

[0012] Pertuzumab has been evaluated in Phase II studies in combination with trastuzumab in patients with HER2-positive metastatic breast cancer who have previously received trastuzumab for metastatic disease. One study, conducted by the National cancer Institute (NCI), enrolled 11 patients with previously treated HER2-positive metastatic breast cancer. Two out of the 11 patients exhibited a partial response (PR) (Baselga et al., J Clin Oncol 2007 ASCO Annual Meeting Proceedings; 25:18 S (June 20 Supplement): 1004. The results of a Phase II neoadjuvant study evaluating the effect of a novel combination regimen of pertuzumab and trastuzumab plus chemotherapy (Docetaxel) in women with early-stage HER2-positive breast cancer, presented at the CTRC-AACR San Antonio Breast Cancer Symposium (SABCS), Dec. 8-12, 2010, showed that the two HER2 antibodies plus Docetaxel given in the neoadjuvant setting prior to surgery significantly improved the rate of complete tumor disappearance (pathological complete response rate, pCR, of 45.8 percent) in the breast by more than half compared to trastuzumab plus Docetaxel (pCR of 29.0 percent), $p=0.014$.

[0013] Pertuzumab, marketed under the tradename PERJETA®, was approved in 2012 for the treatment of patients with advanced or late-stage (metastatic) HER2-positive breast cancer. HER2-positive breast cancers have increased amounts of the HER2 protein that contributes to cancer cell growth and survival.

[0014] On September 30, 2013, the U.S. Food and Drug Administration granted accelerated approval to PERJETA® (pertuzumab) as part of a complete treatment regimen for patients with early stage breast cancer (EBC) before surgery (neoadjuvant setting). PERJETA® is the first FDA-approved drug for the neoadjuvant treatment of breast cancer.

[0015] There is a need in the art for additional safe and effective agents that target HER2 for treatment of HER2-associated conditions, such as breast cancer, for use in monotherapy and combination therapy. The invention fulfills that need and provides other benefits.

SUMMARY

[0016] The disclosure provides anti-HER2 antibodies and immunoconjugates and methods of using the same.

[0017] In one aspect, an isolated antibody that binds to HER2 is provided, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:15; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:16; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:17; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:12; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:13; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:14. In some embodiments, the antibody comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 11 and a light chain variable region comprising the sequence of SEQ ID NO: 10. In some embodiments, the antibody is a monoclonal antibody. In some embodiments, the antibody is a

humanized or chimeric antibody. In some embodiments, the antibody is an antibody fragment that binds HER2.

[0018] In some embodiments, HER2 is human HER2 comprising amino acids 23 to 1255 of SEQ ID NO:

1. In some embodiments, the antibody binds to extracellular domain I of HER2. In some embodiments, extracellular domain I of HER2 has the sequence of SEQ ID NO: 35. In some embodiments, the antibody binds to loop 163-189 and loop 185-189 of extracellular domain I (e.g., a first loop defined by amino acids 163-189 and a second loop defined by amino acids 185-189 of extracellular domain I). In some embodiments, the antibody contacts His171, Ser186, Ser187 and Glu188 of extracellular domain I.

[0019] In some embodiments, the antibody is an IgG1, IgG2a or IgG2b antibody. In some embodiments, the antibody comprises at least one mutation in the heavy chain constant region selected from A118C and S400C. In some embodiments, the antibody comprises at least one mutation in the light chain constant region selected from K149C and V205C.

[0020] In some embodiments, the antibody comprises:

- a) a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 18; or
- b) a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 23; or
- c) a heavy chain comprising the sequence of SEQ ID NO: 24 and a light chain comprising the sequence of SEQ ID NO: 18.

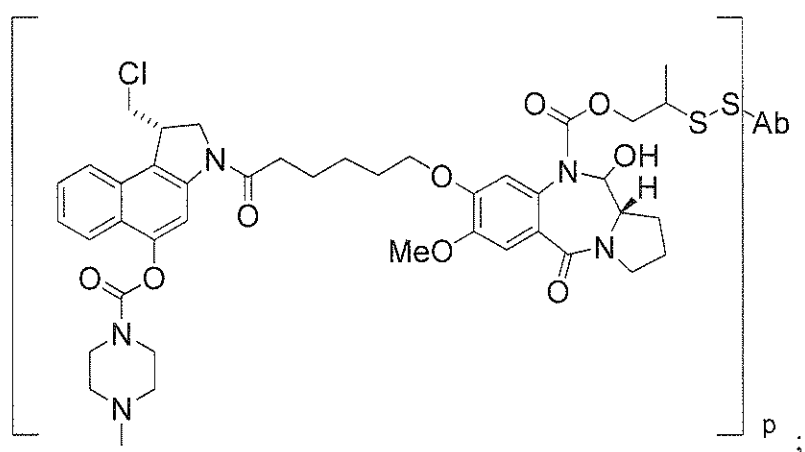
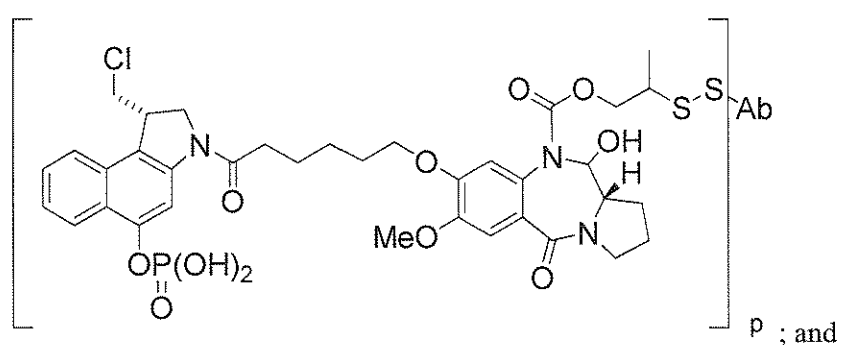
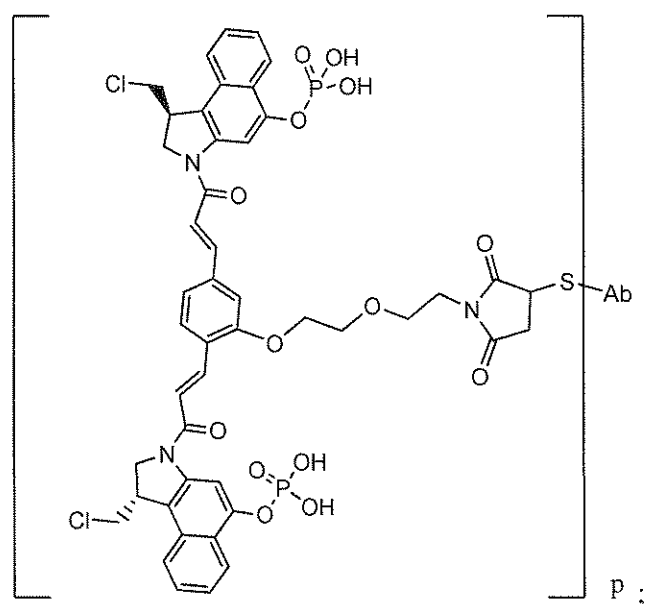
In some embodiments, the antibody comprises the heavy chain constant region of SEQ ID NO: 28. In some embodiments, the antibody comprises the light chain constant region of SEQ ID NO: 25.

