WHAT IS CLAIMED IS

1. An isolated binding molecule or antigen-binding fragment thereof which specifically binds to an epitope within the extracellular domain of HER3, wherein the binding molecule specifically binds to the same HER3 epitope as an antibody or antigen-binding fragment thereof comprising the heavy chain variable region (VH) and light chain variable region (VL) of CL16 or 2C2.

2. As isolated binding molecule or antigen-binding fragment thereof which specifically binds to HER3, and competitively inhibits HER3 binding by an antibody or antigen-binding fragment thereof comprising the VH and VL of CL16 or 2C2.

3. The binding molecule or fragment thereof of claim 1 or claim 2, wherein the VH and VL of CL16 comprise SEQ ID NOs: 2 and 1, respectively, and the VH and VL of 2C2 comprise SEQ ID NOs: 2 and 3, respectively.

4. The binding molecule or fragment thereof of any one of claims 1 to 3, which comprises an antibody or antigen-binding fragment thereof.

5. The binding molecule or fragment thereof of any one of claims 1 to 4, wherein the binding molecule is affinity matured.

6. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises the amino acid sequence:

$[FW_1]X_1GSX_2SNIGLNYVS[FW_2]RNNQRPS[FW_3]AAWDDX_3X_4X_5GEX_6[FW_4]$

wherein $[FW_1]$, $[FW_2]$, $[FW_3]$ and $[FW_4]$ represent VL framework regions, and wherein

(a) X_1 represents amino acid residues Arginine (R) or Serine (S),

(b) X_2 represents amino acid residues Serine (S) or Leucine (L),

(c) X_3 represents amino acid residues Serine (S) or Glycine (G),

(d) X_4 represents amino acid residues Leucine (L) or Proline (P),

(e) X_5 represents amino acid residues Arginine (R), Isoleucine (I), Proline (P) or Serine (S), and

(f) X_6 represents amino acid residues Valine (V) or Alanine (A).

7. The binding molecule or fragment thereof of claim 6, wherein FW_1 comprises SEQ ID NO: 40 or 44, FW_2 comprises SEQ ID NO: 41, FW_3 comprises SEQ ID NO: 42, and FW_4 comprises SEQ ID NO: 43.

8. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises the amino acid sequence:
$[FW_5]YYYMQ[FW_6]X_7IGSSGGVTNYADSVKG[FW_7]VGLGDAFDI[FW_8]$
wherein $[FW_5]$, $[FW_6]$, $[FW_7]$ and $[FW_8]$ represent VH framework regions, and wherein X_7 represents amino acid residues Tyrosine (Y), Isoleucine (I) or Valine (V).

9. The binding molecule or fragment thereof of claim 8, wherein FW_5 comprises SEQ ID NO: 36, FW_6 comprises SEQ ID NO: 37, FW_7 comprises SEQ ID NO: 38 and FW_8 comprises SEQ ID NO: 39.

10. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL and an antibody VH, wherein the VL comprises the amino acid sequence:
$[FW_1]X_1GSX_2SNIGLNYVS[FW_2]RNNQRPS[FW_3]AAWDDX_3X_4X_5GEX_6[FW_4]$
wherein $[FW_1]$, $[FW_2]$, $[FW_3]$ and $[FW_4]$ represent VL framework regions, and wherein

(a) X_1 represents amino acid residues Arginine (R) or Serine (S),

(b) X_2 represents amino acid residues Serine (S) or Leucine (L),

(c) X_3 represents amino acid residues Serine (S) or Glycine (G),

(d) X_4 represents amino acid residues Leucine (L) or Proline (P),

(e) X_5 represents amino acid residues Arginine (R), Isoleucine (I), Proline (P) or Serine (S), and

(f) X_6 represents amino acid residues Valine (V) or Alanine (A), and

wherein the VH comprises the amino acid sequence:
$[FW_5]YYYMQ[FW_6]X7IGSSGGVTNYADSVKG[FW_7]VGLGDAFDI[FW_8]$
wherein $[FW_5]$, $[FW_6]$,$[FW_7]$ and $[FW_8]$ represent VH framework regions, and wherein X_7 represents amino acid residues Tyrosine (Y), Isoleucine (I) or Valine (V).

11. The binding molecule or fragment thereof of claim 10, wherein FW_1 comprises SEQ ID NO: 40 or 44, FW_2 comprises SEQ ID NO: 41, FW_3 comprises SEQ ID NO: 42,

FW_4 comprises SEQ ID NO: 43, FW_5 comprises SEQ ID NO: 36, FW_6 comprises SEQ ID NO: 37, FW_7 comprises SEQ ID NO: 38, and FW_8 comprises SEQ ID NO: 39.

12. The binding molecule or fragment thereof of any one of claims 6 to 11, which comprises an antibody or antigen-binding fragment thereof.

13. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises a VL complementarity determining region-1 (VL-CDR1) amino acid sequence identical to, or identical except for four, three, two or one amino acid substitutions to: SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

14. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises a VL complementarity determining region-2 (VL-CDR2) amino acid sequence identical to, or identical except for four, three, two or one amino acid substitutions to SEQ ID NO: 21.

15. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises a complementarity determining region-3 (VL-CDR3) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to: SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, or SEQ ID NO: 30.

16. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises a complementarity determining region-1 (VH-CDR1) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to SEQ ID NO: 31.

17. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises a complementarity determining region-2 (VH-CDR2) amino acid sequence identical to,

or identical except for four, three, two, or one amino acid substitutions to: SEQ ID NO: 32, SEQ ID NO: 33, or SEQ ID NO: 34.

18. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises a complementarity determining region-3 (VH-CDR3) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to SEQ ID NO: 35.

19. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences identical to, or identical except for four, three, two, or one amino acid substitutions in one or more of the VL-CDRS to: SEQ ID NOs: 18, 21 and 22, SEQ ID NOs: 18, 21, and 26, SEQ ID NOs: 18, 21, and 27 , SEQ ID NOs: 20, 21, and 22, SEQ ID NOs: 19, 21, and 22, SEQ ID NOs: 18, 21, and 25, SEQ ID NOs: 18, 21, and 28, SEQ ID NOs: 18, 21, and 29, SEQ ID NOs: 18, 21, and 30, SEQ ID NOs: 18, 21, and 23, SEQ ID NOs: 19, 21, and 23, SEQ ID NOs: 20, 21, and 23, SEQ ID NOs: 18, 21, and 24, or SEQ ID NOs: 18, 21, and 25, respectively.

20. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences identical to, or identical except for four, three, two, or one amino acid substitutions in one or more of the VH-CDRS to: SEQ ID NOs: 31, 32 and 35, SEQ ID NOs: 31, 33, and 35, or SEQ ID NOs: 31, 34, and 35, respectively.

