include cetuximab, and modified variants of cetuximab and fragments thereof that contain additional modifications.

Also provided herein is a modified anti-EGFR antibody or antigen-binding fragment thereof, comprising an amino acid replacement(s) in a variable heavy chain (VH) of an unmodif333 anti-EGFR antibody or antigen-binding fragment thereof corresponding to replacement with glutamic acid (E) at a position corresponding to position 104 (Y104E), with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, wherein:

corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof and contains only the replacement corresponding toY104E or contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acid replacements in the unmodified antibody or antigen-binding fragment thereof;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity for EGFR of greater than 1.0 in the presence of a pH that is pH 6.0 to 6.5, inclusive compared to in the presence of pH 7.4, when measured under the same conditions except for the difference in pH; and

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi).

Also provided herein is a conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, as described above linked directly or indirectly via a chemical or physical bond to a targeted agent.

Also provided herein is a conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, as described above linked directly or indirectly via a linker (L) to a targeted agent.

Also provided herein is a nucleic acid molecule(s), comprising a sequence of nucleotides encoding an anti-EGFR antibody, or antigen-binding fragment thereof, as described above; or

comprising a sequence of nucleotides encoding the heavy chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, as described above.

Also provided herein is a vector, comprising the nucleic acid molecule(s) as described above.

Also provided herein is a cell, comprising a vector as described above.

Also provided herein is a method of making an anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors as described above encoding the heavy chain and the light chain in a suitable host cell to produce the antibody; and, optionally, recovering the antibody.

Also provided herein is a pharmaceutical composition comprising:

an anti-EGFR antibody or antigen-binding fragment, or conjugate as described above; and

a pharmaceutically acceptable carrier or excipient.

Also provided herein is the use of a pharmaceutical composition as described above, for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

Also provided herein is a pharmaceutical composition as described above for use for treating a condition responsive to treatment with an anti-EGFR antibody in a subject

Also provided herein is the use of an antibody or conjugate as described above for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

Also provided herein is conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, as described above linked directly or indirectly to a therapeutic moiety.

Anti-EGFR antibodies are employed as anti-tumor therapeutics because they bind to EGFR receptors and inhibit ligand binding, thereby preventing EGFR-mediated activities that occur upon ligand binding. As a result, such antibodies can inhibit or treat tumors. Because tissues, other than tumors, such as tissues in the skin, also express EGFRs, the anti-EGFR antibodies also inhibit activities of these receptors, thereby causing undesirable side-effects. The antibodies provided herein exhibit pH-selective binding activity, such that EGFR binding activity is reduced at neutral pH (*e.g.*, pH 7.0 to 7.4) compared to antibodies that do not exhibit pH-selective binding activity and/or compared to EGFR binding activity under acidic pH conditions. By virtue of the pH-selective activity, the anti-EGFR antibodies provided produce fewer or lesser undesirable side-effects and/or exhibit improved efficacy in a treated subject by virtue of the ability to administer higher doses.

For example, provided herein are modified anti-EGFR antibodies, and antigen-binding fragments thereof, that contain an amino acid replacement(s) in a variable heavy chain of an unmodified anti-EGFR antibody, or antigen-binding fragment thereof, corresponding to replacement with glutamic acid (E) at a position corresponding to position 104 with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, as long as the modified anti-EGFR antibody specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof; the unmodified anti-EGFR antibody is cetuximab, an antigen-binding fragment thereof or a variant thereof, specifically binds to EGFR and does not already contain the amino acid replacement; and corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7.

In any of such examples of the modified anti-EGFR antibodies provided herein, the unmodified anti-EGFR antibody, or antigen-binding fragment thereof, to which the amino acid replacement is made contains a variable heavy chain set forth in SEQ ID NO: 2 or 7, or a sequence of amino acids that exhibits at least 70% sequence identity to SEQ ID NO: 2 or 7; and a variable light chain set forth in SEQ ID NO: 4, 9 or 11 or a sequence of amino acids that exhibits at least 70% sequence identity to SEQ ID NO: 4, 9 or 11. For example, the unmodified anti-EGFR antibody, or antigen-binding fragment thereof, contains a variable heavy chain that exhibits at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% sequence identity to the amino acid sequence set forth in SEQ ID NO: 2 or 7; and/or a variable light chain that exhibits at least 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,

Claims:

1. A modified anti-EGFR antibody or antigen-binding fragment thereof, comprising an amino acid replacement(s) in a variable heavy chain (VH) of an unmodified anti-EGFR antibody or antigen-binding fragment thereof corresponding to replacement with glutamic acid (E) at a position corresponding to position 104 (Y104E), with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, wherein:

corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof and contains, in addition to Y104E, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements in the unmodified antibody or antigen-binding fragment thereof;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity for EGFR of greater than 1.0 in the presence of a pH that is pH 6.0 to 6.5, inclusive compared to in the presence of pH 7.4, when measured under the same conditions except for the difference in pH; and

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi) .

2. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1, wherein the unmodified anti-EGFR antibody comprises:

a variable heavy chain set forth in SEQ ID NO:2 and a variable light chain set forth in SEQ ID NO: 4; or

a variable heavy chain set forth in SEQ ID NO: 7 and a variable light chain set forth in SEQ ID NO: 9 or 11.

3. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, wherein the unmodified antibody or antigen-binding fragment thereof, is humanized.

4. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 3, wherein the humanized unmodified anti-EGFR antibody or antigen-binding fragment thereof comprises:

a variable heavy chain set forth in SEQ ID NO: 14 and variable light chain set forth in SEQ ID NO: 15; or

a variable heavy chain set forth in SEQ ID NO: 16 and a variable light chain set forth in SEQ ID NO: 17.

5. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-4 that is a full-length antibody.

6. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-5 that is an antigen-binding fragment selected from among Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

7. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-6, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74 or 75; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

8. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-7, that is a full-length IgG antibody, wherein the modified anti-EGFR antibody comprises:

a) a heavy chain comprising the sequence of amino acids set forth in SEQ ID NO:72, ; and

b) a light chain comprising the sequence of amino acids set forth in any of SEQ ID NOS: 3, 8, 10 or 13.

9. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 7 or claim 8, wherein:

the modified antibody comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the variable heavy chain set forth in SEQ ID NO: 74 or 75 and/or in the light chain set forth in SEQ ID NO: 4, 9 or 11, other than replacement with E at a position corresponding to position 104 in the heavy chain; or

the modified antibody comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the heavy chain set forth in SEQ ID NO:72 and/or in the light chain set forth in any of SEQ ID NOS:3, 8, 10 or 13, other than replacement with E at a position corresponding to position 104 in the heavy chain.

10. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-9, comprising an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among T023K, T023H, T023R, T023A, T023C, T023E, T023G, T023I, T023M, T023N, T023P, T023S, T023V, T023W, T023L, V024R, V024A, V024F, V024G, V024I, V024M, V024P,