[0021] In one aspect, an isolated antibody that binds to HER2 is provided, wherein the antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 23. In another aspect, an isolated antibody that binds to HER2 is provided, wherein the antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 24 and a light chain comprising the sequence of SEQ ID NO: 18. In a further aspect, an isolated antibody that binds to HER2 is provided, wherein the antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 18.

[0022] In one aspect, an isolated nucleic acid is provided, which encodes an antibody described herein. In another aspect, a host cell comprising the nucleic acid described herein is provided. In a further aspect, a method of producing an antibody is provided, comprising culturing the host cell described herein so that the antibody is produced.

[0023] In one aspect, an immunoconjugate is provided, which comprises an antibody described herein and a cytotoxic agent. In some embodiments, the immunoconjugate has the formula Ab-(L-D)_p, wherein:

- a) Ab is the antibody of any one of claim 1 to 16;



wherein Ab is an antibody described herein.

[0031] In any of the immunoconjugates described herein, p may range from 1.3-2, 1.4-2, 1.5-2, or 2-5.

[0032] In one aspect, a pharmaceutical formulation is provided, comprising an immunoconjugate described herein and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical formulation further comprises an additional therapeutic agent. In some embodiments, the additional therapeutic agent is an antibody or immunoconjugate that binds to HER2. In some embodiments, the

additional therapeutic agent is (i) an antibody or immunoconjugate that binds to domain II of HER2, and/or (ii) an antibody or immunoconjugate that binds to domain IV or HER2. In some embodiments, the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to epitope 2C4, and/or (ii) an antibody or immunoconjugate that binds to epitope 4D5. In some embodiments, the additional therapeutic agent is selected from trastuzumab, trastuzumab-MCC-DM1 (T-DM1), and pertuzumab. In some embodiments, the pharmaceutical formulation further comprises (1) trastuzumab or T-DM1, and (2) pertuzumab.

[0033] In one aspect, use of the immunoconjugate described herein in the manufacture of a medicament for treating an individual having a HER2-positive cancer is provided. In another aspect, use of the pharmaceutical formulation described herein in the manufacture of a medicament for treating an individual having a HER2-positive cancer is provided. In some embodiments, methods of treating an individual having a HER2-positive cancer are provided. In some embodiments, a method comprises administering to the individual an effective amount of an immunoconjugate described herein, or a pharmaceutical composition described herein. In some embodiments, the HER2-positive cancer is breast cancer or gastric cancer. In some embodiments, the HER2-positive breast cancer is early-stage breast cancer. In some embodiments, the HER2-positive breast cancer is metastatic breast cancer. In some embodiments, the HER2-positive cancer is recurrent cancer. In some embodiments, the recurrent cancer is locally recurrent cancer. In some embodiments, the HER2-positive cancer is advanced cancer. In some embodiments, the HER2-positive cancer is non-resectable. In some embodiments, the method further comprises administering an additional therapeutic agent to the individual.

[0034] In some embodiments, a method of treating an individual having a HER2-positive cancer comprises administering to the individual an effective amount of an immunoconjugate described herein and at least one additional therapeutic agent to the individual. In some embodiments, the additional therapeutic agent is an antibody or immunoconjugate that binds to HER2. In some embodiments, the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to domain II of HER2, and/or (ii) an antibody or immunoconjugate that binds to domain IV or HER2. In some embodiments, the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to epitope 2C4, and/or (ii) an antibody or immunoconjugate that binds to epitope 4D5. In some embodiments, the additional therapeutic agent is selected from trastuzumab, trastuzumab-MCC-DM1 (T-DM1), and pertuzumab. In some embodiments, the additional therapeutic agents are (1) trastuzumab or T-DM1, and (2) pertuzumab. In some embodiments, the HER2-positive cancer is breast cancer or gastric cancer. In some embodiments, the HER2-positive breast cancer is early-stage breast cancer. In some embodiments, the HER2-positive breast cancer is metastatic breast cancer. In some embodiments, the HER2-positive cancer is recurrent cancer. In some embodiments, the recurrent cancer is locally recurrent cancer. In some embodiments, the HER2-positive cancer is advanced cancer. In some embodiments, the HER2-positive cancer is non-resectable.

[0035] In one aspect, use of the immunoconjugate described herein in the manufacture of a medicament for treating an individual having a HER2-positive cancer is provided, wherein the treating comprises: a) subjecting the individual to neoadjuvant treatment with the immunoconjugate described herein, b) removing the cancer by definitive surgery, and c) subjecting the individual to adjuvant treatment with the immunoconjugate described herein. In another aspect, use of the pharmaceutical formulation described herein in the manufacture of a medicament for treating an individual having a HER2-positive cancer is provided, wherein the treating comprises: a) subjecting the individual to neoadjuvant treatment with the pharmaceutical formulation described herein, b) removing the cancer by definitive surgery, and c) subjecting the individual to adjuvant treatment with the pharmaceutical formulation described herein. In some embodiments, a method of treating an individual having a HER2-positive cancer comprises:

- a) subjecting the individual to neoadjuvant treatment with an immunoconjugate described herein or a pharmaceutical formulation described herein,
- b) removing the cancer by definitive surgery, and
- c) subjecting the individual to adjuvant treatment with an immunoconjugate described herein or a pharmaceutical formulation described herein.