21. The binding molecule of any one of claims 13 to 20, wherein the binding molecule or fragment thereof comprises an antibody or antigen-binding fragment thereof.

22. An isolated antibody or antigen-binding fragment thereof which specifically binds to HER3 comprising a VL and a VH comprising VL-CDR1, VL-CRD2, VL-CDR3, VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences identical or identical except for four, three, two, or one amino acid substitutions in one or more CDRs to: SEQ ID NOs: 18, 21, 22, 31, 32, and 35, SEQ ID NOs: 18, 21, 26, 31, 32 and 35, SEQ ID NOs: 18, 21, 27, 31, 32 and 35, SEQ ID NOs: 20, 21, 22, 31, 32 and 35, SEQ ID

NOs: 19, 21, 22, 31, 32 and 35, SEQ ID NOs: 18, 21, 25, 31, 32 and 35, SEQ ID NOs: 18, 21, 28, 31, 32 and 35, SEQ ID NOs: 18, 21, 29, 31, 32 and 35, SEQ ID NOs: 18, 21, 30, 31, 32 and 35, SEQ ID NOs: 18, 21, 23, 31, 32 and 35, SEQ ID NOs: 19, 21, 23, 31, 32 and 35, SEQ ID NOs: 20, 21, 23, 31, 32 and 35, SEQ ID NOs: 18, 21, 24, 31, 32 and 35, or SEQ ID NOs: 18, 21, 25, 31, 32 and 35, respectively.

23. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL and an antibody VH, wherein the VL comprises an amino acid sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17.

24. An isolated binding molecule or antigen binding fragment thereof which specifically binds to HER3 comprising an antibody VL and an antibody VH, wherein the VH comprises an amino acid sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 12 and SEQ ID NO: 13.

25. The binding molecule or fragment thereof of claim 23 or claim 24, which comprises an antibody or antigen-binding fragment thereof.

26. An isolated antibody or antigen binding fragment thereof which specifically binds to HER3, wherein the antibody or antigen binding fragment comprises a VL comprising a sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17, and wherein the antibody or antigen binding fragment comprises a VH comprising a sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 12 and SEQ ID NO: 13.

27. An isolated antibody or antigen binding fragment thereof, which comprises a VL comprising the VL consensus sequence provided in Table 4 and a VH comprising the VH consensus sequence provided in Table 4.

28. An isolated antibody or antigen binding fragment thereof, which comprises a VL comprising SEQ ID NO: 3 and a VH comprising SEQ ID NO: 2.

29. The antibody or antigen-binding fragment thereof of any one of claims 4, 12, 21, 22, or 25-28, which comprises a heavy chain constant region or fragment thereof.

30. The antibody or antigen-binding fragment thereof of claim 29, wherein the heavy chain constant region or fragment thereof is an IgG constant region.

31. The antibody or antigen-binding fragment thereof of claim 30, wherein the IgG constant region is selected from an IgG1 constant region, an IgG2 constant region, an IgG3 constant region and an IgG4 constant region.

32. The antibody or antigen-binding fragment thereof of claim 30, wherein the IgG constant region is an IgG1 constant region.

33. The antibody or antigen-binding fragment thereof of any one of claims 4, 12, 21, 22, or 25-32, which comprises a light chain constant region selected from the group consisting of a human kappa constant region and a human lambda constant region.

34. The antibody or antigen binding fragment of any one of claims 30-32, wherein the IgG constant domain comprises one or more amino acid substitutions relative to a wild-type IgG constant domain wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type IgG constant domain.

35. The isolated antibody or antigen binding fragment of claim 31, wherein the IgG constant domain comprises one or more amino acid substitutions of amino acid residues at positions 251-257, 285-290, 308-314, 385-389, and 428-436, wherein the numbering is according to the EU index as set forth in Kabat.

36. The isolated antibody or antigen binding fragment of claim 35, wherein at least one IgG constant domain amino acid substitution is selected from the group consisting of:

(a) substitution of the amino acid at position 252 with Tyrosine (Y), Phenylalanine (F), Tryptophan (W), or Threonine (T),

(b) substitution of the amino acid at position 254 with Threonine (T),

(c) substitution of the amino acid at position 256 with Serine (S), Arginine (R), Glutamine (Q), Glutamic acid (E), Aspartic acid (D), or Threonine (T),

(d) substitution of the amino acid at position 257 with Leucine (L),

(e) substitution of the amino acid at position 309 with Proline (P),

(f) substitution of the amino acid at position 311 with Serine (S),

(g) substitution of the amino acid at position 428 with Threonine (T), Leucine (L), Phenylalanine (F), or Serine (S),

(h) substitution of the amino acid at position 433 with Arginine (R), Serine (S), Isoleucine (I), Proline (P), or Glutamine (Q),

(i) substitution of the amino acid at position 434 with Tryptophan (W), Methionine (M), Serine (S), Histidine (H), Phenylalanine (F), or Tyrosine, and

(j) a combination of two or more of said substitutions,

wherein the numbering is according to the EU index as set forth in Kabat.

37. The isolated antibody or antigen binding fragment of claim 36, wherein the human IgG constant domain comprises amino acid substitutions relative to a wild-type human IgG constant domain at positions 252, 254, and 256, wherein

(a) the amino acid at position 252 is substituted with Tyrosine (Y),

(b) the amino acid at position 254 is substituted with Threonine (T), and

(c) the amino acid at position 256 is substituted with Glutamic acid (E),

wherein the numbering is according to the EU index as set forth in Kabat.

38. The isolated antibody or antigen binding fragment of claim 37, wherein the amino acid at position 434 is substituted with an amino acid selected from the group consisting of Tryptophan (W), Methionine (M), Tyrosine (Y), and Serine (S), and wherein the numbering is according to the EU index as set forth in Kabat.

39. The isolated antibody or antigen binding fragment of claim 38, wherein the amino acid at position 428 is substituted with an amino acid selected from the group consisting of Threonine (T), Leucine (L), Phenylalanine (F), and Serine (S), and wherein the numbering is according to the EU index as set forth in Kabat.

40. The isolated antibody or antigen binding fragment of claim 38, wherein the amino acid at position 257 is substituted with Leucine (L), and the amino acid at Kabat position 434 is substituted with Tyrosine (Y), and wherein the numbering is according to the EU index as set forth in Kabat.

41. The isolated antibody or antigen binding fragment of claim 39, wherein the amino acid at Kabat position 428 is substituted with Leucine (L), and the amino acid at Kabat position 434 is substituted with Serine (S).

42. An isolated binding molecule or antigen-binding fragment thereof which specifically binds to an epitope within the extracellular domain of HER3, comprising an antibody VL of SEQ ID NO:3, an antibody VH of SEQ ID NO: 2, and an IgG1 constant region of SEQ ID 46.