V024S, V024T, V024L, V024E, S025H, S025R, S025A, S025C, S025D, S025E, S025F, S025G, S025I, S025M, S025P, S025Q, S025T, S025V, S025L, G026H, G026R, G026D, G026F, G026M, G026N, G026P, G026Q, G026S, G026Y, G026L, F027H, F027R, F027A, F027D, F027E, F027G, F027M, F027P, F027Q, F027S, F027T, F027V, F027W, F027Y, F027L, S028K, S028H, S028R, S028A, S028D, S028I, S028M, S028P, S028Q, S028V, S028W, S028L, S028C, L029K, L029H, L029A, L029D, L029G, L029I, L029M, L029N, L029S, L029V, T030H, T030R, T030D, T030G, T030I, T030M, T030N, T030P, T030S, T030V, T030W, T030Y, N031K, N031H, N031D, N031E, N031G, N031I, N031T, N031V, N031L, Y032H, Y032R, Y032C, Y032M, Y032N, Y032T, Y032V, Y032L, G033E, G033M, G033S, G033T, G033Y, V034A, V034C, V034I, V034M, V034P, V034L, H035I, H035Q, W036K, W036A, W036I, W036V, W036Y, V050K, V050H, V050A, V050D, V050E, V050G, V050I, V050N, V050Q, V050T, V050L, I051K, I051H, I051A, I051C, I051E, I051G, I051N, I051Q, I051S, I051V, I051Y, I051L, W052I, W052N, W052Y, S053H, S053R, S053A, S053C, S053G, S053I, S053M, S053P, S053Q, S053L, S053T, S053V, S053Y, G054H, G054R, G054A, G054C, G054D, G054P, G054S, G055H, G055R, G055M, G055S, G055Y, N056K, N056A, N056P, N056S, N056V, N056G, T057H, T057R, T057L, T057A, T057C, T057D, T057F, T057M, T057N, T057Q, T057W, T057Y, D058L, D058G, D058M, D058N, D058Q, Y059H, Y059R, Y059A, Y059C, Y059D, Y059E, Y059G, Y059I, Y059P, Y059Q, Y059S, Y059T, Y059V, Y059W, N060K, N060A, N060C, N060D, N060F, N060G, N060P, N060Q, N060S, N060T, N060Y, T061N, T061Q, P062G, F063H, F063R, F063L, F063A, F063C, F063D, F063G, F063M, F063N, F063Q, F063S, F063V, F063P, T064R, T064L, T064C, T064F, T064G, T064N, T064Q, T064V, S065H, S065R, S065L, S065C, S065E, S065F, S065G, S065I, S065M, S065N, S065P, S065Q, S065T, S065W, S065Y, R066L, R066A, R066C, R066E, R066F, R066N, R066P, R066Q, R066S, R066T, R066V, R066G, L067A, L067C, L067D, L067E, L067I, L067M, L067Q, L067S, L067T, L067V, L067Y, L067G, S068K, S068H, S068R, S068L, S068C, S068D, S068E, S068F, S068G, S068I, S068N, S068Q, S068T, S068V,I069A, I069C, I069G, 69Y, N070H, N070R, N070L, N070D, N070E, N070F, N070G, N070I, N070P, N070Q, N070S, N070T, N070V, N070Y, K071H, K071R, K071L, K071A, K071C, K071F, K071G, K071Q, K071S, K071T, K071V, K071W, K071Y, D072K, D072H, D072R, D072L, D072A, D072G, D072I, D072M, D072N, D072Q, D072S, D072V, D072W, D072Y, D072P, N073H, N073R, N073L, N073A, N073C, N073G, N073I, N073M, N073P, N073Q, N073S, N073T, N073V, N073W, N073Y, S074K, S074H, S074R, S074L, S074A, S074C, S074D, S074E, S074G, S074I, S074M, S074P, S074T, S074V, S074Y, K075H, K075R, K075L, K075A, K075C, 75E, K075F, K075M, K075Q, K075T, K075V,K075W, K075Y, K075G, K075P, S076H, S076R, S076L, S076A, S076C, S076D, S076E, S076F, S076M, S076P, S076Q, S076T, S076Y, S076I, S076V, Q077H, Q077R, Q077L, Q077A, Q077E, Q077G, Q077I, Q077M, Q077N, Q077S, Q077V, Q077W, Q077Y, Y093H, Y093V, Y093W, Y094R, Y094L, R097H, R097W, A098P, L099N, L099W, T100H, T100L, T100A, T100D, T100I, T100N, T100P, T100Q, T100S, T100V, T100Y, Y101H, Y101E, Y101F, Y101M, Y101W, Y102R,Y102C, Y102D, Y102I, Y102N, Y102W, D103R, D103L, D103A, D103C, D103I, D103P, D103Q, D103Y, E105H, E105T, F106L, F106V, F106W, F106Y, A107K, A107H, A107R, A107L, A107C, A107D, A107E, A107G, A107N, A107S, A107T, A107Y, Y108K, Y108H, Y108R, Y108L, Y108C, Y108F, Y108I, Y108N, Y108S, Y108T, Y108V, Y108W, W109I, W109M, W109Y, G110R, G110A, G110M, G110P, G110T, Q111K, Q111H, Q111R, Q111L, Q111D, Q111E, Q111G, Q111M, Q111P, Q111S, Q111T, Q111W, Q111Y, Q111V, Q111I, G112A, G112N, G112P, G112S, G112T and G112, with reference to positions set forth in SEQ ID NO: 2 or 7.

11. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-10, comprising an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among V24I, V24L, V24E, S25C, S25G, S25I, S25M, S25V, S25Q, S25T, S25L, S25H, S25R, S25A, S25D, F27R, S28C, L29H, T30F, N31H, N31I, N31T, N31V, Y32T, V50L, S53G, G54D, G54S, G54R, G54C, G54P, D58M, Y59E, F63R, F63C, F63G, F63M, F63V, F63P, F63S, T64N, T64V, L67G, S68F, S68Q, D72K, D72L, D72P, D72M, D72W, N73Q, S74H, S74R, S74D, S74G, S74Y, K75H, K75G, K75W, K75P, S76I, S76V, Q77R, Q77E, R97H, T100I, T100P, Y101W, Y105V, A107N, Q111I, Q111P and Q111V with reference to SEQ ID NO:2 or 7, wherein corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7.

12. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-11, comprising an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, and Q111P.

13. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 10-12, wherein the amino acid replacements are HC-Y104E/ HC-Q111P; HC-S25C/ HC-Y104E; HC-Y104E/LC-I29S; HC-Y104E/HC-Q111P/LC-I29S; HC-S53G/HC-Y104E; HC-S53G/HC-Y104E/HC-Q111P; HC-S25V/HC-Y104E; HC-S25V/HC-Y104E/HC-Q111P; HC-S25V/HC-S53G/HC-Y104E; HC-S25V/HC-S53G/HC-Y104E/HC-Q111P; HC-T30F/HC-Y104E; HC-T30F/HC-Y104E/HC-Q111P; HC-T30F/HC-S53G/HC-Y104E; HC-T30F/HC-S53G/HC-Y104E/HC-Q111P; HC-D72L/HC-Y104E; HC-D72L/HC-Y104E/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104E; or HC-S53G/HC-D72L/HC-Y104E/HC-Q111P.

14. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-13, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NOS: 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, or 123; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

15. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-14, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74, 77 or 104; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

16. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15 that is a full-length antibody, wherein the modified anti-EGFR antibody or antigen binding fragment thereof, comprises:

a heavy chain constant region set forth in any of SEQ ID NOS: 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, 115, 118, or 121; and

a light chain constant region set forth in any of SEQ ID NOS: 3, 8, 10 or 13.

17. The modified anti-EGFR antibody of claim 10, wherein the unmodified antibody is cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11.

18. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-17, comprising an amino acid replacement(s) in a variable light chain of the unmodified antibody corresponding to amino acid replacement D001W, I002C, I002V, I002W, L003D, L003F, L003G, L003S, L003T, L003V, L003W, L003Y, L003R, L004C, L004E, L004F, L004I, L004P, L004S, L004T, L004V, L004W, L004K, L004H, L004R, T005A, T005C, T005D, T005E, T005F, T005G, T005N, T005S, T005W, T005L, T005K, T005H, T005R, T005P, R024A, R024C, R024F, R024L, R024M, R024S, R024W, R024Y, R024G, A025C, A025G, A025L, A025V, S026A, S026C, S026D, S026I, S026M, S026N, S026V, S026W, S026L, S026G, S026H, S026R, Q027A, Q027D, Q027E, Q027F, Q027I, Q027M, Q027N, Q027P, Q027T, S028A, S028D, S028N, S028Q, S028L, S028K, S028H, I029A, I029E, I029F, I029S, I029T, I029R, G030A, G030E, G030F, G030I, G030M, G030P, G030Q, G030S, G030V, G030Y, G030L, G030K, G030H, G030R, T031A, T031F, T031G, T031M, T031S, T031V, T031W, T031L, T031K, T031H, N032G, I033F, I033G, I033M, I033T, I033V, I033H, I048M, I048S, I048L, I048K, K049A, K049E, K049F, K049G, K049N, K049Q, K049S, K049T, K049V, K049Y, K049L, K049H, K049R, A051T, A051L, S052A, S052C, S052D, S052E, S052G, S052I, S052M, S052Q, S052V, S052W, S052R, S052K, E053G, S054M, I055A, I055F, S056G, S056L, S056A, S056C, S056D, S056E, S056F, S056N, S056P, S056Q, S056V, S056W, S056H, S056R, S056K, Y086F, Y086M, Y086H, Y087L, Y087C, Y087D, Y087F, Y087G, Y087I, Y087N, Y087P, Y087S, Y087T, Y087V, Y087W, Y087K, Y087H, Y087R, Q089E, N091L, N091A, N091C, N091I, N091M, N091S, N091T, N091V, N091H, N091R, N092C, N092D, N092L, N092M, N092S, N092T, N092V, N092W, N092Y, N092H, N092K, N092R, N093T, T096L, T096C, T096M, T096V, T097L, T097A, T097D, T097G, T097Q, T097S, T097V, T097K, T097R, F098A, F098M, F098S, F098V, F098Y, G099L, G099D, G099E, G099F, G099I, G099M, G099N, G099S, G099T, G099V, G099K, G099H, Q100C, Q100D, Q100E, Q100F, Q100I, Q100M, Q100N, Q100P, Q100T, Q100V, Q100W, Q100Y, Q100K, Q100H or Q100R with reference to amino acid positions set forth in SEQ ID NO:4, wherein corresponding amino acid position are identified by alignment of the variable light chain of the antibody with the variable light chain set forth in SEQ ID NO:4.

19. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-18, comprising an amino acid replacement(s) in a variable light chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among L4C, L4F, L4V, T5P, R24G, I29S, S56H and N91V with reference to SEQ ID NO:4, wherein corresponding amino acid positions are identified by alignment of the variable light chain of the antibody with the variable light chain set forth in SEQ ID NO: 4.

20. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-19, comprising an amino acid replacement in a variable light chain of the unmodified antibody corresponding to amino acid replacement I29S with reference to SEQ ID NO:4.

21. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 18-20, wherein the amino acid replacements are HC-Y104E/LC-I29S or HC-Y104E/HC-Q111P/LC-I29S.

22. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-21, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, or 123; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:125, 126 or 127.

23. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 18-22, that is a full length IgG antibody, wherein the modified antibody comprises:

a heavy chain comprising the sequence of amino acids set forth in any of SEQ ID NOS:72, 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, 115, 118, or 121; and

a light chain comprising the sequence of amino acids set forth in SEQ ID NO: 124.

24. The modified anti-EGFR antibody of claim 13, wherein the unmodified antibody is cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11.

25. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-24 wherein the modified antibody or antigen-binding fragment thereof is humanized and comprises the amino acid replacement with glutamic acid (E) at a position corresponding to position 104.

26. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 25, wherein:

the variable heavy chain exhibits less than 85% sequence identity to the variable heavy chain set forth in SEQ ID NO:2 or 7 and greater than 65% sequence identity to the variable heavy chain set forth in SEQ ID NO:2 or 7; and

the variable light chain exhibits less than 85% sequence identity to the variable light chain set forth in SEQ ID NO:4 and greater than 65% sequence identity to the variable light chain set forth in SEQ ID NO:4.

27. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 25 or claim 26, comprising a sequence of amino acids containing the variable heavy chain set forth in SEQ ID NO: 61 or 63 , and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 .

28. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 27, that comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements in the variable heavy chain set forth in SEQ ID NO: 61 or 63 and/or in the variable light chain set forth in SEQ ID NO: 183, 184 or 186, other than replacement with E at a position corresponding to position 104 in the heavy chain.

29. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-27, that is a full-length IgG antibody, wherein the antibody comprises a sequence of amino acids containing the heavy chain set forth in SEQ ID NO: 59 , and the light chain set forth in SEQ ID NO: 181 .

30. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 29, that comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the

heavy chain set forth in SEQ ID NO: 59 and/or in the light chain set forth ins SEQ ID NO: 181, other than replacement with E at a position corresponding to position 104 in the heavy chain.

31. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-30, comprising:

an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among T023K, T023H, T023R, T023A, T023C, T023E, T023G, T023I, T023M, T023N, T023P, T023S, T023V, T023W, T023L, V024R, V024A, V024F, V024G, V024I, V024M, V024P, V024S, V024T, V024L, V024E, S025H, S025R, S025A, S025C, S025D, S025E, S025F, S025G, S025I, S025M, S025P, S025Q, S025T, S025V, S025L, G026H, G026R, G026D, G026F, G026M, G026N, G026P, G026Q, G026S, G026Y, G026L, F027H, F027R, F027A, F027D, F027E, F027G, F027M, F027P, F027Q, F027S, F027T, F027V, F027W, F027Y, F027L, S028K, S028H, S028R, S028A, S028D, S028I, S028M, S028P, S028Q, S028V, S028W, S028L, S028C, L029K, L029H, L029A, L029D, L029G, L029I, L029M, L029N, L029S, L029V, T030H, T030R, T030D, T030G, T030I, T030M, T030N, T030P, T030S, T030V, T030W, T030Y, N031K, N031H, N031D, N031E, N031G, N031I, N031T, N031V, N031L, Y032H, Y032R, Y032C, Y032M, Y032N, Y032T, Y032V, Y032L, G033E, G033M, G033S, G033T, G033Y, V034A, V034C, V034I, V034M, V034P, V034L, H035I, H035Q, W036K, W036A, W036I, W036V, W036Y, V050K, V050H, V050A, V050D, V050E, V050G, V050I, V050N, V050Q, V050T, V050L, I051K, I051H, I051A, I051C, I051E, I051G, I051N, I051Q, I051S, I051V, I051Y, I051L, W052I, W052N, W052Y, S053H, S053R, S053A, S053C, S053G, S053I, S053M, S053P, S053Q, S053L, S053T, S053V, S053Y, G054H, G054R, G054A, G054C, G054D, G054P, G054S, G055H, G055R, G055M, G055S, G055Y, N056K, N056A, N056P, N056S, N056V, N056G, T057H, T057R, T057L, T057A, T057C, T057D, T057F, T057M, T057N, T057Q, T057W, T057Y, D058L, D058G, D058M, D058N, D058Q, Y059H, Y059R, Y059A, Y059C, Y059D, Y059E, Y059G, Y059I, Y059P, Y059Q, Y059S, Y059T, Y059V, Y059W, N060K, N060A, N060C, N060D, N060F, N060G, N060P, N060Q, N060S, N060T, N060Y, T061N, T061Q, P062G, F063H, F063R, F063L, F063A, F063C, F063D, F063G, F063M, F063N, F063Q, F063S, F063V, F063P, T064R, T064L, T064C, T064F, T064G, T064N, T064Q, T064V, S065H, S065R, S065L, S065C, S065E, S065F, S065G, S065I, S065M, S065N, S065P, S065Q, S065T, S065W, S065Y, R066L, R066A, R066C, R066E, R066F, R066N, R066P, R066Q, R066S, R066T, R066V, R066G, L067A, L067C, L067D, L067E, L067I, L067M, L067Q, L067S, L067T, L067V, L067Y, L067G, S068K, S068H, S068R, S068L, S068C, S068D, S068E, S068F, S068G, S068I, S068N, S068Q, S068T, S068V, I069A, I069C, I069G, 69Y, N070H, N070R, N070L, N070D, N070E, N070F, N070G, N070I, N070P, N070Q, N070S, N070T, N070V, N070Y, K071H, K071R, K071L, K071A, K071C, K071F, K071G, K071Q, K071S, K071T, K071V, K071W, K071Y, D072K, D072H, D072R, D072L, D072A, D072G, D072I, D072M, D072N, D072Q, D072S, D072V, D072W, D072Y, D072P, N073H, N073R, N073L, N073A, N073C, N073G, N073I, N073M, N073P, N073Q, N073S, N073T, N073V, N073W, N073Y, S074K, S074H, S074R, S074L, S074A, S074C, S074D, S074E, S074G, S074I, S074M, S074P, S074T, S074V, S074Y, K075H, K075R, K075L, K075A, K075C, 75E, K075F, K075M, K075Q, K075T, K075V, K075W, K075Y, K075G, K075P, S076H, S076R, S076L, S076A, S076C, S076D, S076E, S076F, S076M, S076P, S076Q, S076T, S076Y, S076I, S076V, Q077H, Q077R, Q077L, Q077A, Q077E, Q077G, Q077I, Q077M, Q077N, Q077S, Q077V, Q077W, Q077Y, Y093H, Y093V, Y093W, Y094R, Y094L, R097H, R097W, A098P, L099N, L099W, T100H, T100L, T100A, T100D, T100I, T100N, T100P, T100Q, T100S, T100V, T100Y, Y101H, Y101E, Y101F, Y101M, Y101W,

Y102R, Y102C, Y102D, Y102I, Y102N, Y102W, D103R, D103L, D103A, D103C, D103I, D103P, D103Q, D103Y, E105H, E105T, F106L, F106V, F106W, F106Y, A107K, A107H, A107R, A107L, A107C, A107D, A107E, A107G, A107N, A107S, A107T, A107Y, Y108K, Y108H, Y108R, Y108L, Y108C, Y108F, Y108I, Y108N, Y108S, Y108T, Y108V, Y108W, W109I, W109M, W109Y, G110R, G110A, G110M, G110P, G110T, Q111K, Q111H, Q111R, Q111L, Q111D, Q111E, Q111G, Q111M, Q111P, Q111S, Q111T, Q111W, Q111Y, Q111V, Q111I, G112A, G112N, G112P, G112S, G112T and G112, with reference to positions set forth in SEQ ID NO: 2 or 7, wherein corresponding amino acid position are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7; and/or

an amino acid replacement(s) in a variable light chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among D001W, I002C, I002V, I002W, L003D, L003F, L003G, L003S, L003T, L003V, L003W, L003Y, L003R, L004C, L004E, L004F, L004I, L004P, L004S, L004T, L004V, L004W, L004K, L004H, L004R, T005A, T005C, T005D, T005E, T005F, T005G, T005N, T005S, T005W, T005L, T005K, T005H, T005R, T005P, R024A, R024C, R024F, R024L, R024M, R024S, R024W, R024Y, R024G, A025C, A025G, A025L, A025V, S026A, S026C, S026D, S026I, S026M, S026N, S026V, S026W, S026L, S026G, S026H, S026R, Q027A, Q027D, Q027E, Q027F, Q027I, Q027M, Q027N, Q027P, Q027T, S028A, S028D, S028N, S028Q, S028L, S028K, S028H, I029A, I029E, I029F, I029S, I029T, I029R, G030A, G030E, G030F, G030I, G030M, G030P, G030Q, G030S, G030V, G030Y, G030L, G030K, G030H, G030R, T031A, T031F, T031G, T031M, T031S, T031V, T031W, T031L, T031K, T031H, N032G, I033F, I033G, I033M, I033T, I033V, I033H, I048M, I048S, I048L, I048K, K049A, K049E, K049F, K049G, K049N, K049Q, K049S, K049T, K049V, K049Y, K049L, K049H, K049R, A051T, A051L, S052A, S052C, S052D, S052E, S052G, S052I, S052M, S052Q, S052V, S052W, S052R, S052K, E053G, S054M, I055A, I055F, S056G, S056L, S056A, S056C, S056D, S056E, S056F, S056N, S056P, S056Q, S056V, S056W, S056H, S056R, S056K, Y086F, Y086M, Y086H, Y087L, Y087C, Y087D, Y087F, Y087G, Y087I, Y087N, Y087P, Y087S, Y087T, Y087V, Y087W, Y087K, Y087H, Y087R, Q089E, N091L, N091A, N091C, N091I, N091M, N091S, N091T, N091V, N091H, N091R, N092C, N092D, N092L, N092M, N092S, N092T, N092V, N092W, N092Y, N092H, N092K, N092R, N093T, T096L, T096C, T096M, T096V, T097L, T097A, T097D, T097G, T097Q, T097S, T097V, T097K, T097R, F098A, F098M, F098S, F098V, F098Y, G099L, G099D, G099E, G099F, G099I, G099M, G099N, G099S, G099T, G099V, G099K, G099H, Q100C, Q100D, Q100E, Q100F, Q100I, Q100M, Q100N, Q100P, Q100T, Q100V, Q100W, Q100Y, Q100K, Q100H and Q100R with reference to amino acid positions set forth in SEQ ID NO:4, wherein corresponding amino acid position are identified by alignment of the variable light chain of the antibody with the variable light chain set forth in SEQ ID NO:4.

32. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-31, further comprising an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among V24I, V24L, V24E, S25C, S25G, S25I, S25M, S25V, S25Q, S25T, S25L, S25H, S25R, S25A, S25D, F27R, S28C, L29H, T30F, N31H, N31I, N31T, N31V, Y32T, V50L, S53G, G54D, G54S, G54R, G54C, G54P, D58M, Y59E, F63R, F63C, F63G, F63M, F63V, F63P, F63S, T64N, T64V, L67G, S68F, S68Q, D72K, D72L, D72P, D72M, D72W, N73Q, S74H, S74R, S74D, S74G, S74Y, K75H, K75G, K75W, K75P, S76I, S76V, Q77R, Q77E, R97H, T100I, T100P, Y101W, Y105V, A107N, Q111I, Q111P and Q111V with reference to SEQ ID NO:2 or 7, wherein corresponding amino acid positions are identified by

alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7.

33. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-32, comprising an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, and Q111P.

34. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-33, wherein the amino acid replacements are HC-Y104E/ HC-Q111P; HC-S25C/ HC-Y104E; HC-Y104E/LC-I29S; HC-Y104E/HC-Q111P/LC-I29S; HC-S53G/HC-Y104E; HC-S53G/HC-Y104E/HC-Q111P; HC-S25V/HC-Y104E; HC-S25V/HC-Y104E/HC-Q111P; HC-S25V/HC-S53G/HC-Y104E; HC-S25V/HC-S53G/HC-Y104E/HC-Q111P; HC-T30F/HC-Y104E; HC-T30F/HC-Y104E/HC-Q111P; HC-T30F/HC-S53G/HC-Y104E; HC-T30F/HC-S53G/HC-Y104E/HC-Q111P; HC-D72L/HC-Y104E; HC-D72L/HC-Y104E/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104E; or HC-S53G/HC-D72L/HC-Y104E/HC-Q111P.

35. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-34, wherein the amino acid replacements are HC-Y104E/ HC-Q111P or HC-T30F/HC-Y104E/HC-Q111P.

36. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-35, comprising a sequence of amino acids selected from among:

a) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 155, 156 or 158 ;

b) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 162, 163 or 165 ;

c) the variable heavy chain set forth in SEQ ID NO: 137 or 139 , and the variable light chain set forth in SEQ ID NO: 155, 156 or 158 ;

d) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 169, 170 or 172 ;

e) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 176, 177 or 179 ;

f) the variable heavy chain set forth in SEQ ID NO: 131 or 133 and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 ;

g) the variable heavy chain set forth in SEQ ID NO: 137 or 139 , and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 ;

h) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 190, 191 or 193 ;

i) the variable heavy chain set forth in SEQ ID NO: 143 or 145 , and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 ;

j) the variable heavy chain set forth in SEQ ID NO: 149 or 151 , and the variable light chain set forth in SEQ ID NO: 197, 198 or 200 ;

k) the variable heavy chain set forth in SEQ ID NO: 143 or 145 , and the variable light chain set forth in SEQ ID NO: 197, 198 or 200 ;

l) the variable heavy chain set forth in SEQ ID NO: 149 or 151 , and the variable light chain set forth in SEQ ID NO: 204, 205 or 207 ;

m) the variable heavy chain set forth in SEQ ID NO: 143 or 145 , and the variable light chain set forth in SEQ ID NO: 204, 205 or 207 or a sequence of amino acids that exhibits at least 85%, 90% or 95% sequence identity to SEQ ID NO: 204, 205 or 207;

n) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 253, 254 or 256 ;

o) the variable heavy chain set forth in SEQ ID NO: 217 or 219 , and the variable light chain set forth in SEQ ID NO: 253, 254 or 256 ;

p) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 260, 261 or 263 ;

q) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 260, 261 or 263 ;

r) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 267, 268 or 270 ;

s) the variable heavy chain set forth in SEQ ID NO: 241 or 243 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

t) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

u) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

v) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

w) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

x) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

y) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

z) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

aa) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

bb) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

cc) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

dd) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 295, 296 or 298 ;

ee) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 302, 303 or 305 ;

ff) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 302, 303 or 305 ;

gg) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ; and

hh) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 .

37. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 7, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO: 74; and

b) a variable light (VL) chain containing the sequence of amino acids set forth in SEQ ID NO: 9

38. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 25-37, that is a full-length antibody, wherein the antibody comprises a sequence of amino acids selected from among:

a) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 153 ;

b) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 160 ;

c) the heavy chain set forth in SEQ ID NO: 135 , and the light chain set forth in SEQ ID NO: 153 ;

d) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 167 ;

e) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 174 ;

f) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 181 ;

g) the heavy chain set forth in SEQ ID NO: 135 , and the light chain set forth in SEQ ID NO: 181 ;

h) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 188 ;

i) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 181 ;

j) the heavy chain set forth in SEQ ID NO: 147 , and the light chain set forth in SEQ ID NO: 195 ;

k) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 195 ;

l) the heavy chain set forth in SEQ ID NO: 147 , and the light chain set forth in SEQ ID NO: 202 ;

m) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 202 ;

n) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 251 ;

o) the heavy chain set forth in SEQ ID NO: 215 , and the light chain set forth in SEQ ID NO: 251 ;

p) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 258 ;

q) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 258 ;

r) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 265 ;

s) the heavy chain set forth in SEQ ID NO: 239 , and the light chain set forth in SEQ ID NO: 272 ;

t) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 272 ;

u) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 272 ;

v) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 279 ;

w) the heavy chain set forth in SEQ ID NO: 245 , and the light chain set forth in SEQ ID NO: 279 ;

x) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 279 ;

y) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 279 ;

z) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 286 ;

aa) the heavy chain set forth in SEQ ID NO: 245 , and the light chain set forth in SEQ ID NO: 286 ;

bb) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 286 ;

cc) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 286 ;

dd) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 293 ;

ee) the heavy chain set forth in SEQ ID NO: 245 , and the light chain set forth in SEQ ID NO: 300 ;

ff) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 300 ;

gg) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 279 ; and

hh) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 286 .

9. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 8, that is a full-length IgG antibody, wherein the modified anti-EGFR antibody comprises: a) a heavy chain comprising the sequence of amino acids set forth in SEQ ID NO:72; and

b) a light chain comprising the sequence of amino acids set forth in SEQ ID NO:8.

40. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-39 that is an antigen-binding fragment selected from among Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

41. The anti-EGFR antibody, or antigen-binding fragment, of claim 40 that is a Fab or scFv.

42. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 27, comprising a sequence of amino acids containing the variable heavy chain set forth in SEQ ID NO: 61 and the variable light chain set forth in SEQ ID NO: 183.

43. The modified anti-EGFR antibody of claim 1, wherein the ratio of binding activity is at least 2.0.

44. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-43, comprising a variable heavy chain comprising 1 to 10 or 1 to 5 amino acid replacements compared to the variable heavy chain set forth in SEQ ID NO: 2 or 7.

45. The anti-EGFR antibody, or antigen-binding fragment, of any of claims 1-44 that is isolated or purified.

46. A conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-45 linked directly or indirectly to a targeted agent.

47. The conjugate of claim 46, comprising the following components:

(Ab), $(L)_q$, and $(\text{targeted agent})_m$, wherein:

Ab is the modified anti-EGFR antibody or antigen-binding fragment thereof that binds to EGFR;

L is a linker for linking the Ab to the targeted agent;

m is at least 1;

q is 0 or more as long as the resulting conjugate binds to the EGFR;

the resulting conjugate binds to the EGFR.

48. The conjugate of claim 47, wherein m is 1 to 8 and q is 0 to 8.

49. The conjugate of claim 47 or claim 48, wherein the conjugate has the following formula: $Ab - [(L)_q - (\text{targeted agent})_m]$.

50. The conjugate of any of claims 46-49, wherein the targeted agent is a protein, peptide, nucleic acid or small molecule.