In some embodiments, the HER2-positive cancer is breast cancer or gastric cancer.

[0036] In some aspects, *in vitro* methods of inhibiting proliferation of a HER2-positive cell are provided, the method comprising exposing the cell to an immunoconjugate described herein under conditions permissive for binding of the immunoconjugate to HER2 on the surface of the cell, thereby inhibiting proliferation of the cell. In some embodiments, the cell is a breast cancer cell or a gastric cancer cell.

[0037] In some embodiments, an antibody described herein conjugated to a label is provided. In some embodiments, the label is a positron emitter. In some embodiments, the positron emitter is ⁸⁹Zr.

[0038] In some aspects, *in vitro* methods of detecting human HER2 in a biological sample are provided, comprising contacting the biological sample with an anti-HER2 antibody described herein under conditions permissive for binding of the anti-HER2 antibody to a naturally occurring human HER2, and detecting whether a complex is formed between the anti-HER2 antibody and a naturally occurring human HER2 in the biological sample. In some embodiments, the biological sample is a breast cancer or gastric cancer sample.

[0039] In one aspect, an anti-HER antibody described herein is provided for use in detecting a HER2-positive cancer in a subject having or suspected of having a HER2-positive cancer. In some embodiments, methods for detecting a HER2-positive cancer in a subject are provided. In some embodiments, a method comprises (i) administering a labeled anti-HER2 antibody to a subject having or suspected of having a HER2-positive cancer, wherein the labeled anti-HER2 antibody comprises an anti-HER2 antibody described herein, and (ii) detecting the labeled anti-HER2 antibody in the subject, wherein detection of the labeled anti-HER2 antibody indicates a HER2-positive cancer in the subject. In some embodiments, the labeled anti-HER2 antibody comprises an anti-HER2 antibody conjugated to a positron emitter. In some embodiments, the positron emitter is ⁸⁹Zr.

BRIEF DESCRIPTION OF THE FIGURES

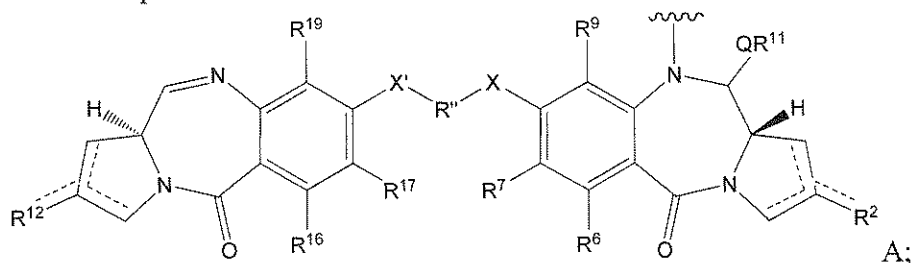
[0040] **Figure 1** shows an alignment of the human VH subgroup I (VH_I) consensus sequence and heavy chain variable region sequences of murine 7C2.B9 (“7C2”) and humanized 7C2.v2.2.LA, as described in Example 1.

[0041] **Figure 2** shows an alignment of the human VL kappa IV (VL_{KIV}) consensus sequence and light chain variable region sequences of murine 7C2.B9 (“7C2”) and humanized 7C2.v2.2.LA, as described in Example 1.

WHAT IS CLAIMED IS:

1. An isolated antibody that binds to HER2, wherein the antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:15; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO:16; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO:17; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO:12; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO:13; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO:14.
2. The antibody of claim 1, wherein the antibody comprises a heavy chain variable region comprising the sequence of SEQ ID NO: 11 and a light chain variable region comprising the sequence of SEQ ID NO: 10.
3. The antibody of any one of the preceding claims, which is a monoclonal antibody.
4. The antibody of any one of the preceding claims, which is a humanized antibody.
5. The antibody of any one of claims 1 to 3, which is a chimeric antibody.
6. The antibody of any one of the preceding claims, which is an antibody fragment that binds HER2.
7. The antibody of any one of the preceding claims, wherein said HER2 is human HER2 comprising amino acids 23 to 1255 of SEQ ID NO: 1.
8. The antibody of any one of the preceding claims, wherein the antibody binds to extracellular domain I of HER2.
9. The antibody of claim 7, wherein the extracellular domain I of HER2 has the sequence of SEQ ID NO: 35.
10. The antibody of any one of the preceding claims, which is an IgG1, IgG2a or IgG2b antibody.
11. The antibody of any one of claims 1 to 10, wherein the antibody comprises at least one mutation in the heavy chain constant region selected from A118C and S400C.
12. The antibody of any one of claims 1 to 10, wherein the antibody comprises at least one mutation in the light chain constant region selected from K149C and V205C.
13. The antibody of any one of claims 1 to 10, wherein the antibody comprises:
 - a) a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 18; or
 - b) a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 23; or
 - c) a heavy chain comprising the sequence of SEQ ID NO: 24 and a light chain comprising the sequence of SEQ ID NO: 18.
14. The antibody of any one of claims 1 to 10, wherein the antibody comprises the heavy chain constant region of SEQ ID NO: 28.
15. The antibody of any one of claims 1 to 10, wherein the antibody comprises the heavy chain constant region of SEQ ID NO: 26.
16. The antibody of any one of claims 1 to 10, wherein the antibody comprises the light chain constant region of SEQ ID NO: 25.

