microenvironments (e.g. having a neutral pH) compared to antibodies that are not conditionally active and/or compared to their activity in the tumor microenvironment. By virtue of the selectivity to a tumor microenvironment, they exhibit fewer or lesser undesirable side-effects and/or exhibit improved efficacy by virtue of the ability to dose higher.

In one aspect there is provided a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising the amino acid replacement Y104D in the variable heavy chain of the unmodified antibody, wherein:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain, or a portion thereof that is sufficient to bind EGFR antigen, whereby one or both of the VH or VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, or an antigen-binding fragment thereof, comprising a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10;

ii) a variant of i) comprising a variable heavy chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:3, and a variable light chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:4 or 10, wherein the variant does not comprise the amino acid replacement and specifically binds to EGFR; and

iii) a humanized form of i) or ii).

In another aspect there is provided a conjugate, comprising a modified anti-EGFR antibody, or antigen-binding fragment thereof, as described herein linked directly or indirectly to a targeted agent.

In another aspect there is provided 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, as described herein; and/or

a nucleic acid molecule, comprising a sequence of nucleotides encoding the light chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, as described herein.

In another aspect there is provided a vector, comprising the nucleic acid molecule(s) as described herein.

In another aspect there is provided a cell, comprising a vector or vectors as described herein.

In another aspect there is provided a method of making a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded

from a vector or vectors as described herein encoding the heavy chain and the light chain in a suitable host cells and recovering the antibody.

In another aspect there is provided a pharmaceutical composition comprising:

a modified anti-EGFR antibody or antigen-binding fragment as decribed herein or a conjugate as described herein; and

a pharmaceutically acceptable carrier or excipient.

In another aspect there is provided use of a modified anti-EGFR antibody or antigen-binding fragment as described herein or a conjugate as described herein for preparation of a medicament for treating a tumor, cancer or metastasis.

Provided herein are an anti-EGFR antibody, or antigen-binding fragment thereof, that is conditionally active under conditions in a tumor microenvironment. wherein the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity to human epidermal growth factor receptor (EGFR) or a soluble fragment thereof under conditions in a tumor environment compared to under conditions in a non-tumor environment of at least 3.0. In such an example, the conditions in a tumor environment contain one or both of pH between or about between 5.6 to 6.8 or lactate concentration between or about between 5 mM to 20 mM, and protein concentration of 10 mg/mL to 50 mg/mL; and the conditions in a non-tumor environment contain one or both of pH between or about between 7.0 to 7.8 or lactate concentration between or about between 0.5 mM to 5 mM, and protein concentration of 10 mg/mL to 50 mg/mL. For example, the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that contain a pH of between or about between 5.6 to 6.8 compared to under conditions that exist in a non-tumor microenvironment that comprise a pH of between or about between 7.0 to 7.8. In another example, the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that contain a pH of between or about between 6.0 to 6.5 compared to under conditions that exist in a non-tumor microenvironment that comprise a pH of about 7.4. In some instances, the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that contain lactate concentration between or about between 5 mM to 20 mM compared to under conditions that exist in a non-tumor microenvironment that contain lactate concentration between or about between 0.5 mM to 5 mM. In particular examples herein,

the anti-EGFR antibody or, or antigen-binding fragment thereof, of any of claims 1-4, exhibits the ratio of activity under conditions of a tumor microenvironment that

CLAIMS:

1. A modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising the amino acid replacement Y104D in the variable heavy chain of the unmodified antibody, wherein:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain, or a portion thereof that is sufficient to bind EGFR antigen, whereby one or both of the VH or VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, or an antigen-binding fragment thereof, comprising a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10;

ii) a variant of i) comprising a variable heavy chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:3, and a variable light chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:4 or 10, wherein the variant does not comprise the amino acid replacement and specifically binds to EGFR; and

iii) a humanized form of i) or ii);

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity to human epidermal growth factor receptor (EGFR) or a soluble fragment thereof under conditions in a tumor environment compared to under conditions in a non-tumor environment of at least 2.0;

conditions in a tumor environment comprise one or both of pH between or about between 6.0 to 6.5 or lactate concentration between or about between 5 mM to 20 mM, and protein concentration of 10 mg/mL to 50 mg/mL;

conditions in a non-tumor environment comprise one or both of pH of about 7.4 or lactate concentration between or about between 0.5 mM to 5 mM, and protein concentration of 10 mg/mL to 50 mg/mL , whereby the anti-EGFR antibody or fragment thereof is conditionally active under conditions in a tumor microenvironment.

2. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1, wherein the ratio of binding activity is at least 3.0 .

3. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 , wherein the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that comprise a pH of between or about between 6.0 to 6.5 compared to under conditions that exist in a non-tumor microenvironment that comprise a pH of about 7.4.

4. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-3, wherein the anti-EGFR antibody or, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions of a tumor microenvironment that comprise

pH of 6.0 to 6.5 and lactate concentration of 10 mM to 20 mM compared to under condition of a non-tumor microenvironment that comprise pH of 7.0 to 7.4, inclusive, and lactate concentration of 0.5 mM to 2 mM.

5. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-4, wherein the protein concentration under conditions in a tumor microenvironment and under conditions in a non-tumor microenvironment is substantially the same or is the same.

6. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-5, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:495, 1062, 1112, 1114-1117, 1124-1126, 1128-1130, 1134-1137, or 1146-1152, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 495, 1062, 1112, 1114-1117, 1124-1126, 1128-1130, 1134-1137, or 1146-1152; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 10, 1138-1145, 1153-1159 or 1186, or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4, 10, 1138-1145, 1153-1159 or 1186.

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

a) the variable heavy chain set forth in SEQ ID NO:495 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:495, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

b) the variable heavy chain set forth in SEQ ID NO:1062 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1062, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

c) the variable heavy chain set forth in SEQ ID NO:1112 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1112, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

d) the variable heavy chain set forth in SEQ ID NO:1114 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1114, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

e) the variable heavy chain set forth in SEQ ID NO:1115 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1115, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

f) the variable heavy chain set forth in SEQ ID NO:1116 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1116, and the variable

light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

g) the variable heavy chain set forth in SEQ ID NO:1117 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1117, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

h) the variable heavy chain set forth in SEQ ID NO:1124 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1124, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

i) the variable heavy chain set forth in SEQ ID NO:1125 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1125, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

j) the variable heavy chain set forth in SEQ ID NO:1126 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1126, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

k) the variable heavy chain set forth in SEQ ID NO:1128 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1128, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

l) the variable heavy chain set forth in SEQ ID NO:1129 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1129, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

m) the variable heavy chain set forth in SEQ ID NO:1130 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1130, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

n) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

o) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1139 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1139;

p) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

q) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1140 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1140;

r) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1141 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1141;

s) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

t) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

u) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1143 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1143;

v) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

w) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

x) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

y) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

z) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

aa) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable

light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

bb) the variable heavy chain set forth in SEQ ID NO:1147 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1147, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

cc) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

dd) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

ee) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1155 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1155;

ff) the variable heavy chain set forth in SEQ ID NO:1151 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1151, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

gg) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

hh) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

ii) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

jj) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

kk) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

ll) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

mm) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

nn) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

oo) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

pp) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

qq) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1158 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1158;

rr) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

ss) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

tt) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

uu) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186; and

vv) the variable heavy chain set forth in SEQ ID NO:1118 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1118, and the

variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10.

8. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 31 or claim 32, wherein sequence identity is at least 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 98%, 99% or more.