51. The conjugate of any of claims 46-50, wherein the targeted agent is a therapeutic moiety.

52. The conjugate of claim 51, wherein the therapeutic moiety is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

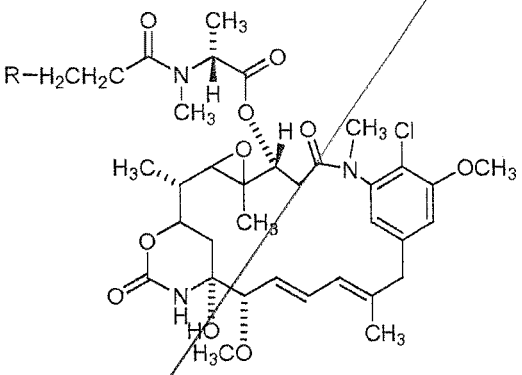
53. The conjugate of claim 52, wherein the therapeutic moiety is selected from among taxol; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; teniposide; vincristine; vinblastine; colchicine; doxorubicin; daunorubicin; dihydroxy anthracin dione; maytansine or an analog or derivative thereof; an auristatin or a functional peptide analog or derivative thereof; dolastatin 10 or 15 or an analogue thereof; irinotecan or an analog thereof; mitoxantrone; mithramycin; actinomycin D; 1-dehydrotestosterone; a glucocorticoid; procaine; tetracaine; lidocaine; propranolol; puromycin; calicheamicin or an analog or derivative thereof; an antimetabolite; an alkylating agent; a platinum derivative; duocarmycin A, duocarmycin SA, rachelmycin (CC-1065), or an analog or derivative thereof; an antibiotic; pyrrolo[2,1-c][1, 4]-benzodiazepine (PBD); a toxin; ribonuclease (RNase); DNase I, Staphylococcal enterotoxin A; and pokeweed antiviral protein.

54. The conjugate of claim 52 or claim 53, wherein the therapeutic moiety is a maytansine derivative that is a maytansinoid selected from among ansamitocin and mertansine (DM1).

55. The conjugate of claim 54, wherein:

the maytansinoid is DM1;

DM1 has the structure;



; and

R is SH.

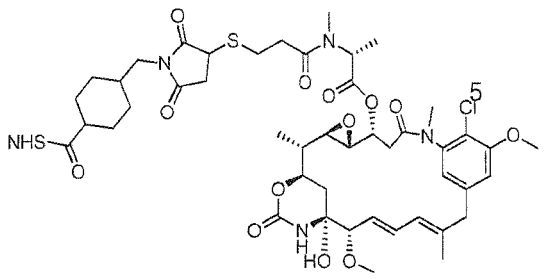
56. The conjugate of claim 54 or claim 55, wherein the linker L is selected from among N-succinimidyl-4(2-pyridylthio)propanoate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate(SMCC) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP).

57. The conjugate of claim 56, wherein the linker L is succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC).

58. The conjugate of claim 57, wherein:

m and q are the same, whereby the conjugate has the formula: Ab – [(L) – (targeted agent)]$_p$; and

(L) – (targeted agent) has the following structure:



59. The conjugate of claim 58, wherein:

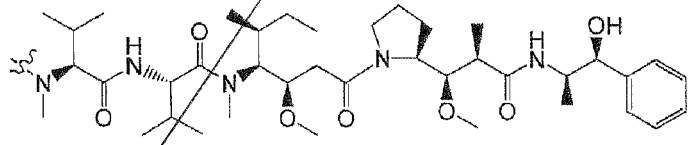
p is 2 to 6; and

the conjugate contains 2 to 6 DM1 molecules per antibody.

60. The conjugate of claim 52 or claim 53 wherein the therapeutic moiety is an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF).

61. The conjugate of claim 60, wherein the therapeutic moiety is MMAE; and

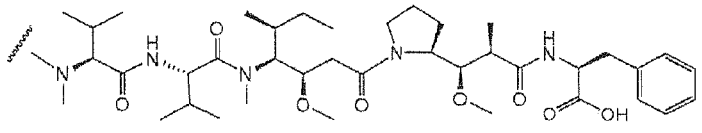
MMAE has the structure



or a pharmaceutically acceptable salt form thereof.

62. The conjugate of claim 60, wherein the therapeutc moiety is MMAF; and

MMAF has the structure



or a pharmaceutically acceptable salt form thereof.

63. The conjugate of claim 61 or claim 62, wherein:

the linker has the formula A_a- Y_y- Z_z - X_x or a pharmaceutically acceptable salt form thereof;

A is a bridge unit capable of reacting with a sulfhydryl group of the antibody;

a is 0 or 1;

each of Y and Z is independently an amino acid unit;

each of y and z is independently an integer ranging from 0 to 12;

X is a Spacer unit; and

x is 0, 1 or 2.

64. The conjugate of claim 63, wherein the bridge unit comprises a maleimide group or a bis-thiol alkylating reagent.

65. The conjugate of claim 63 or claim 64, wherein the bridge unit is selected from among a 4-(3-tosyl-2-(tosylmethyl)propanoyl)benzamide, maleimidocaproyl and maleimidopropanoyl (MP).

66. The conjugate of claim 64 or claim 65, wherein the bridge unit further comprises a polyethylene glycol reactive group.

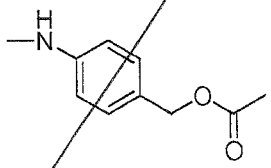
67. The conjugate of any of claims 63-66, wherein Y is alanine, valine, leucine, isoleucine, methionine, phenylalanine, tryptophan or proline.

68. The conjugate of any of claims 63-67, wherein Z is lysine, lysine protected with acetyl or formyl, arginine, arginine protected with tosyl or nitro groups, histidine, ornithine, ornithine protected with acetyl or formyl or citrulline.

69. The conjugate of any of claims 63-68, wherein Y-Z is phenylalanine-lysine, valine-citrulline or valine-lysine.

70. The conjugate of any of claims 63-69, wherein X comprises a p-aminobenzyl.

71. The conjugate of any of claims 63-70, wherein X is a compound having the formula:



72. The conjugate of any of claims 63-71, wherein the linker is 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB) or 4-(3-tosyl-2-(tosylmethyl)propanoyl)benzamide-valine-citruline-p-aminobenzyloxycarbonyl (TB-vc-PAB).

73. The conjugate of any of claims 63-72, wherein:

m and q are the same, whereby the conjugate has the formula: Ab – [(L) – (targeted agent)]$_p$;

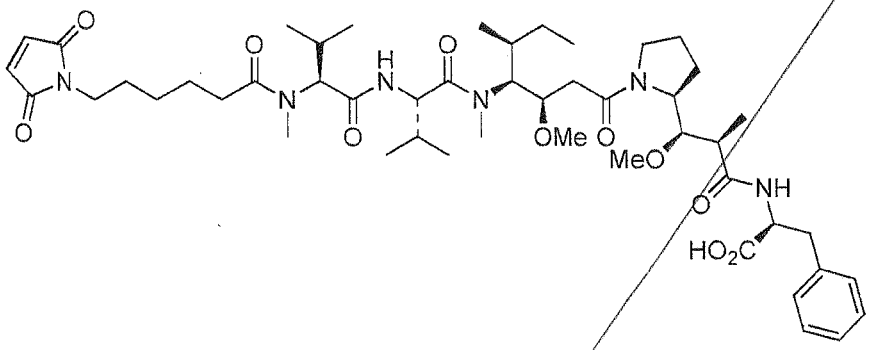
the targeted agent is MMAF;

the linker has the formula A_a, wherein:

A is a bridge unit that is maleimidocaproyl (MC);

a is 1; and

(L) – (targeted agent) has the following structure:



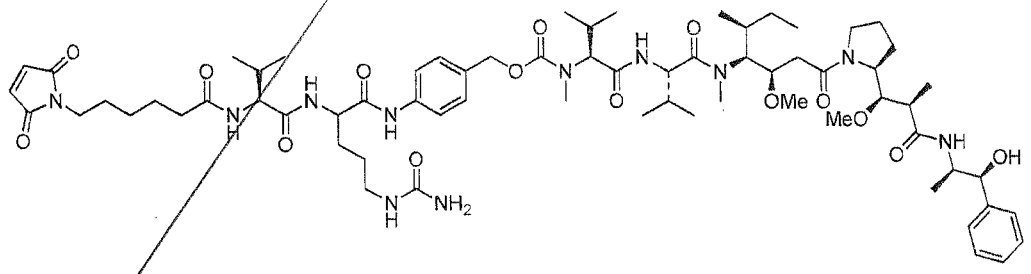
74. The conjugate of any of claims 63-72, wherein:

m and q are the same, whereby the conjugate has the formula: Ab-[(L) – (targeted agent)]$_p$;

the targeted agent is MMAE;

the linker comprises 6-maleimidocaproyl-valine-citrulline-p-aminobenzyloxycarbonyl (MC-vc-PAB); and

(L) – (targeted agent) has the following structure:



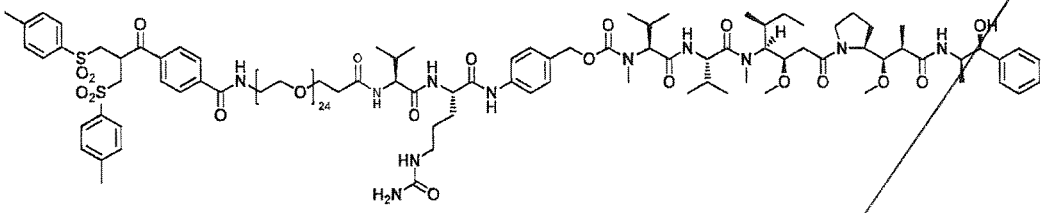
75. The conjugate of any of claims 63-72, wherein:

m and q are the same, whereby the conjugate has the formula: Ab-[(L) – (targeted agent)]$_p$;

the targeted agent is MMAE;

the linker is 4-(3-tosyl-2-(tosylmethyl)propanoyl)benzamide-valine-citruline-p-aminobenzyloxycarbonyl (TB-vc-PAB); and

(L) – (targeted agent) has the following structure:



76. The conjugate of claim 52 or claim 53, wherein the therapeutic moiety is an antimetabolite selected from among methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabine, 5 fluorouracil, decarbazine, hydroxyurea, asparaginase, gemcitabine, and cladribine.