17. The antibody of any one of claims 1 to 10, wherein the antibody comprises the light chain constant region of SEQ ID NO: 27.
18. An isolated antibody that binds to HER2, wherein the antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 23.
19. An isolated antibody that binds to HER2, wherein the antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 24 and a light chain comprising the sequence of SEQ ID NO: 18.
20. An isolated antibody that binds to HER2, wherein the antibody comprises a heavy chain comprising the sequence of SEQ ID NO: 19 and a light chain comprising the sequence of SEQ ID NO: 18.
21. An isolated nucleic acid encoding the antibody of any one of the preceding claims.
22. A host cell comprising the nucleic acid of claim 21.
23. A method of producing an antibody comprising culturing the host cell of claim 22 so that the antibody is produced.
24. An immunoconjugate comprising the antibody of any one of claims 1 to 20 and a cytotoxic agent.
25. The immunoconjugate of claim 24 having the formula Ab-(L-D)_p, wherein:
 - (a) Ab is the antibody of any one of claim 1 to 20;
 - (b) L is a linker;
 - (c) D is a cytotoxic agent; and
 - (d) p ranges from 1-8.
26. The immunoconjugate of claim 24 or claim 25, wherein the cytotoxic agent is selected from an auristatin, a maytansinoid, a calicheamicin, a pyrrolobenzodiazepine, a nemorubicin derivative, and a 1-(chloromethyl)-2,3-dihydro-1H-benzo[e]indole (CBI).
27. The immunoconjugate of claim 24 or claim 25, wherein the cytotoxic agent is a pyrrolobenzodiazepine of Formula A:



wherein the dotted lines indicate the optional presence of a double bond between C1 and C2 or C2 and C3;

R² is independently selected from H, OH, =O, =CH₂, CN, R, OR, =CH-R^D, =C(R^D)₂, O-SO₂-R, CO₂R and COR, and optionally further selected from halo or dihalo, wherein R^D is independently selected from R, CO₂R, COR, CHO, CO₂H, and halo;

R⁶ and R⁹ are independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', NO₂, Me₃Sn and halo;

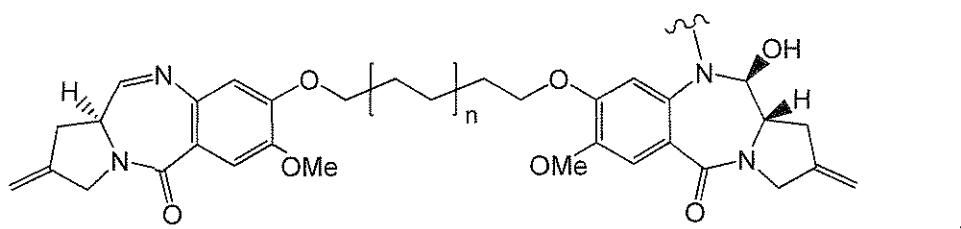
R⁷ is independently selected from H, R, OH, OR, SH, SR, NH₂, NHR, NRR', NO₂, Me₃Sn and halo;

Q is independently selected from O, S and NH, and

R and R' are each independently selected from optionally substituted C₁₋₈ alkyl, C₃₋₈ heterocyclyl and C₅₋₂₀ aryl groups, and optionally in relation to the group NRR', R and R' together with the nitrogen atom to which they are attached form an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring;

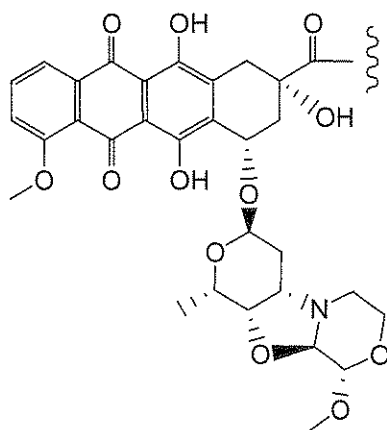
R" is a C₃₋₁₂ alkylene group, which chain may be interrupted by one or more heteroatoms and/or aromatic rings that are optionally substituted; and

28. The immunoconjugate of claim 27, wherein the cytotoxic agent has the structure:



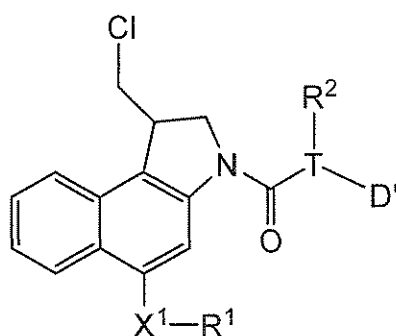
29. The immunoconjugate of claim 24 or claim 25, wherein the cytotoxic agent is a nemorubicin derivative.

Chemical structure of a complex molecule, likely a derivative of a naphthoquinone. The structure includes a naphthoquinone core, a hydroxyl group, a hydroxylamine group, a hydroxymethyl group, a methoxy group, and a morpholine ring.



31. The immunoconjugate of claim 24 or claim 25, wherein the cytotoxic agent comprises a 1-(chloromethyl)-2,3-dihydro-1H-benzo[e]indole (CBI).

32. The immunoconjugate of claim 31, wherein the cytotoxic agent has the formula:



where

R^1 is selected from H, $P(O)_3H_2$, $C(O)NR^aR^b$, or a bond to L;

R^2 is selected from H, $P(O)_3H_2$, $C(O)NR^aR^b$, or a bond to L;

R^a and R^b are independently selected from H and C_1-C_6 alkyl optionally substituted with one or more F,

or R^a and R^b form a five or six membered heterocyclyl group;