43. An isolated binding molecule or antigen-binding fragment thereof which specifically binds to an epitope within the extracellular domain of HER3, consisting of an antibody VL of SEQ ID NO: 3, an antibody VH of SEQ ID NO: 2, and an IgG1 constant region of SEQ ID 46.

44. The isolated antibody or antigen binding fragment of claim 29 or claim 30 wherein the human IgG constant region, comprises amino acid substitutions relative to a wild-type human IgG constant domain at positions 252, 254, and 256, wherein the numbering is according to the EU index as set forth in Kabat , and wherein
    (a) the amino acid at position 252 is substituted with Tyrosine (Y),
    (b) the amino acid at position 254 is substituted with Threonine (T), and
    (c) the amino acid at position 256 is substituted with Glutamic acid (E).

45. The antibody or antigen-binding fragment of any one of claims 4, 12, 21, 22, or 25-44, wherein the antibody is a fully human antibody, a humanized antibody, a chimeric antibody, a monoclonal antibody, a polyclonal antibody, a recombinant antibody, a multispecific antibody, or an antigen-binding fragment thereof.

46. The antigen-binding fragment of any one of claims 4, 12, 21, 22, or 25-45, which is Fv, Fab, F(ab')2, Fab', dsFv, scFv, and sc(Fv)2.

47. The antibody or fragment thereof of any one of claims 4, 12, 21, 22, or 25-46, which is conjugated to at least one heterologous agent.

48. A composition comprising the antibody or a fragment thereof of any one of claims 4, 12, 21, 22, or 25-47, and a carrier.

49. A nucleic acid comprising a sequence encoding the antibody according to any one of claims 4, 12, 21, 22, or 25-48.

50. A composition comprising a nucleic acid according to claim 49.

51. A vector comprising a nucleic acid according to claim 49.

52. A host cell comprising a nucleic acid sequence according to claim 49, the composition according to claim 50, or the vector according to claim 51.

53. A method of making the antibody or antigen-binding fragment of any one of claims 4, 12, 21, 22, or 25-46, comprising (a) culturing the cell of claim 46; and (b) isolating the antibody or antigen-binding fragment thereof.

54. The composition of claim 48, further comprising an anticancer agent.

55. A diagnostic reagent comprising the antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, or 25-47 which is labeled.

56. A kit comprising the antibody according to any one of claims 4, 12, 21, 22, or 25-47, or the composition of any one of claims 48 or 54.

57. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, or 25-47, which does not induce antibody dependent cell mediated cytotoxicity (ADCC).

58. The antibody or antigen binding fragment of claim 57, which does not induce antibody dependent cell mediated cytotoxicity (ADCC) in BT-474 cells, SkBR3 cells, or a combination thereof.

59. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47, 57 or 52, which is an antagonist of HER3.

60. The antibody or antigen binding fragment of claim 59, which is an antagonist of HER3 in cells selected from the group consisting of BT-474 cells, SkBR3 cells, MDA-MB-175 cells, MDA-MB-361 cells, A549 cells, HARA-B cells, HMCB cells, HCC827 cells, MCF-7 cells, MKN45 cells, Kato III cells, gefitinib-resistant HCC827 cells, or a combination of two or more of the recited cells.

61. The antibody or antigen binding fragment of any one of claims 59 or 60, wherein the HER3 is human HER3.

62. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-61, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce cell proliferation.

63. The antibody or antigen binding fragment of claim 62, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce cell proliferation in BT-474 cells, MDA-MB-175 cells, MDA-MB-361 cells, HMCB cells, or a combination of two or more of the recited cells.

64. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47, or 57-63, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce HER3-mediated signal transduction.

65. The antibody or antigen binding fragment of claim 64, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce HER3-mediated signal transduction in cells selected from the group consisting of BT-474 cells, SkBR3 cells, MDA-MB-175 cells, MDA-MB-361 cells, A549 cells, HARA-B cells, HMCB cells, HCC827 cells, MCF-7 cells, MKN45 cells, Kato III cells, gefitinib-resistant HCC827 cells, or a combination of two or more of the recited cells.

66. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-65, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce ligand-dependent HER3 phosphorylation.

67. The antibody or antigen binding fragment of claim 66, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce ligand-dependent HER3

phosphorylation in MCF-7 cells, HMCB cells, HCC827 cells, MKN45 cells, Kato III cells, or a combination of two or more of the recited cells.

68. The antibody or antigen binding fragment of any one of claims 66 or 67, wherein the ligand-dependent HER3 phosphorylation is HRG-driven, EGFR-driven, cMET-driven, or FGFR2-driven, or a combination thereof.

69. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-68, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce ligand-dependent phosphorylation of Akt protein kinase.

70. The antibody or antigen binding fragment of claim 69, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce ligand-dependent phosphorylation of Akt protein kinase in A549 cells, HMCB cells, MKN45 cells, Kato III cells, or a combination of two or more of the recited cells.

71. The antibody or antigen binding fragment of any one of claims 69 or 70, wherein the ligand-dependent Akt phosphorylation is cMET-driven, FGFR2-driven, or both.

72. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-71, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce ligand-independent AKT or HER3 phosphorylation.

73. The antibody or antigen binding fragment of claim 72, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce ligand-independent AKT phosphorylation, HER3 phosphorylation, or both, in BT-474 cells.

74. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-73, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce HER3 phosphorylation in cells resistant to Tyrosine Kinase Inhibitors (TKI) targeting EGFR.

75. The antibody or antigen binding fragment of claim 74, wherein the binding of the antibody or antigen binding fragment to HER3 can reduce HER3 phosphorylation in cells resistant to tyrosine kinase inhibitors (TKI) targeting EGFR in gefitinib-resistant HCC827 cells.

76. The antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-75, wherein the antibody or antigen binding fragment can bind to human HER3, cynomolgus monkey HER3, and mouse HER3.

77. A method of inhibiting the growth of a cell expressing HER3 comprising contacting the cell with the antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47, or 57-76.

78. A method of treating cancer in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen binding fragment thereof of any one of claims 4, 12, 21, 22, 25-47, or 57-76.

79. The method of claim 78, wherein the cancer is selected from the group consisting of colon cancer, lung cancer, gastric cancer, breast cancer, and head and neck cancer.

80. The method of claim 79, wherein the cancer comprises cells comprising a KRAS mutation.

81. The method of claim 80, wherein the KRAS mutation comprises a mutation of codon 12 of a human KRAS gene.

82. The method of any one of claims 78-81, wherein the subject is human.

83. A method of treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a first agent which is the antibody or antigen binding fragment thereof of claims 4, 12, 21, 22, 25-47, or 57-76, in combination with a therapeutically effective amount of a second agent, which is an anti-cancer agent other than the first agent.

