(2004) Cancer Res. 64, 3395-3405; Schaefer *et al.* (2006) Neoplasia 8, 612-622). Accordingly, therapies that effectively interfere with HER3 phosphorylation are desirable.

[0010] In addition, HER3 has been found to be overexpressed and/or overactivated in several types of cancers such as breast cancer, ovarian cancer, prostate cancer, liver cancer, kidney and urinary bladder cancers, pancreatic cancers, brain cancers, hematopoietic neoplasms, retinoblastomas, melanomas, colorectal cancers, gastric cancers, head and neck cancers, lung cancer, etc. (see, *e.g.*, Sithanandam & Anderson (2008) Cancer Gene Ther. 15, 413-448). In general, HER3 is frequently activated in EGFR, HER2, C-Met, and FGFRII-expressing cancers.

[0011] A correlation between the expression of HER2/HER3 and the progression from a non-invasive to an invasive stage has been shown (Alimandi *et al.*, Oncogene 10, 1813-1821; DeFazio *et al.*, Cancer 87, 487-498; Naidu *et al.*, Br. J. Cancer 78, 1385-1390). Thus, HER3 can be used as a diagnostic marker for increased tumor aggressiveness and poor survival. Sustained HER3 activation of PI3K/AKT has been repetitively shown to account for tumor resistance to EGFR/HER2 inhibitors.

[0012] Although the role of HER3 in the development and progression of cancer has been explored (see, *e.g.*, Horst et al. (2005) Int. J. Cancer 115, 519-527; Xue *et al.* (2006) Cancer Res. 66, 1418-1426), HER3 remains largely unappreciated as a target for clinical intervention. Most current immunotherapies primarily focus on inhibiting the action of HER2 and, in particular, heterodimerization of HER2/HER3 complexes (see, *e.g.*, Sliwkowski *et al.* (1994) J. Biol. Chem. 269, 14661-14665). Thus, it is an object of the present invention to provide improved immunotherapeutic agents that effectively inhibit HER3-mediated cell signaling that can be used for diagnosis, prognosis prediction, and treatment of a variety of cancers.

BRIEF SUMMARY ~~OF THE INVENTION~~

[0013] In a first aspect, the present invention refers to an 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(SEQ ID NO:19)[FW2]RNNQRPS(SEQ ID NO:21)[FW3]AAWDDSPPGEA(SEQ ID NO:23)[FW4], wherein [FW1], [FW2], [FW3] and [FW4] represent VL framework regions, and wherein the VH comprises the amino acid sequence: [FW5]YYYMQ(SEQ ID

NO:31)[FW6]YIGSSGGVTNYADSVKG(SEQ ID NO:32) [FW7]VGLGDAFDI(SEQ ID NO:35)[FW8], wherein [FW5], [FW6], [FW7] and [FW8] represent VH framework regions. In another aspect, the present invention refers to a composition comprising the antibody of the present invention, and a pharmaceutically acceptable carrier. In another aspect, the present invention refers to a A nucleic acid comprising a sequence encoding the antibody or antigen-binding fragment according to the present invention. In another aspect, the present invention refers to a vector comprising a nucleic acid according to the present invention. In another aspect, the present invention refers to an *in vitro* or *ex vivo* host cell comprising a nucleic acid sequence according to the present invention. In another aspect, the present invention refers to a method of making an antibody or antigen-binding fragment thereof, comprising (a) culturing a cell comprising the nucleic acid of the present inventon; and (b) isolating the antibody or antigen-binding fragment thereof. In another aspect, the present invention refers to the use of the antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for inhibiting the proliferation of a cell expressing HER3. In another aspect, the present invention refers to the use of the antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for reducing tumor volume of a HER3-expressing tumor in a subject. In another aspect, the present invention refers to the use of the antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for treating cancer in a subject. In another aspect, the present invention refers to the use of the antibody or antigen-binding fragment thereof of the present invention in the manufacture of a medicament for treating cancer in a subject, said treating comprising administration of the antibody or antigen binding fragment to the subject with an additional therapy. In another aspect, the present invention refers to a kit comprising the antibody or antigen-binding fragment thereof of the present invention. In another aspect, the present invention refers to a 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 the present invention; (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. In another aspect, the present invention refers to 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 from the patient with an antibody or antigen-binding fragment according to the present invention; (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. In another aspect, the present invention refers to a method of monitoring HER3 protein activity level during treatment of cancer in a patient being administered the antibody or antigen-binding fragment of any one of claims 1-16, wherein the method comprises the steps of: (a) contacting a biological sample 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. The disclosure provides anti-HER3 binding molecules, *e.g.*, antibodies or antigen-binding fragments thereof, *e.g.*, monoclonal antibodies capable of suppressing HER3 activity in both ligand-dependent and independent settings. In contrast, other anti-HER3