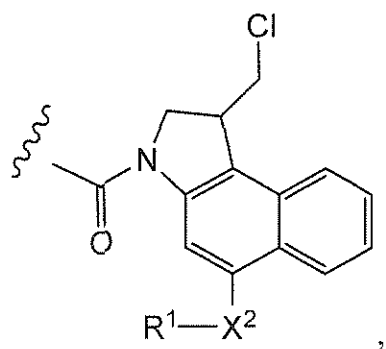
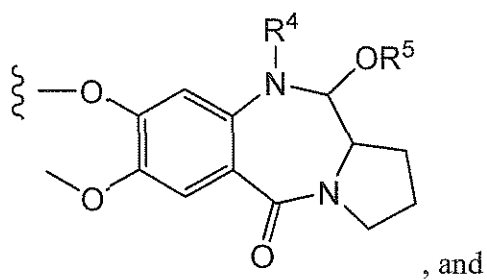
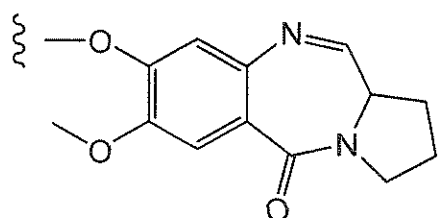
T is a tether group selected from C_3-C_{12} alkylene, Y, $(C_1-C_6 \text{ alkylene})-Y-(C_1-C_6 \text{ alkylene})$, $(C_1-C_6 \text{ alkylene})-Y-(C_1-C_6 \text{ alkylene})-Y-(C_1-C_6 \text{ alkylene})$, $(C_2-C_6 \text{ alkenylene})-Y-(C_2-C_6 \text{ alkenylene})$, and $(C_2-C_6 \text{ alkynylene})-Y-(C_2-C_6 \text{ alkynylene})$;

where Y is independently selected from O, S, NR^1 , aryl, and heteroaryl;

where alkylene, alkenylene, aryl, and heteroaryl are independently and optionally substituted with F, OH, $O(C_1-C_6 \text{ alkyl})$, NH_2 , $NHCH_3$, $N(CH_3)_2$, $OP(O)_3H_2$, and C_1-C_6 alkyl, where alkyl is optionally substituted with one or more F;

or alkylene, alkenylene, aryl, and heteroaryl are independently and optionally substituted with a bond to L;

D' is a drug moiety selected from:



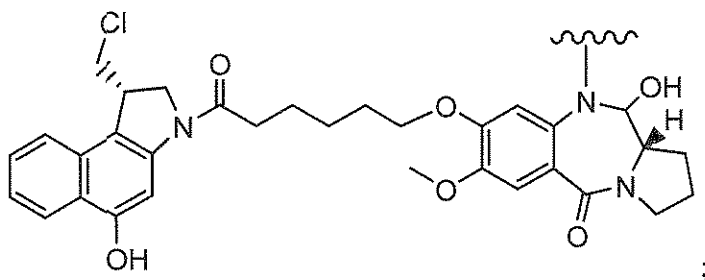
where the wavy line indicates the site of attachment to T;

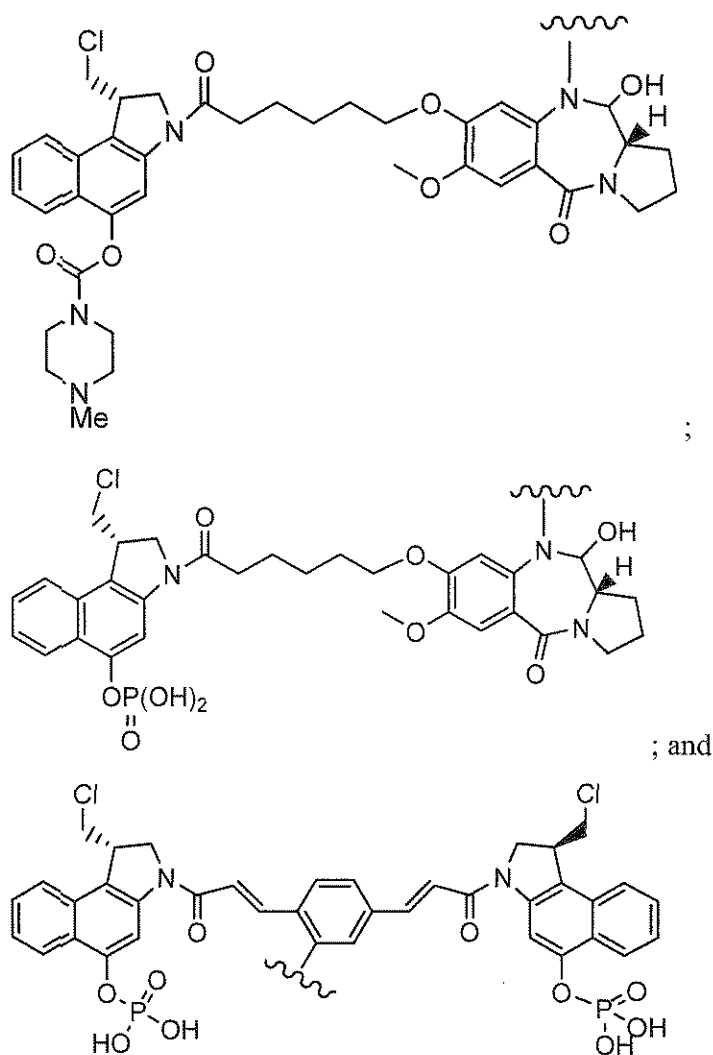
X^1 and X^2 are independently selected from O and NR^3 , where R^3 is selected from H and C_1-C_6 alkyl optionally substituted with one or more F;

R^4 is H, CO_2R , or a bond to a linker (L), where R is C_1-C_6 alkyl or benzyl; and