77. The conjugate of claim 52 or claim 53, wherein the therapeutic moiety is an alkylating agent selected from among mechlorethamine, thiotepa, chlorambucil, melphalan, carmustine (BCNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine and mitomycin C.

78. The conjugate of claim 52 or claim 53 wherein the therapeutic moiety is a platinum derivative that is cisplatin or carboplatin.

79. The conjugate of claim 52 or claim 53, wherein the therapeutic moiety is an antibiotic selected from among dactinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicamycin and anthramycin (AMC).

80. The conjugate of claim 52 or claim 53, wherein the therapeutic moiety is a toxin selected from among a diphtheria toxin and active fragments thereof and hybrid molecules, a ricin toxin, cholera toxin, a Shiga-like toxin, LT toxin, C3 toxin, Shiga toxin, pertussis toxin, tetanus toxin, soybean Bowman-Birk protease inhibitor, Pseudomonas exotoxin, alorin, saporin, modeccin, gelanin, abrin A chain, modeccin A chain, alpha-sarcin, Aleurites fordii proteins, dianthin proteins, Phytolacca americana proteins, momordica charantia inhibitor, curcin, crotin, gelonin, mitogillin, restrictocin, phenomycin, and enomycin toxins.

81. The conjugate of any of claims claim 46-80, wherein the antibody and targeted agent are linked directly.

82. The conjugate of any of claims 46-81, wherein the antibody and targeted agent are joined via a linker.

83. The conjugate of claim 82, wherein the linker comprises a peptide or a polypeptide or is a chemical linker.

84. The conjugate of claim 82 or claim 83, wherein the linker is a cleavable linker or a non-cleavable linker.

85. The conjugate of any of claims 82-84, wherein the linker is conjugated to one or more free thiols on the antibody.

86. The conjugate of any of claims 82-85, wherein the linker is conjugated to one or more primary amines on the antibody.

87. A nucleic acid molecule(s), comprising a sequence of nucleotides encoding an anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-45.

88. A nucleic acid molecule, comprising a sequence of nucleotides encoding the heavy chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-45.

89. A vector, comprising the nucleic acid molecule(s) of claim 87 or claim 88.

90. A cell, comprising a vector or vectors of claim 89.

91. The cell of claim 90, wherein the cell is a prokaryotic or eukaryotic cell.

92. A method of making an anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors of claim 89 encoding the heavy chain and the light chain in a suitable host cell and recovering the antibody.

93. A combination, comprising:

an anti-EGFR antibody or antigen-binding fragment of any of claims 1-45 or a conjugate of any of claims 46-85; and

a chemotherapeutic agent or anti-cancer agent.

94. The combination of claim 93, wherein the chemotherapeutic agent is selected from among alkylating agents, nitrosoureas, topoisomerase inhibitors, and antibodies.

95. The combination of claim 94, wherein the chemotherapeutic agent is selected from among irinotecan, oxaliplatin, 5-fluorouracil (5-FU), Xeloda, Camptosar, Eloxatin, Adriamycin, paclitaxel, docetaxel, Cisplatin, gemcitabine and carboplatin.

96. The combination of any of claims 93-95, wherein the chemotherapeutic agent is an additional anti-EGFR antibody or antigen-binding fragment thereof that differs from the first antibody.

97. The combination of claim 96, wherein the additional anti-EGFR antibody is selected from among cetuximab, panitumumab, nimotuzumab, and antigen-binding fragments thereof or variants thereof.

98. A kit, comprising:

the antibody or antigen-binding fragment of any of claims 1-50, conjugates of any of claims 51-90 or the combination of any of claims 98-102, in one or more containers; and

instructions for use.

99. A pharmaceutical composition comprising:

an anti-EGFR antibody or antigen-binding fragment of any of claims 1-45, or conjugate of any of claims 46-85; and

a pharmaceutically acceptable carrier or excipient.

100. The pharmaceutical composition of claim 99 that is formulated as a gel, ointment, liquid, solution, suspension, aerosol, tablet, pill, powder or lyophile.

101. The pharmaceutical composition of claim 99 or claim 100 that is formulated for systemic, topical, oral, mucosal, intranasal, subcutaneous, aerosolized, intravenous, bronchial, pulmonary, vaginal, vulvovaginal, esophageal, or oroesophageal administration .

102. The pharmaceutical composition of any of claims 99-101 that is formulated for single dosage administration.

103. The pharmaceutical composition of any of claims 99-101 that is formulated for multiple dosage administration.

104. The pharmaceutical composition of any of claims 99-103 that is a sustained release formulation.

105. The pharmaceutical composition of any of claims 99-104, comprising a stabilizing agent that is selected from among an amino acid, an amino acid derivative, an amine, a sugar, a polyols, a salt and a surfactant.

106. The pharmaceutical composition of claim 105, wherein the stabilizing is a sugar or polyol selected from among glycerol, sorbitol, mannitol, inositol, sucrose and trehalose.

107. The pharmaceutical composition of claim 105 or claim 106, wherein the stabilizing agent is sucrose or trehalose.

108. The pharmaceutical composition of claim 106 or claim 107, wherein the concentration of the sugar or polyol is from 100 mM to 500 mM, 100 mM to 400 mM, 100 mM to 300 mM, 100 mM to 200 mM, 200 mM to 500 mM, 200 mM to 400 mM, 200 mM to 300 mM, 250 mM to 500 mM, 250 mM to 400 mM, 250 mM to 300 mM, 300 mM to 500 mM, 300 mM to 400 mM, or 400 mM to 500 mM, each inclusive.

109. The pharmaceutical composition of claim 105, wherein the stabilizing agent is a surfactant selected from among a polypropylene glycol, polyethylene glycol, glycerin, sorbitol, poloxamer and polysorbate.

110. The pharmaceutical composition of claim 109, wherein the surfactant is selected from among poloxamer 188, polysorbate 20 and polysorbate 80.

111. The pharmaceutical composition of claim 109 or claim 110, wherein the concentration of surfactant, as a % of mass concentration (w/v) in the formulation, is between 0.005% to 1.0%, 0.01% to 0.5%, 0.01% to 0.1%, 0.01% to 0.05%, or 0.01% to 0.02%, each inclusive.

112. The pharmaceutical composition of any of claims 109-111, wherein the surfactant is polysorbate 80.

113. A method of treating a condition responsive to treatment with an anti-EGFR antibody in a subject, comprising administering to the subject a pharmaceutically effective amount of the pharmaceutical composition of any of claims 99-112, wherein the condition responsive to treatment with an anti-EGFR antibody is a tumor, cancer or metastasis.

114. The method of claim 113, wherein the tumor expresses EGFR.

115. The method of claim 113 or claim 114, wherein the tumor is a solid tumor.

116. The method of any of claims 113-115, wherein the condition responsive to treatment with an anti-EGFR antibody is head and neck cancer, non-small cell lung cancer or colorectal cancer.

117. The method of any of claims 113-115, wherein the condition responsive to treatment with an anti-EGFR antibody is breast cancer.

118. The method of any of claims 113-117, wherein the subject has a tumor that does not comprise a marker that confers resistance to anti-EGFR therapy.

119. The method of claim 118, wherein the marker is a mutation in KRAS, NRAS or BRAF.

120. The method of any of claims 113-119, wherein the subject has a KRAS mutation-negative epidermal growth factor receptor (EGFR)-expressing colorectal cancer.

121. The method of any of claims 113-120, wherein the subject is a mammal.

122. The method of any of claims 113-121, wherein the subject is a human.

123. The method of any of claims 113-122, wherein the pharmaceutical composition is administered topically, parenterally, locally, or systemically.

124. The method of any of claims 113-123, wherein the pharmaceutical composition is administered intranasally, intramuscularly, intradermally, intraperitoneally, intravenously, subcutaneously, orally, or by pulmonary administration.

125. The method of any of claims 113-124, further comprising administration of one or more anticancer agents or treatments

126. The method of claim 125, wherein the anticancer agent or treatment is selected from among irinotecan, oxaliplatin, 5-fluorouracil (5-FU), Xeloda, Camptosar, Eloxatin, Adriamycin, paclitaxel, docetaxel, Cisplatin, gemcitabine, carboplatin and radiation.

127. The method of any of claims 113-126, further comprising administering one or more additional anti-EGFR antibodies or antigen-binding fragments thereof.

128. The method of claim 127, wherein the one or more additional anti-EGFR antibodies are selected from among cetuximab, panitumumab, nimotuzumab, and antigen-binding fragments thereof.

129. The method of any of claims 125-128, wherein the pharmaceutical composition and the anticancer agent are formulated as a single composition or as separate compositions.

130. The method of any of claims 125-129, wherein the pharmaceutical composition and the anticancer agent are administered sequentially, simultaneously or intermittently.

131. The method of any of claims 113-130, wherein the antibody, or antigen-binding fragment thereof, is administered at a dosage of r 0.1 mg/kg to 100 mg/kg, 0.5 mg/kg to 50 mg/kg, 5 mg/kg to 50 mg/kg, 1 mg/kg to 20 mg/kg, 1 mg/kg to 100 mg/kg, 10 mg/kg to 80 mg/kg, or 50 mg/kg to 100 mg/kg.

