₁₄ is T or A,

the binding affinity to CD3 at a pH of 5.0 to 6.8 is greater than the binding affinity to CD3 at a pH of 7.0 to 7.6, and

the antibody or antibody fragment has up to a total of three point mutations in the L1, L3-L4, and L6-L7, sequences of the light chain variable region, in comparison with the parent antibody or antibody fragment in which X₉-X₁₄ are A, H, G, G, A, and T, respectively.

3. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, wherein the H1 sequence is GFWIKDTYIH (SEQ ID NO: 7) or GFNIKDTYIH (SEQ ID NO: 50).

4. The antibody or antigen-binding antibody fragment thereof or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, wherein the H2 sequence is selected from the group consisting of:

KIYPTNGYTRYADSVKG (SEQ ID NO: 8);

RIKPTNGYTRYADSVKG (SEQ ID NO: 9);

RIDPTNGYTRYADSVKG (SEQ ID NO: 10);

RIYPTAGYTRYADSVKG (SEQ ID NO: 11);

RIYPTNKYTRYADSVKG (SEQ ID NO: 12);

RIYPTNGYDRYADSVKG (SEQ ID NO: 13);

RIYPTNGYTEYADSVKG (SEQ ID NO: 14); and

RIYPTNGYTRYADSVKG (SEQ ID NO: 49).

5. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, wherein the H3 sequence is WGGDGFYEMDY (SEQ ID NO: 15) or WGGDGFYAMDY (SEQ ID NO: 51).

6. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, wherein the L1 sequence is RASQDVNTDVA (SEQ ID NO: 16) or RASQDVNTAVA (SEQ ID NO: 52).
7. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, wherein the L3 sequence is QQDYTTTPPT (SEQ ID NO: 17), QQEYTTTPPT (SEQ ID NO: 18), or QQHYTTTPPT (SEQ ID NO: 53).
8. The bispecific antibody or antigen-binding antibody fragment thereof of claim 2, wherein the L6 sequence is any one of SEQ ID NOs: 56 and 60-67 and the L7 sequence is SEQ ID NO: 57, 68 or 69.
9. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region is one of:
- EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAKIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 19);
- EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTEYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFY
AMDYWGQGTLVTVSS (SEQ ID NO: 20);
- EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIKPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 21);
- EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIDPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 22);
- EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
AGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 23);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NKYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 24);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYDRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 25);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YEMDYWGQGTLVTVSS (SEQ ID NO: 26);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVES (SEQ ID NO: 27); or

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 28); and

the light chain variable region is one of:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
(SEQ ID NO: 29);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
(SEQ ID NO: 30);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQDYTTPPTFGQGTKVEIK
(SEQ ID NO: 31); or

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQEYTPPTFGQGTKVEIK
(SEQ ID NO: 32).

10. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 1 or 2, wherein the heavy chain variable region is one of:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 33);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAKIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 19);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTEYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFY
 AMDYWGQGTLVTVSS (SEQ ID NO: 20);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIKPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 21);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIDPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 22);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 AGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 23);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NKYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 24);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYDRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 25);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YEMDYWGQGTLVTVSS (SEQ ID NO: 26);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVES (SEQ ID NO: 27); or

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 28), and

the light chain variable region is one of:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
 (SEQ ID NO: 30);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQDYTTPPTFGQGTKVEIK
 (SEQ ID NO: 31); or

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQEYTPPTFGQGTKVEIK
 (SEQ ID NO: 32).

11. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 9, wherein the heavy chain variable region and the light chain variable region are selected from:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAKIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 19) and

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
 (SEQ ID NO: 29), or

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTEYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFY
 AMDYWGQGTLVTVSS (SEQ ID NO: 20) and

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
 (SEQ ID NO: 29).

12. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 10, wherein the heavy chain variable region is:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 33); and

the light chain variable region is one of:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
 (SEQ ID NO: 30);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQDYTTPPTFGQGTKVEIK
 (SEQ ID NO: 31); or

DIQMTQSPSSLSASVGDRVTITCRASQDVNTAVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQEYTPPTFGQGTKVEIK
 (SEQ ID NO: 32).

13. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 9, wherein the light chain variable region is:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
 SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIK
 (SEQ ID NO: 30); and

the heavy chain variable region is one of:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 33);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVAKIYPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 19);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 NGYTEYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGFY
 AMDYWGQGTLVTVSS (SEQ ID NO: 20);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIKPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 21);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIDPT
 NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 22);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
 AGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
 YAMDYWGQGTLVTVSS (SEQ ID NO: 23);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NKYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 24);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 25);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YEMDYWGQGTLVTVSS (SEQ ID NO: 26);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVES (SEQ ID NO: 27); or

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSS (SEQ ID NO: 28).

14. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claims 1 or 2, wherein the heavy chain variable region is one of:

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIKPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 35);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NKYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLH

QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 36);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYDRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 37);

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YEMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 38); or

EVQLVESGGGLVQPGGSLRLSCAASGFNIKDTYIHWVRQAPGKGLEWVARIYPT
NGYTRYADSVKGRFTISADTSKNTAYLQMNSLRAEDTAVYYCSRWGGDGF
YAMDYWGQGTLVTVESASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP
VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVT
CVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYQSTYRVVSVLTVLH
QDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQ
VSLTCLVKGFYPSDIAVEWESNGQPENNYKTTTPVLDSDGSFFLYSKLTVDKS
RWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 39); and

the light chain variable region is one of:

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE

SVTEQDSKDSTYSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNERGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHSNFGNSKVSWFQYWQGGLTVTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSTGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 41);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNERGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHGNFGNSKVSWFQYWQGGLTVTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSTGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 42);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNERGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHGNFPNSKVSWFQYWQGGLTVTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSTGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 43);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGRSGTDFTLTISLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSTLTLSKADYEEKHKVYACEVTHQGLSSPVTKSFNERGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHANFGNSKVSWFAYWGQGLTVTVSSGGSGGSGGSGGSGGQAVVT

QEPSLTVSPGGTVTLTCRSSTGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 44);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHGNFPNSKVSWFAYWGQGTLLTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSTGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 45);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHTNFGNSKVSWFAYWGQGTLLTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSTGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 46);

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYSLSSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHSNFGNSKVSWFAYWGQGTLLTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSAGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 47); or

DIQMTQSPSSLSASVGDRVTITCRASQDVNTDVAWYQQKPGKAPKLLIYSASFLY
SGVPSRFSGSRSGTDFTLTISSLQPEDFATYYCQQHYTTPPTFGQGTKVEIKRT
VAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQE
SVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGE
CSRSGGGGEVQLVESGGGLVQPGGSLRLSCAASGFTFNTYAMNWVRQAPGK
GLEWVARIRSKYNNYATYYADSVKDRFTISRDDSKNSLYLQMNSLKTEDTA
VYYCVRHTNFGNSKVSWFAYWGQGT LTVSSGGSGGSGGSGGSGGQAVVT
QEPSLTVSPGGTVTLTCRSSAGAVTTSNYDNWVQQKPGQAPRGLIGGTNKRA
PWTPARFSGSLLGGKAALTITGAQAEDEADYYCALWYSNLWVFGGGTKLTV
LSR (SEQ ID NO: 48).

15. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 14, wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 35 and the light chain variable region has the amino acid sequence of any one of SEQ ID NOs: 41-48.

16. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 14, wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 36 and the light chain variable region has the amino acid sequence of any one of SEQ ID NOs: 41-48.

17. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 14, wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 37 and the light chain variable region has the amino acid sequence of any one of SEQ ID NOs: 41-48.

18. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 14, wherein the heavy chain variable region has the amino acid sequence of SEQ ID NO: 38 and the light chain variable region has the amino acid sequence of any one of SEQ ID NOs: 41-48.

19. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claim 14, wherein the heavy chain variable region

has the amino acid sequence of SEQ ID NO: 39 and the light chain variable region has the amino acid sequence of any one of SEQ ID NOs: 41-48.

20. The antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of claims 1 or 2, having a ratio of binding affinity to the HER2 protein at a pH of 6.0 in a tumor microenvironment to a binding affinity to the HER2 protein at a pH of 7.4 in a non-tumor microenvironment of at least 1.5:1.

21. An immunoconjugate comprising the antibody or antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of any one of claims 1 to 20 conjugated to at least one agent.

22. The immunoconjugate of claim 21, wherein the immunoconjugate the at least one agent is selected from a chemotherapeutic agent, a radioactive atom, a cytostatic agent and a cytotoxic agent.

23. The immunoconjugate of claim 22, comprising at least two said agents.

24. The immunoconjugate of claim 21, wherein the at least one agent is a radioactive agent.

25. The immunoconjugate of claim 24, wherein the radioactive agent is selected from an alpha emitter, a beta emitter and a gamma emitter.

26. The immunoconjugate of claim 22, wherein one said at least one agent is selected from maytansinoids, auristatins, dolastatins, calicheamicin, pyrrolobenzodiazepines, and anthracyclines.

27. The immunoconjugate of any one of claims 21 to 26, wherein the antibody or antigen-binding antibody fragment thereof and the at least one agent are covalently bonded to a linker molecule.

28. A pharmaceutical composition comprising:

the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of any one of claims 1 to 20, or the immunoconjugate of any one of claims 21 to 27; and
a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, further comprising an immune checkpoint inhibitor molecule.

30. The pharmaceutical composition of claim 29, wherein the immune checkpoint inhibitor molecule is an antibody or antibody fragment against an immune checkpoint.

31. The pharmaceutical composition of claim 30, wherein the immune checkpoint is selected from CTLA4, LAG3, TIM3, TIGIT, VISTA, BTLA, OX40, CD40, 4-1BB, PD-1, PD-L1, GITR, B7-H3, B7-H4, KIR, A2aR, CD27, CD70, DR3, and ICOS.

32. The pharmaceutical composition of claim 31, wherein the immune checkpoint is CTLA4, PD-1 or PD-L1.

33. The pharmaceutical composition of claim 28, further comprising an antibody or antibody fragment against an antigen selected from CTLA4, PD1, PD-L1, AXL, ROR2, CD3, EpCAM, B7-H3, ROR1, SFRP4 and a WNT protein.

34. The pharmaceutical composition of any one of claims 28 to 33, further comprising a tonicity agent.

35. Use of the polypeptide of any one of claims 1-19, the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of any one of claims 1 to 20, the immunoconjugate of any one of claims 21 to 27, or the pharmaceutical composition of any one of claims 28 to 34, in the manufacture of a medicament for treating cancer, wherein the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof is at least 80% identical to the amino acid sequence of the heavy chain variable region of SEQ ID NO: 33 and is at least 80% identical to the amino acid sequence of the light chain variable region of SEQ ID NO: 29.

36. A kit for diagnosis or treatment, said kit comprising the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, of any one of claims 1 to 20, or the immunoconjugate of any one of claims 21 to 27, or the pharmaceutical composition of any one of claims 28 to 34, and instructions for using the antibody or antigen-binding antibody fragment thereof, or the bispecific antibody or antigen-binding antibody fragment thereof, the immunoconjugate and/or the pharmaceutical composition for diagnosis or treatment.