84. The method of claim 83, wherein the combination of the first agent and the second agent is synergistically effective.

85. The method of any one of claims 83 or 84, wherein the second agent is a EGFR inhibitor, a HER2 inhibitor, a HER3 inhibitor or a MEK inhibitor.

86. The method of any one of claims 83-85, wherein the second agent comprises an antibody or antigen binding fragment thereof.

87. The method of any one of claims 86, wherein the second agent specifically binds to epidermal growth factor receptor (EGFR).

88. The method of any one of claims 83-87 where the second agent is cetuximab, panitumumab, matuzumab or nimotuzumab.

89. The method of claim 86, wherein the second agent specifically binds to HER2.

90. The method of any one of claims 83-87 and 89, wherein the second agent is trastuzumab, trastuzumab emtansine, pertuzumab, MM-111 or pertuzumab.

91. The method of claim 85, wherein selected from the group consisiting of gefitinib, canertinib, lapatinib, erlotinib, afatinib, neratinib, selumetinib, WX-554, selumetinib, trametinib, refametinib, E-6201 and MEK-162.

92. A method of inhibiting the grow of a cell resistant to tyrosine kinase inhibitors, comprising contacting the cell with a therapeutically effective amount of the antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-75.

93. A method of treating resistance to tyrosine kinase inhibitors in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-75.

94. The method of any one of claims 92 or 93, wherein the tyrosine kinase inhibitors target EGFR or HER2.

95. A method of inhibiting the grow of a cell resistant to threonine kinase inhibitors, comprising contacting the cell with a therapeutically effective amount of the antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-75.

96. A method of treating resistance to a threonine inhibitor in a subject, comprising administering to the subject a therapeutically effective amount of the antibody or antigen binding fragment of any one of claims 4, 12, 21, 22, 25-47 or 57-75.

97. The method of claims 95 or 96, wherein the threonine kinase inhibitors target MEK.

98. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically bind to an HER3 polypeptide or

fragment thereof with an affinity characterized by a dissociation constant (K_D) of about 0.45 nM (+/- 0.05 nM) or better as measured by a Biacore™ surface plasmon resonance assay wherein the antibody or antigen binding fragment thereof is bound to the Biacore™ chip.

99. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically bind to an HER3 polypeptide or fragment thereof with an affinity characterized by a dissociation constant (K_D) of about 0.1 nM or better as measured by a Biacore™ surface plasmon resonance assay wherein the HER3 polypeptide or fragment thereof is bound to the Biacore™ chip.

100. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically bind to an HER3 polypeptide or fragment thereof with an affinity characterized by a Kon of between 1×10^5 M^{-1} s^{-1} and 6×10^5 M^{-1} $s^{-}1$ and/or a K_{off} of between 0.5×10^{-4} s^{-1} and 2.0×10^{-4} s^{-1} as measured by a Biacore™ surface plasmon resonance assay wherein the antibody or antigen binding or fragment thereof is bound to the Biacore™ chip.

101. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in HRG-driven MCF-7 cells with an IC_{50} of about 30 ng/mL or better as measured by ELISA.

102. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in HRG-driven MCF-7 cells with an IC_{50} of about 10 ng/mL or better as measured by ELISA.

103. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress cell growth in MDAMB-175 cells with an IC_{50} of about 0.90 μg/mL or better.

104. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress cell growth in MDAMB-175 cells with an IC_{50} of about 0.15 μg/mL or better.

105. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress cell growth in HMCB cells with an IC_{50} of about 0.2 μg/mL or better.

106. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress cell growth in HMCB cells with an IC_{50} of about 0.03 μg/mL or better.

107. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in HCC827 cells with an IC_{50} of about 20 ng/mL or better.

108. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in HCC827 cells with an IC_{50} of about 2 ng/mL or better.

109. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in HCC827 cells resistant to tyrosine kinase inhibitor with an IC_{50} of about 25 ng/mL or better.

110. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in HCC827 cells resistant to tyrosine kinase inhibitor with an IC_{50} of about 5 ng/mL or better.

111. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in MKN45 cells with an IC_{50} of about 10 ng/mL or better.

112. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress HER3 phosphorylation in MKN45 cells with an IC_{50} of about 5 ng/mL or better.

113. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress pAKT in MKN45 cells with an IC_{50} of about 10 ng/mL or better.

114. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress pAKT in MKN45 cells with an IC_{50} of about 5 ng/mL or better.

115. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress pHER in Kato III cells with an IC_{50} of about 8 ng/mL or better.

116. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress pHER in Kato III cells with an IC_{50} of about 1 ng/mL or better.

117. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress pAKT in Kato III cells with an IC_{50} of about 5 ng/mL or better.

118. The antibody or antigen binding fragment thereof according to any one of claims 4, 12, 21, 22, 25-47, or 57-76, which can specifically suppress pAKT in Kato III cells with an IC_{50} of about 1 ng/mL or better.

119. An ex-vivo method of detecting the activity level of HER3 comprising detecting the level of phosphorylated HER3 in a skin biopsy from a subject, wherein the skin is treated with HRG prior to or after biopsy.

WHAT IS CLAIMED IS:

1. A monoclonal antibody or an antigen-binding fragment thereof, which specifically binds to HER3, comprising an antibody variable light chain region (VL) and an antibody variable heavy chain region (VH), wherein the VL comprises the amino acid sequence:

[FW1]SGSLSNIGLNYVS[FW2]RNNQRPS[FW3]AAWDDSPPGEA[FW4]

wherein [FW1], [FW2], [FW3] and [FW4] represent VL framework regions, and

wherein the VH comprises the amino acid sequence:

[FW5]YYYMQ[FW6]YIGSSGGVTNYADSVKG[FW7]VGLGDAFDI[FW8]

wherein [FW5], [FW6], [FW7] and [FW8] represent VH framework regions.

2. The antibody or antigen-binding fragment of claim 1, wherein the VL comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 3, and wherein the VH comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID NO: 2.

3. The antibody or antigen-binding fragment of claim 1, wherein the VL comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 3, and wherein the VH comprises an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO: 2.

4. The antibody or antigen-binding fragment of claim 1, wherein the VL comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 3, and wherein the VH comprises an amino acid sequence at least 95% identical to the amino acid sequence of SEQ ID NO: 2.

5. The antibody or antigen-binding fragment thereof of claim 1, wherein FW1 comprises SEQ ID NO: 40 or 44, FW2 comprises SEQ ID NO: 41, FW3 comprises SEQ ID NO: 42, FW4 comprises SEQ ID NO: 43, FW5 comprises SEQ ID NO: 36, FW6 comprises SEQ ID NO: 37, FW7 comprises SEQ ID NO: 38 and FW8 comprises SEQ ID NO: 39.