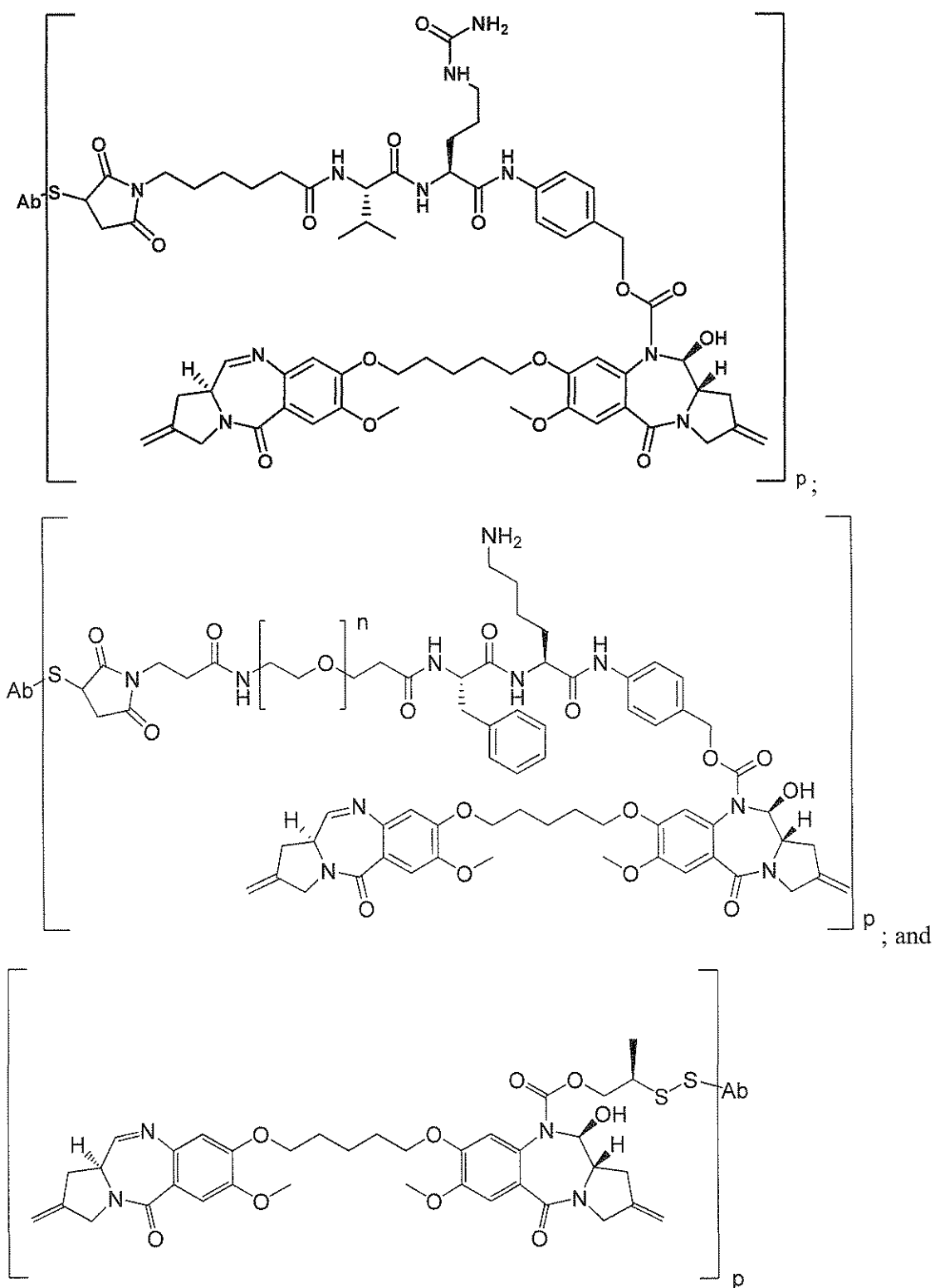
R^5 is H or C_1-C_6 alkyl.

33. The immunoconjugate of claim 32, wherein the cytotoxic agent has a structure selected from:

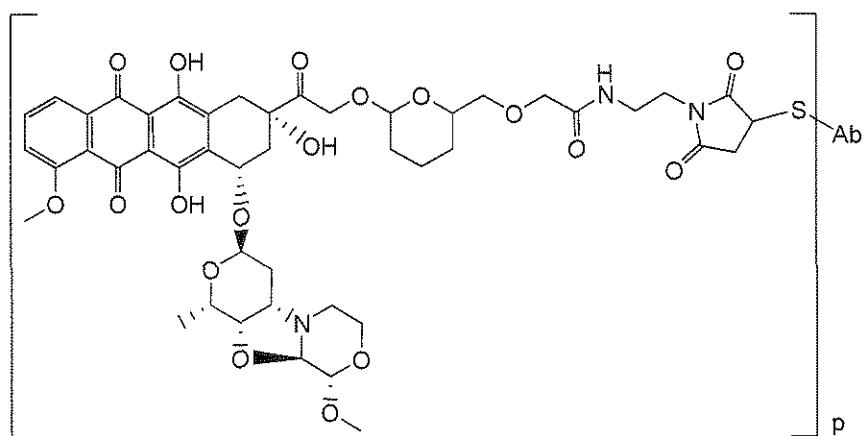




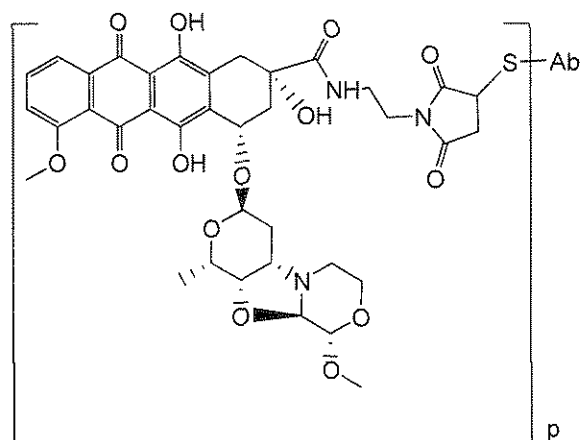
34. The immunoconjugate of any one of claims 25 to 33, wherein the linker is cleavable by a protease.
35. The immunoconjugate of any one of claims 25 to 33, wherein the linker is acid-labile.
36. The immunoconjugate of claim 35, wherein the linker comprises hydrazone.
37. The immunoconjugate of any one of claims 25 to 33, wherein the linker comprises a disulfide.
38. The immunoconjugate of claim 25 or claim 28 having a structure selected from:



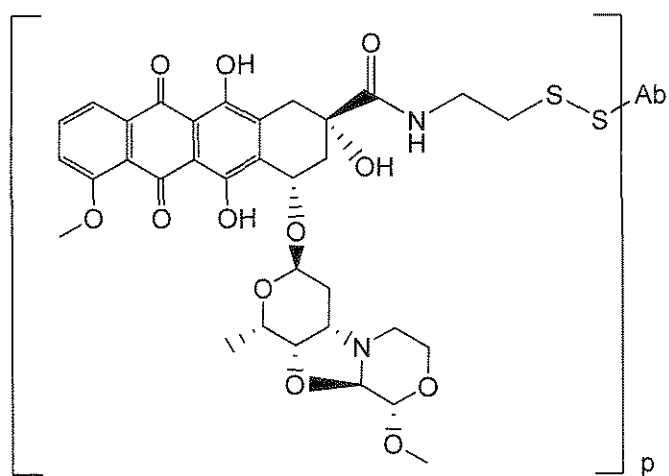
39. The immunoconjugate of claim 25 or claim 30 having a formula selected from:



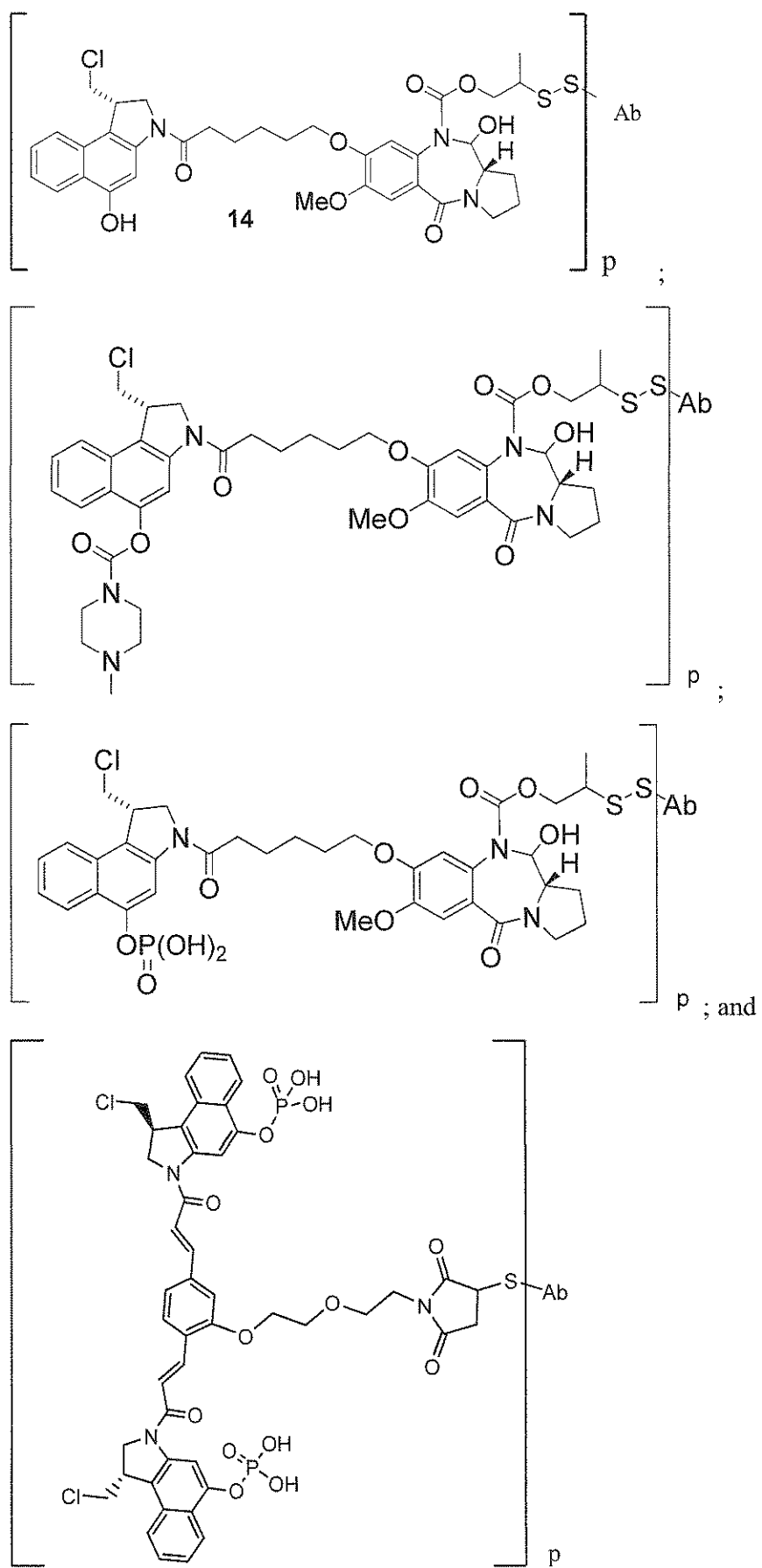
;