9. A modified anti-EGFR antibody or antigen-binding fragment thereof, comprising an amino acid replacement(s) in a variable heavy chain, variable light chain or both of the unmodified antibody, wherein:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain, or a portion thereof that is sufficient to bind EGFR antigen, whereby one or both of the VH or VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, or an antigen-binding fragment thereof, comprising a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10;

ii) a variant of i) comprising a variable heavy chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:3, and a variable light chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:4 or 10, wherein the variant does not comprise the amino acid replacement and specifically binds to EGFR; and

iii) a humanized form of i) or ii);

the modified anti-EGFR antibody or fragment thereof exhibits a ratio of binding activity for EGFR at or about pH 6.0 to pH 6.5 compared to at or about pH 7.4 of at least 2.0, when measured under the same conditions except for the difference in pH; and

the modified anti-EGFR antibody exhibits less than 40% of the binding activity for EGFR at pH 7.4 compared to the unmodified antibody at pH 7.4 when measured under the same conditions, with the proviso that the modified anti-EGFR antibody or fragment thereof does not comprise:

a) a variable heavy chain comprising an amino acid replacement selected from among N31I, N31V, V50L, Y59E and T64N; or

b) a variable light chain comprising an amino acid replacement L4C.

10. The modified anti-EGFR antibody or fragment thereof of claim 9, wherein the modified anti-EGFR antibody exhibits at least 20% of the binding activity for EGFR at or about pH 6.0 to pH 6.5 compared to the unmodified antibody at pH 6.0 to pH 6.5 when measured under the same conditions.

11. The modified anti-EGFR antibody or fragment thereof of claims 9 or claim 10, wherein:

a) the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among V24E, V24I, V24L, S25C, S25H, S25R, S25A, S25D, S25G, S25M, S25Q, S25V, S25L, S28C, L29H, N31H, G54D, G54S, F63R, F63C, F63M, F63P, F63S, T64V, L67G, D72L, D72P, D72W, N73Q, K75H, K75G, K75P, K75W, S76I, S76V, Q77E, T100P, Y104D, Y104S, Y104V, Q111I and Q111V, with reference to amino acid positions set forth in SEQ ID NO:3, wherein:

corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement; and/or

b) the variable light chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among L4F, L4V, T5P and R24G, with reference to amino acid positions set forth in SEQ ID NO:4, wherein:

corresponding amino acid positions are identified by alignment of the VL chain of the antibody with the VL chain set forth in SEQ ID NO:4; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement.

12. The modified anti-EGFR antibody of any of claims 9-11 , wherein the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains the amino acid replacement Y104D.

13. The modified anti-EGFR antibody or fragment thereof of claim 1, wherein:

a) the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among V24E, V24I, V24L, S25C, S25H, S25R, S25A, S25D, S25G, S25M, S25Q, S25V, S25L, S28C, L29H, N31H, G54D, G54S, F63R, F63C, F63M, F63P, F63S, T64V, L67G, D72L, D72P, D72W, N73Q, K75H, K75G, K75P, K75W, S76I, S76V, Q77E, T100P, Y104S, Y104V, Q111I and Q111V, with reference to amino acid positions set forth in SEQ ID NO:3, wherein:

corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement; and/or

b) the variable light chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among L4F, L4V, T5P and R24G, with reference to amino acid positions set forth in SEQ ID NO:4, wherein:

corresponding amino acid positions are identified by alignment of the VL chain of the antibody with the VL chain set forth in SEQ ID NO:4; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement.

14. The modified anti-EGFR antibody of claims 11-13 , wherein

the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains a further amino acid replacement selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, Y104D and Q111P.

15. A modified anti-EGFR antibody or antigen-binding fragment thereof, comprising at least two amino acid replacement, wherein:

the amino acid replacements are in a variable heavy (VH) chain, variable light (VL) chain or both of the unmodified antibody:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain or a portion thereof that is sufficient to bind EGFR antigen, whereby one or both of the VH or VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, or an antigen-binding fragment thereof, comprising a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10;

ii) a variant of i) comprising a variable heavy chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:3, and a variable light chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:4 or 10, wherein the variant does not comprise the amino acid replacement and specifically binds to EGFR; and

iii) a humanized form of i) or ii);

the amino acid replacements in the VH chain of the modified anti-EGFR antibody corresponds to an amino acid replacement selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, Y104D and Q111P, with reference to amino acid positions set forth in SEQ ID NO:3, wherein corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3; and

the amino acid replacement in the VL chain of the modified anti-EGFR antibody corresponds to amino acid replacement I29S, with reference to the amino acid position set forth in SEQ ID NO:4; wherein corresponding amino acid positions are identified by alignment of the VL chain of the antibody with the VL chain set forth in SEQ ID NO:4.

16. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 12-15 , wherein the amino acid replacements are HC-Y104D/ HC-Q111P; HC-S25C/ HC-Y104D; HC-Y104D/LC-I29S; HC-Y104D/HC-Q111P/LC-I29S; HC-S53G/HC-Y104D; HC-S53G/HC-Y104D/HC-Q111P; HC-S25V/HC-Y104D; HC-S25V/HC-Y104D/HC-Q111P; HC-S25V/HC-S53G/HC-Y104D; HC-S25V/HC-

S53G/HC-Y104D/HC-Q111P; HC-T30F/HC-Y104D; HC-T30F/HC-Y104D/HC-Q111P; HC-T30F/HC-S53G/HC-Y104D; HC-T30F/HC-S53G/HC-Y104D/HC-Q111P; HC-D72L/HC-Y104D; HC-D72L/HC-Y104D/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104D; or HC-S53G/HC-D72L/HC-Y104D/HC-Q111P.

17. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 13 or claim 15, wherein the amino acid replacements are HC-S25C/ HC-Q111P; HC-V24E/ HC-F27R/ HC-R97H/ HC-Q111P; HC-S25C/LC-I29S; and HC-Q111P/LC-I29S.

18. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 15-17, wherein the modified anti-EGFR antibody or fragment thereof exhibits a ratio of binding activity for EGFR at or about pH 6.0 to pH 6.5 compared to at or about pH 7.4 of at least 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.5, 3.0, 4.0, 4.5, 5.0 or greater.

19. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 18, wherein the modified anti-EGFR antibody or fragment thereof exhibits a ratio of binding activity for EGFR at or about pH 6.0 to pH 6.5 compared to at or about pH 7.4 of at least 2.0.

20. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 19, wherein the amino acid replacements are HC-Y104D/ HC-Q111P; HC-S25C/ HC-Y104D; HC-S53G/HC-Y104D; HC-S53G/HC-Y104D/HC-Q111P; HC-S25V/HC-Y104D; HC-S25V/HC-Y104D/HC-Q111P; HC-S25V/HC-S53G/HC-Y104D; HC-S25V/HC-S53G/HC-Y104D/HC-Q111P; HC-T30F/HC-Y104D; HC-T30F/HC-Y104D/HC-Q111P; HC-T30F/HC-S53G/HC-Y104D; HC-T30F/HC-S53G/HC-Y104D/HC-Q111P; HC-D72L/HC-Y104D; HC-D72L/HC-Y104D/HC-Q111P; HC-S53G/ HC-D72L/HC-Y104D; or HC-S53G/HC-D72L/HC-Y104D/HC-Q111P.

21. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-20, wherein the unmodified cetuximab antibody, antigen-binding fragment thereof or variant thereof comprises:

a heavy chain having a sequence of amino acids set forth in SEQ ID NO:1 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:1 and a light chain having a sequence of amino acids set forth SEQ ID NO:2 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:2; or

a heavy chain having a having a sequence of amino acids set forth in SEQ ID NO: 8 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:8 and a light chain having a sequence of amino acids set forth SEQ ID NO:9 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:9.

22. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-21, wherein the unmodified anti-EGFR antibody is humanized.

23. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 22, wherein the unmodified anti-EGFR antibody comprises the variable heavy chain set forth in SEQ ID NO:28 and the variable light chain set forth in SEQ ID NO:29.

24. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-20, wherein:

the unmodified anti-EGFR antibody is an antigen-binding fragment; and

the antigen-binding fragment is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

25. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 24, wherein the unmodified anti-EGFR antibody is a Fab fragment; and

the Fab comprises a heavy chain having the sequence of amino acids set forth in SEQ ID NO:5 or a sequence of amino acids that exhibits at least 75% sequence identity to SEQ ID NO:5 and a light chain having the sequence of amino acids set forth in SEQ ID NO:2 or a sequence of amino acids that exhibits at least 75% sequence identity to a sequence of amino acids set forth in SEQ ID NO:2.

26. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 11-25, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:495, 1062, 1112, 1114, 1115, 1116, 1117, 1118, 1119, 1124, 1125, 1126, 1127, 1128, 1129, 1130 or 1131, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 495, 1062, 1112, 1114, 1115, 1116, 1117, 1118, 1119, 1124, 1125, 1126, 1127, 1128, 1129, 1130 or 1131; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4 or 10, or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10.

27. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 53 1-8 or 11-26, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:1062 or 1125, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 1062 or 1125; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4 or 10, or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10.

28. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-27 that is humanized.

29. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 28, wherein:

the variable heavy chain of the modified anti-EGFR antibody exhibits less than 85% sequence identity to the variable heavy chain set forth in SEQ ID NO:3 and greater than 65% sequence identity to the variable heavy chain set forth in SEQ ID NO:3; and

the variable light chain of the modified anti-EGFR antibody 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.

30. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 28 or claim 29, wherein:

the modified anti-EGFR antibody comprises amino acid replacements Y104D/Q111P or T30F/Y104D/Q111P; and

the modified anti-EGFR antibody comprises a sequence of amino acids selected from among:

a) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

b) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1139 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1139;

c) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

d) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1140 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1140;

e) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1141 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1141;

f) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

g) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

h) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1143 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1143;

i) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

j) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

k) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

l) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

m) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

n) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

o) the variable heavy chain set forth in SEQ ID NO:1147 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1147, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

p) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

q) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

r) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1155 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1155;

s) the variable heavy chain set forth in SEQ ID NO:1151 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1151, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

t) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable

light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

u) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

v) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

w) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

x) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

y) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

z) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

aa) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

bb) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

cc) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

dd) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1158 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1158;

ee) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

ff) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

gg) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157; and

hh) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186.

31. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 26, 27 or 30 , wherein the sequence identity is at least 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more thereto.

32. The anti-EGFR antibody or antigen binding fragment of any of claims 1-31 that is a full-length IgG antibody.

33. The modified anti-EGFR antibody or antigen binding fragment of claim 32, that comprises:

a heavy chain constant region set forth in any of SEQ ID NOS:22-25, 1069 and 1070, or a variant thereof that exhibits at least 85% sequence identity thereto; and

a light chain constant region set forth in any of SEQ ID NOS: 1072-1073, or a variant thereof that exhibits at least 85% sequence identity thereto.

34. The modified anti-EGFR antibody or antigen binding fragment of any of claims 1-31 that is an antigen-binding fragment selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

35. The modified anti-EGFR antibody, or antigen-binding fragment, of claim 34 that is a Fab or scFv.

36. The modified anti-EGFR antibody, or antigen-binding fragment, of any of claims 1-35 that is isolated or purified.

37. A conjugate, comprising a modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-36 linked directly or indirectly to a targeted agent.

38. The conjugate of claim 37, 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.

39. The conjugate of claim 38, wherein m is 1 to 8 and q is 0 to 8.

40. The conjugate of any of claims 36-39, wherein the targeted agent is a protein, peptide, nucleic acid or small molecule.

41. The conjugate of any of claims 36-40, wherein the targeted agent is a therapeutic moiety.

42. The conjugate of claim 41, wherein the therapeutic moiety is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

43. The conjugate of claim 42, wherein the therapeutic moiety is selected from among taxol; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; tenoposide; vincristine; vinblastine; colchicin; 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 analogue 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]-benzodiazepines (PDB); a toxin; ribonuclease (RNase); DNase I, Staphylococcal enterotoxin A; and pokeweed antiviral protein.

44. The conjugate of claim 42 or claim 43, wherein the therapeutic moiety is a maytansine derivative that is a maytansinoids selected from among ansamitocin or mertansine (DM1).

45. The conjugate of claim 42 or claim 43, wherein the therapeutic moiety is an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF)..

46. The conjugate of claim 42 or claim 43, wherein the therapeutic moiety is an antimetabolite selected from among methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabin, 5 fluorouracil, decarbazine, hydroxyurea, asparaginase, gemcitabine, and cladribine.