132. The method of any of claims 113-131, wherein the antibody, or antigen-binding fragment thereof, is administered at a dosage of 0.01 mg/m^2 to 800 mg/m^2.

133. The method of any of claims 113-132, wherein the antibody, or antigen-binding fragment thereof, is administered at a dosage of at least 0.01 mg/m^2, 0.1 mg/m^2, 0.5 mg/m^2, 1 mg/m^2, 5 mg/m^2, 10 mg/m^2, 15 mg/m^2, 20 mg/m^2, 25 mg/m^2, 30 mg/m^2, 35 mg/m^2, 40 mg/m^2, 45 mg/m^2, 50 mg/m^2, 100 mg/m^2, 150 mg/m^2, 200 mg/m^2, 250 mg/m^2, 300 mg/m^2, 400 mg/ m^2, 500 mg/ m^2, 600 mg/ m^2 or 700 mg/ m^2.

134. A pharmaceutical composition of any of claims 99-112 for treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition responsive to treatment with an anti-EGFR antibody is a tumor, cancer or metastasis.

135. Use of an antibody of any of claims 1-45 or conjugate of any of claims 46-85 for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject, wherein the condition responsive to treatment with an anti-EGFR antibody is a tumor, cancer or metastasis.

136. Use of a pharmaceutical composition of any of claims 109-112 for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

137. The pharmaceutical composition or use of claim 136, wherein the tumor expresses an EGFR.

138. The pharmaceutical composition or use of claim 136 or claim 137, wherein the tumor is a solid tumor.

139. The pharmaceutical composition or use of any of claims 134-138, wherein the condition responsive to treatment with an anti-EGFR antibody is head and neck cancer, non-small cell lung cancer or colorectal cancer.

140. The pharmaceutical composition or use of any of claims 134-138, wherein the condition responsive to treatment with an anti-EGFR antibody is breast cancer.

141. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 36, comprising the variable heavy chain set forth in SEQ ID NO: 137 and the variable light chain set forth in SEQ ID NO: 183.

142. A conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, of claim 29 linked directly or indirectly to a therapeutic moiety.

143. The conjugate of claim 142, wherein the therapeutic moiety is an auristatin.

144. The conjugate of claim 143, wherein the auristatin is monomethyl auristatin E (MMAE).

CLAIMS:

1. A modified anti-EGFR antibody or antigen-binding fragment thereof, comprising an amino acid replacement(s) in a variable heavy chain (VH) of an unmodif333 anti-EGFR antibody or antigen-binding fragment thereof corresponding to replacement with glutamic acid (E) at a position corresponding to position 104 (Y104E), with reference to amino acid positions set forth in SEQ ID NO: 2 or 7, wherein:

corresponding amino acid positions are identified by alignment of the variable heavy chain of the antibody with the variable heavy chain set forth in SEQ ID NO: 2 or 7;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, specifically binds epidermal growth factor receptor (EGFR) or a soluble fragment thereof and contains only the replacement corresponding toY104E or contains 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 additional amino acid replacements in the unmodified antibody or antigen-binding fragment thereof;

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity for EGFR of greater than 1.0 in the presence of a pH that is pH 6.0 to 6.5, inclusive compared to in the presence of pH 7.4, when measured under the same conditions except for the difference in pH; and

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi).

2. The modified anti-EGFR antibody of claim 1, wherein the ratio of binding activity is at least 2.0.

3. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, wherein the unmodified anti-EGFR antibody comprises:

a variable heavy chain set forth in SEQ ID NO:2 and a variable light chain set forth in SEQ ID NO: 4; or

a variable heavy chain set forth in SEQ ID NO: 7 and a variable light chain set forth in SEQ ID NO: 9 or 11.

4. The modified anti-EGFR antibody, or antigen-binding fragment thereof, o claim 1 or claim 2, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74 or 75; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

5. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 4, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO: 74; and

b) a variable light (VL) chain containing the sequence of amino acids set forth in SEQ ID NO: 9.

6. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2 that is a full-length IgG antibody, wherein the modified anti-EGFR antibody comprises:

a) a heavy chain comprising the sequence of amino acids set forth in SEQ ID NO:72 ; and

b) a light chain comprising the sequence of amino acids set forth in any of SEQ ID NOS: 3, 8, 10 or 13.

7. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, wherein:

the modified antibody comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the variable heavy chain set forth in SEQ ID NO: 74 or 75 and/or in the light chain set forth in SEQ ID NO: 4, 9 or 11, other than replacement with E at a position corresponding to position 104 in the heavy chain; or

the modified antibody comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid replacements in the heavy chain set forth in SEQ ID NO:72 and/or in the light chain set forth in any of SEQ ID NOS:3, 8, 10 or 13, other than replacement with E at a position corresponding to position 104 in the heavy chain.

8. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-7, comprising an amino acid replacement(s) in a variable heavy chain of the unmodified antibody corresponding to amino acid replacement(s) selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, and Q111P in addition to the replacement corresponding to Y104E.

9. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-8, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NOS: 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, or 123; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11.

10. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-9,

comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74, 77 or 104; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 9 or 11; or

comprising:

a) a heavy chain constant region set forth in any of SEQ ID NOS: 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, 115, 118, or 121; and

b) a light chain constant region set forth in any of SEQ ID NOS: 3, 8, 10 or 13; or

comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:74, 75, 77, 78, 80, 81, 83, 84, 86, 87, 89, 90, 92, 93, 95, 96, 98, 99, 101, 102, 104, 105, 107, 108, 110, 111, 113, 114, 116, 117, 119, 120, 122, or 123; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:125, 126 or 127; or

comprising:

a) a heavy chain comprising the sequence of amino acids set forth in any of SEQ ID NOS:72, 76, 79, 82, 85, 88, 91, 94, 97, 100, 103, 106, 109, 112, 115, 118, or 121; and

b) a light chain comprising the sequence of amino acids set forth in SEQ ID NO: 124.

11. The anti-EGFR antibody or antigen-binding fragment thereof, of claim 1 or claim 2 that has a single amino acid replacement corresponding to Y104E in the variable heavy chain of an unmodified anti-EGFR antibody or antigen-binding fragment thereof, wherein:

the unmodified anti-EGFR antibody or antigen-binding fragment thereof is selected from among:

i) cetuximab or an antigen-binding fragment thereof comprising a variable heavy chain set forth in SEQ ID NO:2 or 7 and a variable light chain set forth in SEQ ID NOS: 4, 9 or 11;

ii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:1 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof

iii) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:5 and the light chain sequence set forth in SEQ ID NO:3, or an antigen-binding fragment thereof;

iv) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:12 and the light chain sequence set forth in SEQ ID NO:13, or an antigen-binding fragment thereof;

v) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:8, or an antigen-binding fragment thereof;

vi) an antibody comprising the heavy chain sequence set forth in SEQ ID NO:6 and the light chain sequence set forth in SEQ ID NO:10, or an antigen-binding fragment thereof; and

vii) a humanized form of any of i)-vi).

12. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of ao claims 1-11 that comprises up to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 amino acid replacements in the variable heavy chain set forth in SEQ ID NO: 61 or 63 and/or in the variable light chain set forth in SEQ ID NO: 183, 184 or 186, in addition to replacement with E at a position corresponding to position 104 in the heavy chain.

13. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-12, wherein the amino acid replacements are HC-Y104E/ HC-Q111P; HC-S25C/ HC-Y104E; HC-Y104E/LC-I29S; HC-Y104E/HC-Q111P/LC-I29S; HC-S53G/HC-Y104E; HC-S53G/HC-Y104E/HC-Q111P; HC-S25V/HC-Y104E; HC-S25V/HC-Y104E/HC-Q111P; HC-S25V/HC-S53G/HC-Y104E; HC-S25V/HC-S53G/HC-Y104E/HC-Q111P; HC-T30F/HC-Y104E; HC-T30F/HC-Y104E/HC-Q111P; HC-T30F/HC-S53G/HC-Y104E; HC-T30F/HC-S53G/HC-Y104E/HC-Q111P; HC-D72L/HC-Y104E; HC-D72L/HC-Y104E/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104E; or HC-S53G/HC-D72L/HC-Y104E/HC-Q111P.

14 A modified anti-EGFR antibody, or antigen-binding fragment thereof of claim 1, comprising the heavy chain whose sequence is set forth in SEQ ID NO: 59 , and the light chain whose sequence is set forth in SEQ ID NO: 181, or is an antigen-binding fragment thereof.

15. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claim 1 or claim 2, comprising a sequence of amino acids selected from among:

a) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 155, 156 or 158 ;

b) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 162, 163 or 165 ;

c) the variable heavy chain set forth in SEQ ID NO: 137 or 139 , and the variable light chain set forth in SEQ ID NO: 155, 156 or 158 ;

d) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 169, 170 or 172 ;

e) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 176, 177 or 179 ;

f) the variable heavy chain set forth in SEQ ID NO: 131 or 133 and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 ;

g) the variable heavy chain set forth in SEQ ID NO: 137 or 139 , and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 ;

h) the variable heavy chain set forth in SEQ ID NO: 131 or 133 , and the variable light chain set forth in SEQ ID NO: 190, 191 or 193 ;

i) the variable heavy chain set forth in SEQ ID NO: 143 or 145 , and the variable light chain set forth in SEQ ID NO: 183, 184 or 186 ;

j) the variable heavy chain set forth in SEQ ID NO: 149 or 151 , and the variable light chain set forth in SEQ ID NO: 197, 198 or 200 ;

k) the variable heavy chain set forth in SEQ ID NO: 143 or 145 , and the variable light chain set forth in SEQ ID NO: 197, 198 or 200 ;

l) the variable heavy chain set forth in SEQ ID NO: 149 or 151 , and the variable light chain set forth in SEQ ID NO: 204, 205 or 207 ;

m) the variable heavy chain set forth in SEQ ID NO: 143 or 145 , and the variable light chain set forth in SEQ ID NO: 204, 205 or 207;

n) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 253, 254 or 256 ;

o) the variable heavy chain set forth in SEQ ID NO: 217 or 219 , and the variable light chain set forth in SEQ ID NO: 253, 254 or 256 ;

p) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 260, 261 or 263 ;

q) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 260, 261 or 263 ;

r) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 267, 268 or 270 ;

s) the variable heavy chain set forth in SEQ ID NO: 241 or 243 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

t) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

u) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 274, 275 or 277 ;

v) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

w) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

x) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

y) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ;

z) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

aa) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

bb) the variable heavy chain set forth in SEQ ID NO: 223 or 225 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

cc) the variable heavy chain set forth in SEQ ID NO: 229 or 231 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291 ;

dd) the variable heavy chain set forth in SEQ ID NO: 235 or 237 , and the variable light chain set forth in SEQ ID NO: 295, 296 or 298 ;

ee) the variable heavy chain set forth in SEQ ID NO: 247 or 249 , and the variable light chain set forth in SEQ ID NO: 302, 303 or 305 ;

ff) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 302, 303 or 305 ;

gg) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 281, 282 or 284 ; and

hh) the variable heavy chain set forth in SEQ ID NO: 211 or 213 , and the variable light chain set forth in SEQ ID NO: 288, 289 or 291.

16. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 15, comprising the variable heavy chain set forth in SEQ ID NO: 137 and the variable light chain set forth in SEQ ID NO: 183.

17. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, that is a full-length antibody, wherein the antibody comprises a sequence of amino acids selected from among:

a) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 153 ;

b) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 160 ;

c) the heavy chain set forth in SEQ ID NO: 135 , and the light chain set forth in SEQ ID NO: 153 ;

d) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 167 ;

e) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 174 ;

f) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 181 ;

g) the heavy chain set forth in SEQ ID NO: 135 , and the light chain set forth in SEQ ID NO: 181 ;

h) the heavy chain set forth in SEQ ID NO: 129 , and the light chain set forth in SEQ ID NO: 188 ;

i) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 181 ;

j) the heavy chain set forth in SEQ ID NO: 147 , and the light chain set forth in SEQ ID NO: 195 ;

k) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 195 ;

l) the heavy chain set forth in SEQ ID NO: 147 , and the light chain set forth in SEQ ID NO: 202 ;

m) the heavy chain set forth in SEQ ID NO: 141 , and the light chain set forth in SEQ ID NO: 202 ;

n) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 251 ;

o) the heavy chain set forth in SEQ ID NO: 215 , and the light chain set forth in SEQ ID NO: 251 ;

p) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 258 ;

q) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 258 ;

r) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 265 ;

s) the heavy chain set forth in SEQ ID NO: 239 , and the light chain set forth in SEQ ID NO: 272 ;

t) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 272 ;

u) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 272 ;

v) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 279 ;

w) the heavy chain set forth in SEQ ID NO: 245 , and the light chain set forth in SEQ ID NO: 279 ;

x) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 279 ;

y) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 279 ;

z) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 286 ;

aa) the heavy chain set forth in SEQ ID NO: 245 , and the light chain set forth in SEQ ID NO: 286 ;

bb) the heavy chain set forth in SEQ ID NO: 221 , and the light chain set forth in SEQ ID NO: 286 ;

cc) the heavy chain set forth in SEQ ID NO: 227 , and the light chain set forth in SEQ ID NO: 286 ;

dd) the heavy chain set forth in SEQ ID NO: 233 , and the light chain set forth in SEQ ID NO: 293 ;

ee) the heavy chain set forth in SEQ ID NO: 245 , and the light chain set forth in SEQ ID NO: 300 ;

ff) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 300 ;

gg) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 279 ; and

hh) the heavy chain set forth in SEQ ID NO: 209 , and the light chain set forth in SEQ ID NO: 286 .

18. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 6, wherein the modified anti-EGFR antibody comprises:

a) a heavy chain comprising the sequence of amino acids set forth in SEQ ID NO:72; and

b) a light chain comprising the sequence of amino acids set forth in SEQ ID NO:8.

19. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 or claim 2, comprising a sequence of amino acids containing the variable heavy chain set forth in SEQ ID NO: 61 and the variable light chain set forth in SEQ ID NO: 183.

20. The modified anti-EGFR antibody, or antigen-binding fragment thereof of any of claims 1-19, wherein the unmodified antibody or antigen-binding fragment thereof is humanized.

21. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 20, wherein the humanized unmodified anti-EGFR antibody or antigen-binding fragment thereof comprises:

a variable heavy chain set forth in SEQ ID NO: 14 and variable light chain set forth in SEQ ID NO: 15; or

a variable heavy chain set forth in SEQ ID NO: 16 and a variable light chain set forth in SEQ ID NO: 17.

22. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-21 that is a full-length antibody.

23. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-21 that is an antigen-binding fragment selected from among Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

24. A conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-23 linked directly or indirectly via a chemical or physical bond to a targeted agent.

25. A conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, of claim 19 linked directly or indirectly via a linker (L) to a targeted agent.

26. The conjugate of claim 24 or claim 25, comprising the following components: (Ab), $(L)_q$, and $(\text{targeted agent})_m$, wherein:

the conjugate has the following formula: Ab – $[(L)_q$ – $(\text{targeted agent})_m]$;

Ab is the modified anti-EGFR antibody or antigen-binding fragment thereof that binds to EGFR;

L is a linker links the Ab to the targeted agent;

m is an integer that is at least 1;

q is 0 or more as long as the resulting conjugate binds to the EGFR;

the resulting conjugate binds to the EGFR.

27. The conjugate of claim 26, wherein m is 1 to 8 and q is 0 to 8.

28. The conjugate of any of claims 24-27, wherein the targeted agent is a protein, peptide, nucleic acid or small molecule.

29. The conjugate of any of claims 24-27, wherein the targeted agent is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

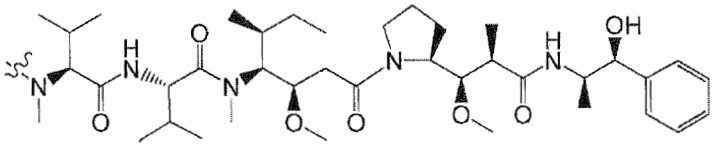
30. The conjugate of any of claims 24-29, wherein the targeted agent is an auristatin.

31. The conjugate of any of claims 24-30, wherein the linker L is selected from among N-succinimidyl-4(2-pyridylthio)propanoate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate(SMCC) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP).

32. The conjugate of any of claims 24-31, wherein the targeted agent is an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF).

33. The conjugate of claim 32, wherein the therapeutic moiety is MMAE; and

MMAE has the structure:



or a pharmaceutically acceptable salt form thereof.

34. A nucleic acid molecule(s), comprising a sequence of nucleotides encoding an anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-23; or

comprising a sequence of nucleotides encoding the heavy chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-23.

35. A vector, comprising the nucleic acid molecule(s) of claim 34.

36. A cell, comprising a vector of claim 35.

37. A method of making an anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors of claim 35 encoding the heavy chain and the light chain in a suitable host cell to produce the antibody; and, optionally, recovering the antibody.

38. A pharmaceutical composition comprising:

an anti-EGFR antibody or antigen-binding fragment of any of claims 1-23, or conjugate of any of claims 24-33; and

a pharmaceutically acceptable carrier or excipient.

39. Use of a pharmaceutical composition of claim 38, for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

40. A pharmaceutical composition of claim 38 for use for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

41. Use of an antibody of any of claims 1-23 or conjugate of any of claims 24-33 for formulation of a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

42. The use of or the pharmaceutical composition of any of claims 39-41, wherein the condition responsive to treatment with an anti-EGFR antibody is a tumor, cancer or metastasis.

43. The use of or the pharmaceutical composition of any of claims 39-41, wherein the condition responsive to treatment with an anti-EGFR antibody comprises a solid tumor.

44. The use of or the pharmaceutical composition of any of claims 39-43, wherein the condition responsive to treatment with an anti-EGFR antibody is head and neck cancer, non-small cell lung cancer or colorectal cancer.

45. The use of or the pharmaceutical composition of any of claims 39-43, wherein the condition responsive to treatment with an anti-EGFR antibody is breast cancer.

46. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 15, comprising the variable heavy chain set forth in SEQ ID NO: 137 and the variable light chain set forth in SEQ ID NO: 183.

47. A conjugate, comprising an anti-EGFR antibody, or antigen-binding fragment thereof, of claim 46 linked directly or indirectly to a therapeutic moiety.

48. The conjugate of claim 47, wherein the therapeutic moiety is an auristatin.

49. The conjugate of claim 48, wherein the auristatin is monomethyl auristatin E (MMAE).