6. The antibody or antigen-binding fragment thereof of claim 1, which comprises a VL comprising SEQ ID NO: 3 and a VH comprising SEQ ID NO: 2.

7. The antibody or antigen-binding fragment thereof of claim 1, which comprises a heavy chain constant region.

8. The antibody or antigen-binding fragment thereof of claim 7, wherein the heavy chain constant region is a human IgG constant region.

9. The antibody or antigen-binding fragment thereof of claim 8, wherein the human IgG constant region is an IgG1 constant region.

10. The antibody or antigen-binding fragment thereof of claim 1, which comprises a light chain constant region selected from the group consisting of a human kappa constant region and a human lambda constant region.

11. The antibody or antigen-binding fragment thereof of claim 9, which comprises a light chain constant region selected from the group consisting of a human kappa constant region and a human lambda constant region.

12. The antibody or antigen-binding fragment thereof of claim 11, which comprises a human lambda constant region.

13. The antibody or antigen-binding fragment of claim 8,

(i) wherein the human IgG constant region comprises amino acid substitutions relative to a wild-type human IgG constant domain at positions 252, 254, and 256, wherein the numbering is according to the EU index as set forth in Kabat, and wherein

(a) the amino acid at position 252 is substituted with Tyrosine (Y),

(b) the amino acid at position 254 is substituted with Threonine (T), and

(c) the amino acid at position 256 is substituted with Glutamic acid (E).

14. The antibody or antigen-binding fragment of claim 1, wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, a recombinant antibody, a multispecific antibody, or an antigen-binding fragment thereof; wherein the antigen-binding fragment is an Fv, Fab, F(ab')2, Fab', dsFv, scFv, or sc(Fv)2; or wherein the antibody or antigen-binding fragment thereof is conjugated to at least one heterologous agent.

15. An antibody or an antigen-binding fragment thereof, which specifically binds to HER3, comprising an antibody VL and an antibody VH, wherein the VL comprises the amino acid sequence:

[FW1]X_1GSX_2SNIGLNYVS[FW2]RNNQRPS[FW3]AAWDD$X_3X_4X_5$GEX_6[FW4]

wherein [FW1], [FW2], [FW3] and [FW4] represent VL framework regions, and wherein

(a) X_1 represents amino acid residues Arginine (R) or Serine (S),

(b) X_2 represents amino acid residues Serine (S) or Leucine (L),

(c) X_3 represents amino acid residues Serine (S) or Glycine (G),

(d) X_4 represents amino acid residues Leucine (L) or Proline (P),

(e) X_5 represents amino acid residues Arginine (R), Isoleucine (I), Proline (P) or Serine (S), and

(f) X_6 represents amino acid residues Valine (V) or Alanine (A), and

wherein the VH comprises the amino acid sequence:

[FW5]YYYMQ[FW6]X_7IGSSGGVTNYADSVKG[FW7]VGLGDAFDI[FW8]

wherein [FW5], [FW6] ,[FW7] and [FW8] represent VH framework regions, and wherein X_7 represents amino acid residues Tyrosine (Y), Isoleucine (I) or Valine (V).

16. The antibody or antigen-binding fragment of claim 15, wherein the VL comprises a complementarity determining region (CDR) 1 comprising an amino acid sequence selected

from the group consisting of SEQ ID NOS: 18, 19, and 20, a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 21, a CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 22, 23, 24, 25, 26, 27, 28, 29, and 30, and

wherein the VH comprises a CDR1 comprising the amino acid sequence of SEQ ID NO: 31, a CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 32, 33, and 34, a CDR3 comprising the amino acid sequence of SEQ ID NO: 35.

17. A composition comprising the antibody or antigen-binding fragment thereof of claim 1, and a pharmaceutically acceptable carrier.

18. A nucleic acid comprising a sequence encoding the antibody or antigen-binding fragment according to claim 1.

19. A vector comprising a nucleic acid according to claim 18.

20. A host cell comprising a nucleic acid sequence according to claim 18.

21. A method of making an antibody or antigen-binding fragment thereof, comprising (a) culturing the cell of claim 20; and (b) isolating the antibody or antigen-binding fragment thereof.

22. An *in vitro* method of inhibiting the proliferation of a cell expressing HER3, said method comprising contacting the cell with the antibody or antigen-binding fragment of claim 1.

23. Use of an antibody or antigen-binding fragment thereof of claim 1 in the manufacture of a medicament for treating cancer in a subject.

24. The use of claim 23, wherein the cancer is selected from the group consisting of colon cancer, lung cancer, gastric cancer, breast cancer, head and neck cancer, and melanoma.

25. The use of claim 24, wherein the cancer comprises cells comprising a KRAS mutation.

26. Use of a first agent which is the antibody or antigen-binding fragment thereof of claim 1, in combination with a therapeutically effective amount of a second agent, which is an anti-cancer agent other than the first agent in the manufacture of a medicament for treating cancer in a subject.

27. A kit comprising the antibody or antigen-binding fragment thereof of claim 1.

28. An *in vitro* method of diagnosing a HER3-expressing cancer in a patient, wherein the method comprises the steps of:

(a) contacting a biological sample from the patient with the antibody or antigen-binding fragment of claim 1;

(b) detecting binding of the antibody or antigen-binding fragment to HER3 to determine a HER3 protein level in the biological sample from the patient; and

(c) comparing the HER3 protein level with a standard HER3 protein level.

29. A method of monitoring the HER3 protein level during treatment of a HER3-expressing cancer in a patient, wherein the method comprises the steps of:

(a) contacting a biological sample obtained from the patient who was administered the antibody or antigen-binding fragment of claim 1;

(b) detecting binding of the antibody or antigen-binding fragment to HER3 to determine a HER3 protein level in the biological sample from the patient; and

(c) comparing the HER3 protein level with a standard HER3 protein level.

30. The method of claim 23, wherein the cancer is characterized as expressing heregulin.

31. An *in vitro* method of monitoring HER3 protein activity level during treatment of cancer in a patient being administered the antibody or antigen-binding fragment of claim 1, wherein the method comprises the steps of:

(a) contacting a biological sample obtained from the patient with an antibody or antigen-binding fragment that specifically binds to phosphorylated HER3;

(b) detecting binding of the antibody or antigen-binding fragment to phosphorylated HER3 to determine a HER3 protein activity level in the biological sample from the patient; and

(c) comparing the HER3 protein activity level with a standard HER3 protein activity level.

32. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to an epitope within the extracellular domain of HER3, wherein the binding molecule specifically binds to the same HER3 epitope as an antibody or antigen-binding fragment thereof comprising the heavy chain variable region (VH) and light chain variable region (VL) of CL16 or 2C2.

33. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3, and competitively inhibits HER3 binding by an antibody or antigen-binding fragment thereof comprising the VH and VL of CL16 or 2C2.