monoclonal antibodies in the art (*e.g.*, Ab #6 (International Patent Publication WO 2008/100624) and U1-59 (International Patent Publication WO 2007077028; also referred to herein as AMG), can only suppress ligand-dependent HER3 activity. Also disclosed are affinity matured anti-HER3-binding molecules with increased potency and extended half-life, which consequently can be administered less frequently, at an increased inter-dose interval, and in smaller dose volumes. The disclosure also provides methods of treating diseases such as cancer in a human subject comprising administration of an anti-HER3 binding molecule. In some specific ~~aspects~~ examples a 2C2-derived YTE mutant human antibody is used.

[0014] The disclosure provides 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. Also provided is an 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.

[0015] The disclosure also provides 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:

$[FW_1]X1GSX2SNIGLNYVS[FW_2]RNNQRPS[FW_3]AAWDDX_3X_4X_5GEX_6[FW_4]$

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) X2 represents amino acid residues Serine (S) or Leucine (L),

(c) X3 represents amino acid residues Serine (S) or Glycine (G),

(d) X4 represents amino acid residues Leucine (L) or Proline (P),

(e) X5 represents amino acid residues Arginine (R), Isoleucine (I), Proline (P) or Serine (S), and

(f) X6 represents amino acid residues Valine (V) or Alanine (A).

[0016] Furthermore, the disclosure provides 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:

$[FW_5]YYYMQ[FW_6]X_7IGSSGGVTNYADSVKG[FW_7]VGLGDAFDI[FW_8]$

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.

WHAT IS CLAIMED IS:

1. An 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(SEQ ID NO:19)[FW2]RNNQRPS(SEQ ID NO:21)[FW3]AAWDDSPPGEA(SEQ ID NO:23)[FW4]
wherein [FW1], [FW2], [FW3] and [FW4] represent VL framework regions, and
wherein the VH comprises the amino acid sequence:
[FW5]YYYMQ(SEQ ID NO:31)[FW6]YIGSSGGVTNYADSVKG(SEQ ID NO:32)[FW7]VGLGDAFDI(SEQ ID NO:35)[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 any one of claims 1-4, 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 any one of claims 1-6, 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 any one of claims 1-9, which comprises a light chain constant region selected from the group consisting of a human kappa constant region and a human lambda constant region.

11. The antibody or antigen-binding fragment thereof of claim 10, which comprises a human lambda constant region.

12. 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 (Methionine) is substituted with Tyrosine (Y),
(b) the amino acid at position 254 (Serine) is substituted with Threonine (T), and
(c) the amino acid at position 256 (Threonine) is substituted with Glutamic acid (E).

13. The antibody or antigen-binding fragment of any one of claim 1-6, 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.

14. The antibody or antigen-binding fragment thereof of claim 1, comprising (i) an antibody light chain comprising an antibody VL comprising SEQ ID NO: 3 and a human lambda light chain constant region, and (ii) an antibody heavy chain comprising an antibody VH comprising SEQ ID NO: 2 and a human IgG1 heavy chain constant region, wherein the human IgG1 constant region comprises amino acid substitutions relative to a wild-type human IgG1 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 (Methionine) is substituted with Tyrosine (Y),

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

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

15. The antibody or antigen-binding fragment of any one of claims 1-14, wherein the antibody is a monoclonal antibody.

16. The antibody of any one of claims 1-15, wherein the antibody is a human antibody.

17. A composition comprising the antibody of any one of claims 1-16, and a pharmaceutically acceptable carrier.

18. The composition of claim 17, wherein the composition is refrigerator stable, wherein the antibody or antigen-binding fragment thereof is at a concentration of 25-100 mg/mL, and wherein the composition further comprises 25 mM histidine/histidine HCl, 205 mM sucrose, and 0.02% polysorbate 80 at pH 6.0.

19. A nucleic acid comprising a sequence encoding the antibody or antigen-binding fragment according to any one of claims 1-16.

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

21. An *in vitro* or *ex vivo* host cell comprising a nucleic acid sequence according to claim 19.

22. A method of making an antibody or antigen-binding fragment thereof, comprising (a) culturing a cell comprising the nucleic acid of claim 19; and (b) isolating the antibody or antigen-binding fragment thereof.

23. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-16 in the manufacture of a medicament for inhibiting the proliferation of a cell expressing HER3.

24. The use of claim 23, wherein said cell is a human head and neck tumor cell, a human non-small cell lung cancer cell, a human colorectal tumor cell, a human prostate tumor cell, or a human breast cancer cell.

25. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-16 in the manufacture of a medicament for reducing tumor volume of a HER3-expressing tumor in a subject.

26. The use of claim 25, wherein said tumor is a human head and neck tumor, a human non-small cell lung cancer tumor, a human colorectal tumor, a human prostate tumor, or a human breast cancer tumor.

27. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-16 in the manufacture of a medicament for treating cancer in a subject.

28. The use of claim 27, wherein the cancer is a carcinoma.

29. The use of claim 27, wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, gastric cancer, breast cancer, head and neck cancer, prostate cancer, pancreatic cancer, thyroid cancer, melanoma, esophageal cancer, ovarian cancer, kidney cancer, and bladder cancer.

30. The use of claim 29, wherein the cancer is a squamous cell carcinoma of the head and neck.

31. The use of claim 27, wherein the cancer comprises cells comprising a KRAS mutation.

32. The use of claim 27, wherein the cancer comprises cells expressing heregulin.

33. Use of the antibody or antigen-binding fragment thereof of any one of claims 1-16 in the manufacture of a medicament for treating cancer in a subject, said treating comprising administration of the antibody or antigen binding fragment to the subject with an additional therapy.

34. The use of claim 33, wherein the additional therapy is surgery.

35. The use of claim 33, wherein the additional therapy is radiation therapy.

36. The use of claim 33, wherein the additional therapy is a therapeutically effective amount of a second agent, wherein the second agent is an anti-cancer agent other than the antibody or antigen-binding fragment thereof.

37. The use of claim 36, wherein the second agent is an EGFR inhibitor, a HER2 inhibitor, a HER3 inhibitor, or a MEK inhibitor.

38. The use of claim 36, wherein the second agent is cetuximab, panitumumab, matuzumab, nimotuzumab, MM-151, or Sym004.

39. The use of claim 36, wherein the second agent is trastuzumab, trastuzumab emtansine, or pertuzumab.

40. The use of claim 36, wherein the second agent is a kinase inhibitor.

41. The use of claim 36, wherein the second agent is gefitinib, canertinib, lapatinib, erlotinib, afatinib, neratinib, selumetinib, WX-554 , trametinib, refametinib, E-6201, MEK-162, or MEHD-7945 A.

42. The use of claim 36, wherein the cancer comprises cells comprising a BRAF mutation.

43. The use of claim 42, wherein the second agent is a MEK inhibitor.

44. The use of claim 36, wherein the cancer comprises cells comprising a KRAS mutation.

45. The use of claim 44, wherein the second agent is a MEK inhibitor.

46. The use of claim 36, wherein the cancer is a head and neck cancer.

47. The use of claim 36, wherein the cancer is a squamous cell carcinoma of the head and neck.

48. The use of claim 36, wherein the cancer is a squamous cell carcinoma of the head and neck, and wherein the second agent is cetuximab.

49. The use of claim 36, wherein the cancer is a non-small cell lung cancer.

50. The use of claim 49, wherein the non-small cell lung cancer cells comprise a KRAS mutation, and wherein the second agent is a MEK inhibitor.

51. The use of claim 36, wherein the cancer is a thyroid cancer.

52. The use of claim 51, wherein the thyroid cancer comprises cells copmrising a BRAF mutation.

53. The use of claim 52, wherein the second agent is a MEK inhibitor.

54. The use of claim 36, wherein the cancer is colorectal cancer.

55. The use of claim 36, wherein the cancer is breast cancer.

56. The use of claim 36, wherein the cancer is a HER2-amplified cancer.

57. The use of claim 36, wherein the cancer is melanoma.

58. The use of claim 57, wherein the second agent is a MEK inhibitor.

59. The use of claim 36, wherein the cancer is gastric cancer.

60. The use of claim 36, wherein the cancer is prostrate cancer.

61. A kit comprising the antibody or antigen-binding fragment thereof of any one of claims 1-16.

62. A 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 any one of claims 1-16;
(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.

63. 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 from the patient with an antibody or antigen-binding fragment according to any one of claims 1-16;
(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.

64. A method of monitoring HER3 protein activity level during treatment of cancer in a patient being administered the antibody or antigen-binding fragment of any one of claims 1-16, wherein the method comprises the steps of:
(a) contacting a biological sample 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.

ABSTRACT

The present invention relates to antibodies and antigen binding fragments thereof that bind the extracellular domain of the HER3 receptor and inhibit various HER3 receptor related functions via ligand-dependent and/or ligand-independent mechanisms. Also provided are compositions with increased half-life. In addition, the invention provides compositions and methods for diagnosing and treating diseases associated with HER3 mediated signal transduction.