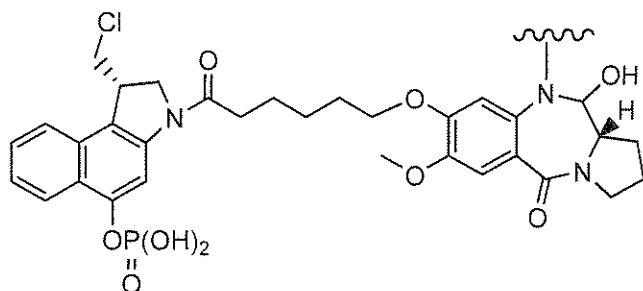
; and



40. The immunoconjugate of claim 25 or claim 33, having a structure selected from:



41. The immunoconjugate of claim 24 or claim 25, wherein the cytotoxic agent comprises the structure:



42. The immunoconjugate of any one of claims 25 to 41, wherein p ranges from 1.3-2 or from 2-5.
43. A pharmaceutical formulation comprising the immunoconjugate of any one of claims 24 to 42 and a pharmaceutically acceptable carrier.
44. The pharmaceutical formulation of claim 43, further comprising an additional therapeutic agent.
45. The pharmaceutical formulation of claim 44, wherein the additional therapeutic agent is an antibody or immunoconjugate that binds HER2.
46. The pharmaceutical formulation of claim 45, wherein the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to domain II of HER2, and/or (ii) an antibody or immunoconjugate that binds to domain IV or HER2.
47. The pharmaceutical formulation of claim 45, wherein the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to epitope 2C4, and/or (ii) an antibody or immunoconjugate that binds to epitope 4D5.
48. The pharmaceutical formulation of claim 44, wherein the additional therapeutic agent is selected from trastuzumab, trastuzumab-MCC-DM1 (T-DM1), and pertuzumab.
49. The pharmaceutical formulation of claim 44, further comprising (1) trastuzumab or T-DM1, and (2) pertuzumab.
50. Use of the immunoconjugate of any one of claims 24 to 42 in the manufacture of a medicament for treating an individual having a HER2-positive cancer.
51. The use of claim 50, wherein the HER2-positive cancer is breast cancer or gastric cancer.
52. The use of claim 51, wherein the HER2-positive breast cancer is early-stage breast cancer.
53. The use of claim 51, wherein the HER2-positive breast cancer is metastatic breast cancer.
54. The use of any one of claims 50 to 53, wherein the medicament is to be administered with an additional therapeutic agent to the individual.
55. Use of the pharmaceutical formulation of any one of claims 43 to 49 in the manufacture of a medicament for treating an individual having a HER2-positive cancer.
56. The use of claim 55, wherein the HER2-positive cancer is breast cancer or gastric cancer.
57. The use of claim 56, wherein the HER2-positive breast cancer is early-stage breast cancer.
58. The use of claim 56, wherein the HER2-positive breast cancer is metastatic breast cancer.
59. The use of any one of claims 55 to 58, wherein the medicament is to be administered with an additional therapeutic agent to the individual.

60. The use of claim 54, wherein the additional therapeutic agent is an antibody or immunoconjugate that binds HER2.
61. The use of claim 60, wherein the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to domain II of HER2, and/or (ii) an antibody or immunoconjugate that binds to domain IV or HER2.
62. The use of claim 60, wherein the additional therapeutic agent is (i) an antibody or immunoconjugate that binds to epitope 2C4, and/or (ii) an antibody or immunoconjugate that binds to epitope 4D5.
63. The use of claim 54, wherein the additional therapeutic agent is selected from trastuzumab, trastuzumab-MCC-DM1 (T-DM1), and pertuzumab.
64. The use of claim 54, wherein the additional therapeutic agents are selected from (1) trastuzumab, (2) T-DM1, (3) pertuzumab, (4) trastuzumab and pertuzumab, (5) a chemotherapeutic agent, and (6) trastuzumab, pertuzumab, and a chemotherapeutic agent.
65. The use of claim 54, wherein the additional therapeutic agent comprises a chemotherapeutic agent.
66. The use of claim 60, wherein the additional therapeutic agent further comprises a chemotherapeutic agent.
67. The use of any one of claims 64 to 66, wherein the chemotherapeutic agent is selected from doxorubicin, cyclophosphamide, paclitaxel, and docetaxel.
68. The use of any one of claims 54 and 60 to 67, wherein the HER2-positive cancer is breast cancer or gastric cancer.
69. The use of claim 68, wherein the HER2-positive breast cancer is metastatic breast cancer.
70. The use of claim 68, wherein the HER2-positive breast cancer is early-stage breast cancer.
71. The use of any one of claims 50 to 70, wherein the HER2-positive cancer is recurrent cancer.
72. The use of claim 71, wherein the recurrent cancer is locally recurrent cancer.
73. The use of any one of claims 50 to 69, wherein the HER2-positive cancer is advanced cancer.
74. The use of any one of claims 50 to 73, wherein the HER2-positive cancer is non-resectable.
75. Use of the immunoconjugate of any one of claims 24 to 42 in the manufacture of a medicament for treating an individual having a HER2-positive cancer, wherein the treating comprises:
 - a) subjecting the individual to neoadjuvant treatment with the immunoconjugate of any one of claims 24 to 42,
 - b) removing the cancer by definitive surgery, and
 - c) subjecting the individual to adjuvant treatment with the immunoconjugate of any one of claims 24 to 42.
76. The use of claim 75, wherein the HER2-positive cancer is breast cancer or gastric cancer.
77. The use of claim 76, wherein the HER2-positive cancer is breast cancer.
78. The use of the pharmaceutical formulation of any one of claims 43 to 49 in the manufacture of a medicament for treating an individual having a HER2-positive cancer, wherein the treating comprises:
 - a) subjecting the individual to neoadjuvant treatment with the pharmaceutical formulation of any one of claims 43 to 49,
 - b) removing the cancer by definitive surgery, and
 - c) subjecting the individual to adjuvant treatment with the pharmaceutical formulation of any one of claims 43 to 49.
79. The use of claim 78, wherein the HER2-positive cancer is breast cancer or gastric cancer.
80. The use of claim 79, wherein the HER2-positive cancer is breast cancer.
81. An *in vitro* method of inhibiting proliferation of a HER2-positive cell, the method comprising exposing the cell to the immunoconjugate of any one of claims 25 to 42 under conditions permissive for binding of the immunoconjugate to HER2 on the surface of the cell, thereby inhibiting proliferation of the cell.

82. The method of claim 80, wherein the cell is a breast cancer cell of a gastric cancer cell.
83. The antibody of any one of claims 1 to 20 conjugated to a label.
84. The antibody of claim 83, wherein the label is a positron emitter.
85. The antibody of claim 84, wherein the positron emitter is ^{89}Zr .
86. An *in vitro* method of detecting human HER2 in a biological sample comprising contacting the biological sample with the anti-HER2 antibody of any one of claims 1 to 20 and 83 to 85 under conditions permissive for binding of the anti-HER2 antibody to a naturally occurring human HER2, and detecting whether a complex is formed between the anti-HER2 antibody and a naturally occurring human HER2 in the biological sample.
87. The method of claim 86, wherein the biological sample is a breast cancer or gastric cancer sample.
88. The anti-HER2 antibody of any one of claims 1 to 20 for use in detecting a HER2-positive cancer in a subject having or suspected of having a HER2-positive cancer.
89. The anti-HER2 antibody of claim 88, wherein the anti-HER2 antibody is conjugated to a label, wherein the label is a positron emitter.
90. The anti-HER2 antibody of claim 89, wherein the positron emitter is ^{89}Zr .