34. The isolated binding molecule or antigen-binding fragment of claim 1 or claim 2, wherein the VH and VL of CL16 comprise SEQ ID NOs: 2 and 1, respectively, and the VH and VL of 2C2 comprise SEQ ID NOs: 2 and 3, respectively.

35. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises a VL complementarity determining region-1 (VL-CDR1) amino acid sequence identical to, or identical except for four, three, two or one amino acid substitutions to: SEQ ID NO: 18, SEQ ID NO: 19, or SEQ ID NO: 20.

36. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises a VL complementarity determining region-2 (VL-CDR2) amino acid sequence identical to, or identical except for four, three, two or one amino acid substitutions to SEQ ID NO: 21.

37. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises a complementarity determining region-3 (VL-CDR3) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to: SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, or SEQ ID NO: 30.

38. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises a complementarity determining region-1 (VH-CDR1) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to SEQ ID NO: 31.

39. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises a complementarity determining region-2 (VH-CDR2) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to: SEQ ID NO: 32, SEQ ID NO: 33, or SEQ ID NO: 34.

40. An isolated binding molecule an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises a complementarity determining region-3 (VH-CDR3) amino acid sequence identical to, or identical except for four, three, two, or one amino acid substitutions to SEQ ID NO: 35.

41. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VL, wherein the VL comprises VL-CDR1, VL-CDR2, and VL-CDR3 amino acid sequences identical to, or identical except for four, three, two, or one amino acid substitutions in one or more of the VL-CDRS to: SEQ ID NOs: 18, 21 and 22, SEQ ID NOs: 18, 21, and 26, SEQ ID NOs: 18, 21, and 27 , SEQ ID NOs: 20, 21, and 22, SEQ ID NOs: 19, 21, and 22, SEQ ID NOs: 18, 21, and 25, SEQ ID NOs: 18, 21, and 28, SEQ ID NOs: 18, 21, and 29, SEQ ID NOs: 18, 21, and 30, SEQ ID NOs: 18, 21, and 23, SEQ ID NOs: 19, 21, and 23, SEQ ID NOs: 20, 21, and 23, SEQ ID NOs: 18, 21, and 24, or SEQ ID NOs: 18, 21, and 25, respectively.

42. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VH, wherein the VH comprises VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences identical to, or identical except for four, three, two, or one amino acid substitutions in one or more of the VH-CDRS to: SEQ ID NOs: 31, 32 and 35, SEQ ID NOs: 31, 33, and 35, or SEQ ID NOs: 31, 34, and 35, respectively.

43. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising a VL and a VH comprising VL-CDR1, VL-CRD2, VL-CDR3, VH-CDR1, VH-CDR2, and VH-CDR3 amino acid sequences identical or identical except for four, three, two, or one amino acid substitutions in one or more CDRs to: SEQ ID NOs: 18, 21, 22, 31, 32, and 35, SEQ ID NOs: 18, 21, 26, 31, 32 and 35, SEQ ID NOs: 18, 21, 27, 31, 32 and 35, SEQ ID NOs: 20, 21, 22, 31, 32 and 35, SEQ ID NOs: 19, 21, 22, 31, 32 and 35, SEQ ID NOs: 18, 21, 25, 31, 32 and 35, SEQ ID NOs: 18, 21, 28, 31, 32 and 35, SEQ ID NOs: 18, 21, 29, 31, 32 and 35, SEQ ID NOs: 18, 21, 30, 31, 32 and 35, SEQ ID NOs: 18, 21, 23, 31, 32 and 35, SEQ ID NOs: 19, 21, 23, 31, 32 and 35, SEQ ID NOs: 20, 21, 23, 31, 32 and 35, SEQ ID NOs: 18, 21, 24, 31, 32 and 35, or SEQ ID NOs: 18, 21, 25, 31, 32 and 35, respectively.

44. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VL and an antibody VH, wherein the VL comprises an amino acid sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17.

45. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3 comprising an antibody VL and an antibody VH, wherein the VH comprises an amino acid sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 12 and SEQ ID NO: 13.

46. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to HER3, wherein the antibody or antigen binding fragment comprises a VL comprising a sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, and SEQ ID NO: 17, and wherein the antibody or antigen binding fragment comprises a VH comprising a sequence at least about 90% to about 100% identical to a reference amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 12 and SEQ ID NO: 13.

47. The isolated binding molecule or antigen-binding fragment thereof of any one of claims 32-46, which comprises a heavy chain constant region or fragment thereof.

48. The isolated binding molecule or antigen-binding fragment thereof of claim 47, wherein the heavy chain constant region or fragment thereof is an IgG constant region.

49. The isolated binding molecule or antigen-binding fragment thereof of claim 48, wherein the IgG constant region is selected from an IgG1 constant region, an IgG2 constant region, an IgG3 constant region and an IgG4 constant region.

50. The isolated binding molecule or antigen-binding fragment thereof of claim 48, wherein the IgG constant region is an IgG1 constant region.

51. The isolated binding molecule or antigen-binding fragment thereof of any one of claims of any one of claims 32-50, which comprises a light chain constant region selected from the group consisting of a human kappa constant region and a human lambda constant region.

52. The isolated binding molecule or antigen binding fragment of any one of claims 48-50, wherein the IgG constant domain comprises one or more amino acid substitutions relative to a wild-type IgG constant domain wherein the modified IgG has an increased half-life compared to the half-life of an IgG having the wild-type IgG constant domain.

53. The isolated binding molecule or antigen binding fragment of claim 49, wherein the IgG constant domain comprises one or more amino acid substitutions of amino acid residues at

positions 251-257, 285-290, 308-314, 385-389, and 428-436, wherein the numbering is according to the EU index as set forth in Kabat.

54. The isolated binding molecule or antigen binding fragment of claim 53, wherein at least one IgG constant domain amino acid substitution is selected from the group consisting of:

(a) substitution of the amino acid at position 252 with Tyrosine (Y), Phenylalanine (F), Tryptophan (W), or Threonine (T),

(b) substitution of the amino acid at position 254 with Threonine (T),

(c) substitution of the amino acid at position 256 with Serine (S), Arginine (R), Glutamine (Q), Glutamic acid (E), Aspartic acid (D), or Threonine (T),

(d) substitution of the amino acid at position 257 with Leucine (L),

(e) substitution of the amino acid at position 309 with Proline (P),

(f) substitution of the amino acid at position 311 with Serine (S),

(g) substitution of the amino acid at position 428 with Threonine (T), Leucine (L), Phenylalanine (F), or Serine (S),

(h) substitution of the amino acid at position 433 with Arginine (R), Serine (S), Isoleucine (I), Proline (P), or Glutamine (Q),

(i) substitution of the amino acid at position 434 with Tryptophan (W), Methionine (M), Serine (S), Histidine (H), Phenylalanine (F), or Tyrosine, and

(j) a combination of two or more of said substitutions,

wherein the numbering is according to the EU index as set forth in Kabat.