47. The conjugate of claim 42 or claim 43, wherein the therapeutic moiety is an alkylating agent selected from among mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine and mitomycin C.

48. The conjugate of claim 42 or claim 43, wherein the therapeutic moiety is a platinum derivative that is cisplatin or carboplatin.

49. The conjugate of claim 42 or claim 43, wherein the therapeutic moiety is an antibiotic selected from among dactinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicamycin and anthramycin (AMC).

50. The conjugate of claim 42 or claim 43, 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, mitogellin, restrictocin, phenomycin, and enomycin toxins.

51. The conjugate of any of claims claim 37-50, wherein the antibody and targeted agent are linked directly.

52. The conjugate of any of claims 37-50, wherein the antibody and targeted agent are joined via a linker.

53. The conjugate of claim 52, wherein the linker comprises a peptide or a polypeptide or is a chemical linker.

54. The conjugate of claim 52 or claim 53, wherein the linker is a cleavable linker or a non-cleavable linker.

55. The conjugate of any of claims 52-54, wherein the linker is conjugated to one or more free thiols on the antibody.

56. The conjugate of any of claims 52-54, wherein the linker is conjugated to one or more primary amines.

57. A nucleic acid molecule(s), comprising a sequence of nucleotides encoding modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-36.

58. 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 1-36.

59. A nucleic acid molecule, comprising a sequence of nucleotides encoding the light chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-36.

60. A vector, comprising the nucleic acid molecule(s) of any of claims 57-59.

61. A cell, comprising a vector or vectors of claim 60.

62. The cell of claim 61, wherein the cell is a prokaryotic or eukaryotic cell.

63. A method of making a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors of claim 60 encoding the heavy chain and the light chain in a suitable host cells and recovering the antibody.

64. The method of claim 63, wherein:

the encoded antibody, or antigen-bind fragment thereof are any of claims 21-28 ; and

greater than 1 mg/mL antibody is produced by the host cell.

65. A combination, comprising:

a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-36 or a conjugate of any of claims 37-58; and

a chemotherapeutic agent or anti-cancer agent.

66. The combination of claim 65, wherein the chemotherapeutic agent is selected from among alkylating agents, nitrosoureas, topoisomerase inhibitors, and antibodies.

67. The combination of claim 65, wherein the chemotherapeutic agent is selected from among irinotecan, oxaliplatin, 5-fluorouracil (5-FU), Xeloda, Camptosar, Eloxatin, Adriamycin, paclitaxel, docetaxel, Cisplatin, gemcitabine and carboplatin.

68. The combination of any of claims 65-67, wherein the chemotherapeutic agent is an additional anti-EGFR antibody or antigen-binding fragment thereof that differs from the first antibody.

69. The combination of claim 68, wherein the additional anti-EGFR antibody is selected from among cetuximab, panitumumab, nimotuzumab, and antigen-binding fragments thereof or variants thereof.

70. A kit comprising the antibody or antigen-binding fragment of any of claims 1-36, conjugates of any of claims 37-56 or the combination of any of claims 65-69, in one or more containers, and instructions for use.

71. A pharmaceutical composition comprising:

a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-36, conjugate of any of claims 27-56 or the combination of any of claims 65-69; and

a pharmaceutically acceptable carrier or excipient.

72. The pharmaceutical composition of claim 71 that is formulated as a gel, ointment, liquid, suspension, aerosol, tablet, pill, powder or lyophile.

73. The pharmaceutical composition of claim 71 or claim 72 that is formulated for systemic, parenteral, topical, oral, mucosal, intranasal, subcutaneous, aerosolized, intravenous, bronchial, pulmonary, vaginal, vulvovaginal, esophageal, or oroesophageal administration .

74. The pharmaceutical composition of any of claims 71-73- that is formulated for single dosage administration.

75. The pharmaceutical composition of any of claims 71-73 that is formulated for multiple dosage administration.

76. The pharmaceutical composition of any of claims 71-73 that is a sustained release formulation.

77. 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 71-76.

78. The method of claim 77, wherein the condition responsive to treatment with an anti-EGFR antibody is a tumor, cancer or metastasis.