55. The isolated binding molecule or antigen binding fragment of claim 54, wherein the human IgG constant domain comprises amino acid substitutions relative to a wild-type human IgG constant domain at positions 252, 254, and 256, wherein

(a) the amino acid at position 252 is substituted with Tyrosine (Y),

(b) the amino acid at position 254 is substituted with Threonine (T), and

(c) the amino acid at position 256 is substituted with Glutamic acid (E),

wherein the numbering is according to the EU index as set forth in Kabat.

56. The isolated binding molecule or antigen binding fragment of claim 55, wherein the amino acid at position 434 is substituted with an amino acid selected from the group consisting of Tryptophan (W), Methionine (M), Tyrosine (Y), and Serine (S), and wherein the numbering is according to the EU index as set forth in Kabat.

57. The isolated binding molecule or antigen binding fragment of claim 56, wherein the amino acid at position 428 is substituted with an amino acid selected from the group consisting of Threonine (T), Leucine (L), Phenylalanine (F), and Serine (S), and wherein the numbering is according to the EU index as set forth in Kabat.

58. The isolated binding molecule or antigen binding fragment of claim 56, wherein the amino acid at position 257 is substituted with Leucine (L), and the amino acid at Kabat position 434 is substituted with Tyrosine (Y), and wherein the numbering is according to the EU index as set forth in Kabat.

59. The isolated binding molecule or antigen binding fragment of claim 57, wherein the amino acid at Kabat position 428 is substituted with Leucine (L), and the amino acid at Kabat position 434 is substituted with Serine (S).

60. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to an epitope within the extracellular domain of HER3, comprising an antibody VL of SEQ ID NO:3, an antibody VH of SEQ ID NO: 2, and an IgG1 constant region of SEQ ID 46.

61. An isolated binding molecule or an antigen-binding fragment thereof, which specifically binds to an epitope within the extracellular domain of HER3, consisting of an antibody VL of SEQ ID NO: 3, an antibody VH of SEQ ID NO: 2, and an IgG1 constant region of SEQ ID 46.

62. The binding molecule or antigen-binding fragment of any one of claims 32-61, wherein the antibody is a human antibody, a humanized antibody, a chimeric antibody, a recombinant antibody, a multispecific antibody, or an antigen-binding fragment thereof.

63. The antigen-binding fragment of any one of claims 32-62, which is Fv, Fab, F(ab')2, Fab', dsFv, scFv, and sc(Fv)2.

64. The binding molecule or fragment thereof of any one of claims 32-63, which is conjugated to at least one heterologous agent.

65. The binding molecule or fragment thereof of any one of claims 32-64, wherein the binding molecule is an antibody.

66. The binding molecule or fragment thereof of claim 65, wherein the antibody is a monoclonal antibody.

67. A composition comprising the binding molecule or fragment thereof of any one of claims 32-66, and a carrier.

68. A nucleic acid comprising a sequence encoding the binding molecule according to any one of claims 32-63, 65, and 66.

69. A composition comprising a nucleic acid according to claim 68.

70. A vector comprising a nucleic acid according to claim 68.

71. A host cell comprising a nucleic acid sequence according to claim 68, the composition according to claim 69, or the vector according to claim 70.

72. A method of making a binding molecule or antigen-binding fragment, comprising (a) culturing the cell of claim 71; and (b) isolating the antibody or antigen-binding fragment thereof.

73. The composition of claim 69, further comprising an anticancer agent.

74. A diagnostic reagent comprising the binding molecule or fragment of any one of claims 32-66 which is labeled.

75. A kit comprising the binding molecule according to any one of claims 32-66, or the composition of claim 67 or 73.

76. The binding molecule or antigen binding fragment of any one of claims 32-66, which does not induce antibody dependent cell mediated cytotoxicity (ADCC).

77. The binding molecule or antigen binding fragment of claim 76, which does not induce antibody dependent cell mediated cytotoxicity (ADCC) in BT-474 cells, SkBR3 cells, or a combination thereof.

78. The binding molecule or antigen binding fragment of any one of claims 32-66, which is an antagonist of HER3.

79. The binding molecule or antigen binding fragment of claim 78, which is an antagonist of HER3 in cells selected from the group consisting of BT-474 cells, SkBR3 cells, MDA-MB-175 cells, MDA-MB-361 cells, A549 cells, HARA-B cells, HMCB cells, HCC827 cells, MCF-7 cells, MKN45 cells, Kato III cells, gefitinib-resistant HCC827 cells, or a combination of two or more of the recited cells.

80. The binding molecule or antigen binding fragment of claim 78 or 79, wherein the HER3 is human HER3.

81. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce cell proliferation.

82. The binding molecule or antigen binding fragment of claim 81, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce cell proliferation in BT-474 cells, MDA-MB-175 cells, MDA-MB-361 cells, HMCB cells, or a combination of two or more of the recited cells.

83. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce HER3-mediated signal transduction.

84. The binding molecule or antigen binding fragment of claim 83, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce HER3-mediated signal transduction in cells selected from the group consisting of BT-474 cells, SkBR3 cells, MDA-

MB-175 cells, MDA-MB-361 cells, A549 cells, HARA-B cells, HMCB cells, HCC827 cells, MCF-7 cells, MKN45 cells, Kato III cells, gefitinib-resistant HCC827 cells, or a combination of two or more of the recited cells.

85. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce ligand-dependent HER3 phosphorylation.

86. The binding molecule or antigen binding fragment of claim 85, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce ligand-dependent HER3 phosphorylation in MCF-7 cells, HMCB cells, HCC827 cells, MKN45 cells, Kato III cells, or a combination of two or more of the recited cells.

87. The binding molecule or antigen binding fragment of claim 85 or 86, wherein the ligand-dependent HER3 phosphorylation is HRG-driven, EGFR-driven, cMET-driven, or FGFR2-driven, or a combination thereof..

88. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce ligand-dependent phosphorylation of Akt protein kinase.

89. The binding molecule or antigen binding fragment of claim 88, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce ligand-dependent phosphorylation of Akt protein kinase in A549 cells, HMCB cells, MKN45 cells, Kato III cells, or a combination of two or more of the recited cells.

90. The binding molecule or antigen binding fragment of claim 88 or 89, wherein the ligand-dependent Akt phosphorylation is cMET-driven, FGFR2-driven, or both.

91. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce ligand-independent AKT or HER3 phosphorylation.

92. The binding molecule or antigen binding fragment of claim 91, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce ligand-independent AKT phosphorylation, HER3 phosphorylation, or both, in BT-474 cells.

93. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce HER3 phosphorylation in cells resistant to Tyrosine Kinase Inhibitors (TKI) targeting EGFR.

94. The binding molecule or antigen binding fragment of claim 93, wherein the binding of the binding molecule or antigen binding fragment to HER3 can reduce HER3 phosphorylation in cells resistant to tyrosine kinase inhibitors (TKI) targeting EGFR in gefitinib-resistant HCC827 cells.

95. The binding molecule or antigen binding fragment of any one of claims 32-66, wherein the binding molecule or antigen binding fragment can bind to human HER3, cynomolgus monkey HER3, and mouse HER3.

96. An *in vitro* method of inhibiting the growth of a cell expressing HER3 comprising contacting the cell with the binding molecule or antigen binding fragment.

97. Use of a binding molecule or antigen binding fragment thereof of any one of claims 32-66 in the manufacture of a medicament for treating cancer in a subject.

98. The use of claim 97, wherein the cancer is selected from the group consisting of colon cancer, lung cancer, gastric cancer, breast cancer, and head and neck cancer.

99. The use of claim 98, wherein the cancer comprises cells comprising a KRAS mutation.

100. The use of claim 99, wherein the KRAS mutation comprises a mutation of codon 12 of a human KRAS gene.

101. The use of any one of claims 97-100, wherein the subject is human.

102. Use of a first agent which is the binding molecule or antigen binding fragment thereof of claims 32-66, in combination with a therapeutically effective amount of a second agent, which is an anti-cancer agent other than the first agent in the manufacture of a medicament for treating cancer in a subject .

103. The use of claim 102, wherein the combination of the first agent and the second agent is synergistically effective.

104. The use of claim 102 or 103, wherein the second agent is a EGFR inhibitor, a HER2 inhibitor, or a HER3 inhibitor.

105. The use of claim 102 or 103, wherein the second agent is a MEK inhibitor.

106. The use of any one of claims 104, wherein the second agent comprises an antibody or antigen binding fragment thereof.

107. The use of claim 104, wherein the second agent specifically binds to epidermal growth factor receptor (EGFR).

108. The use of claim 104, wherein the second agent is cetuximab, panitumumab, matuzumab or nimotuzumab.

109. The use of claim 104, wherein the second agent specifically binds to HER2.

110. The use of claim 104, wherein the second agent is trastuzumab, trastuzumab emtansine, MM-111 or pertuzumab.

111. The use of claim 104, wherein the second agent is selected from the group consisiting of gefitinib, canertinib, lapatinib, erlotinib, afatinib, and neratinib.

112. The use of claim 105, wherein the second agent is selected from the group consisiting of selumetinib, WX-554, trametinib, refametinib, E-6201 and MEK-162.

113. An *in vitro* method of inhibiting the growth of a cell resistant to tyrosine kinase inhibitors, comprising contacting the cell with a therapeutically effective amount of the binding molecule or antigen binding fragment of any one of claims 32-66.

114. Use of the binding molecule or antigen binding fragment of any one of claims 32-66 in the manufacture of a medicament for treating resistance to tyrosine kinase inhibitors in a subject.

115. The method of claim 113 or the use of claim 114, wherein the tyrosine kinase inhibitors target EGFR or HER2.

116. An *in vitro* method of inhibiting the growth of a cell resistant to threonine kinase inhibitors, comprising contacting the cell with a therapeutically effective amount of the binding molecule or antigen binding fragment of any one of claims 32-66.

117. Use of the binding molecule or antigen binding fragment of any one of claims 32-66 in the manufacture of a medicament for treating resistance to a threonine inhibitor in a subject.

118. The method of claim 116 or the use of claim 117, wherein the threonine kinase inhibitors target MEK.

119. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically bind to an HER3 polypeptide or fragment thereof with an affinity characterized by a dissociation constant (K_D) of about 0.45 nM (+/- 0.05 nM) or better as measured by a Biacore™ surface plasmon resonance assay wherein the binding molecule or antigen binding fragment thereof is bound to the Biacore™ chip.

120. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically bind to an HER3 polypeptide or fragment thereof with an affinity characterized by a dissociation constant (K_D) of about 0.1 nM or better as measured by a Biacore™ surface plasmon resonance assay wherein the HER3 polypeptide or fragment thereof is bound to the Biacore™ chip.

121. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically bind to an HER3 polypeptide or fragment thereof with an affinity characterized by a Kon of between 1×10^5 M^{-1} s^{-1} and 6×10^5 M^{-1} s^{-1} and/or a K_{off} of between 0.5×10^{-4} s^{-1} and 2.0×10^{-4} s^{-1} as measured by a Biacore™ surface plasmon resonance

assay wherein the binding molecule or antigen binding or fragment thereof is bound to the Biacore™ chip

122. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in HRG-driven MCF-7 cells with an IC_{50} of about 30 ng/mL or better as measured by ELISA.

123. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in HRG-driven MCF-7 cells with an IC_{50} of about 10 ng/mL or better as measured by ELISA.

124. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress cell growth in MDAMB-175 cells with an IC_{50} of about 0.90 μg/mL or better.

125. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress cell growth in MDAMB-175 cells with an IC_{50} of about 0.15 μg/mL or better.

126. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress cell growth in HMCB cells with an IC_{50} of about 0.2 μg/mL or better.

127. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress cell growth in HMCB cells with an IC_{50} of about 0.03 μg/mL or better.

128. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in HCC827 cells with an IC_{50} of about 20 ng/mL or better.

129. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in HCC827 cells with an IC_{50} of about 2 ng/mL or better.

130. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in HCC827 cells resistant to tyrosine kinase inhibitor with an IC_{50} of about 25 ng/mL or better.

131. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in HCC827 cells resistant to tyrosine kinase inhibitor with an IC_{50} of about 5 ng/mL or better.

132. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in MKN45 cells with an IC_{50} of about 10 ng/mL or better.

133. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress HER3 phosphorylation in MKN45 cells with an IC_{50} of about 5 ng/mL or better.

134. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress pAKT in MKN45 cells with an IC_{50} of about 10 ng/mL or better.

135. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress pAKT in MKN45 cells with an IC_{50} of about 5 ng/mL or better.

136. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress pHER in Kato III cells with an IC_{50} of about 8 ng/mL or better.

137. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress pHER in Kato III cells with an IC_{50} of about 1 ng/mL or better.

138. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress pAKT in Kato III cells with an IC_{50} of about 5 ng/mL or better.

139. The binding molecule or antigen binding fragment thereof according to any one of claims 32-66, which can specifically suppress pAKT in Kato III cells with an IC_{50} of about 1 ng/mL or better.

140. An ex-vivo method of detecting the activity level of HER3 comprising detecting the level of phosphorylated HER3 in a skin biopsy from a subject, wherein the skin is treated with HRG prior to or after biopsy.