79. The method of claim 78, wherein the tumor expresses EGFR.

80. The method of claim 78 or claim 79, wherein the tumor is a solid tumor.

81. The method of any of any of claims 77-80, wherein the condition responsive to treatment with an anti-EGFR antibody is head and neck cancer, non-small cell lung cancer or colorectal cancer.

82. The method of any of claims 77-81, wherein the subject has a tumor that does not comprise a marker that confers resistance to anti-EGFR therapy.

83. The method of claim 82, wherein the marker is a mutation in *KRAS*, *NRAS* or *BRAF*.

84. The method of any of claims 77-81, wherein the subject has a KRAS mutation-negative epidermal growth factor receptor (EGFR)-expressing colorectal cancer.

85. The method of any of claims 77-84, wherein the subject is a mammal.

86. The method of any of claims 77-85, wherein the subject is a human.

87. The method of any of claims 77-86, wherein the pharmaceutical composition is administered topically, parenterally, locally, or systemically.

88. The method of any of claims 77-87, wherein the pharmaceutical composition is administered intranasally, intramuscularly, intradermally, intraperitoneally, intravenously, subcutaneously, orally, or by pulmonary administration.

89. The method of any of claims 77-88, further comprising administration of one or more anticancer agents or treatments

90. The method of claim 89, 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.

91. The method of any of claims 77-90, further comprising administering one or more additional anti-EGFR antibodies or antigen-binding fragments thereof.

92. The method of claim 91, wherein the one or more additional anti-EGFR antibodies are selected from among cetuximab, panitumumab, nimotuzumab, and antigen-binding fragments thereof.

93. The method of any of claims 89-92, wherein the pharmaceutical composition and the anticancer agent are formulated as a single composition or as separate compositions.

94. The method of any of claims 89-93, wherein the pharmaceutical composition and the anticancer agent are administered sequentially, simultaneously or intermittently.

95. The method of any of claims 77-94, wherein the antibody, or antigen-binding fragment thereof, is administered at a dosage of about or 0.1 mg/kg to 100 mg/kg, 0.5 mg/kg to 50 mg/kg, 5 mg/kg to 50 mg/kg, 5 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.

96. The method of any of claims 77-95, wherein the antibody, or antigen-binding fragment thereof, is administered at a dosage of about or 0.01 mg/m^2 to about or 800 mg/m^2.

97. The method of any of claims 77-96, wherein the antibody, or antigen-binding fragment thereof, is administered at a dosage of at least or at least about or about or 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.

98. A pharmaceutical composition of any of claims 71-76 formulated as a medicament for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

99. Use of a pharmaceutical composition of any of claims 71-76 for treating a condition responsive to treatment with an anti-EGFR antibody in a subject.

100. The pharmaceutical composition of claim 98 or the use of claim 99, wherein the condition responsive to treatment with an anti-EGFR antibody is a tumor, cancer or metastasis.

101. The pharmaceutical composition or use of claim 100, wherein the tumor expressess EGFR.

102. The pharmaceutical composition or use of claim 100 or claim 101, wherein the tumor is a solid tumor.

103. The pharmaceutical composition or use of any of claims 99-102, wherein the condition responsive to treatment with an anti-EGFR antibody is head and neck cancer, non-small cell lung cancer or colorectal cancer.

CLAIMS:

1. A modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising the amino acid replacement Y104D in the variable heavy chain of the unmodified antibody, wherein:

the modified anti-EGFR antibody or antigen-binding fragment thereof comprises a variable heavy (VH) chain and a variable light (VL) chain, or a portion thereof that is sufficient to bind EGFR antigen, whereby one or both of the VH or VL is modified;

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement;

the unmodified anti-EGFR antibody is selected from among:

i) cetuximab, or an antigen-binding fragment thereof, comprising a variable heavy chain set forth in SEQ ID NO:3 and a variable light chain set forth in SEQ ID NO:4 or 10;

ii) a variant of i) comprising a variable heavy chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:3, and a variable light chain having a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:4 or 10, wherein the variant does not comprise the amino acid replacement and specifically binds to EGFR; and

iii) a humanized form of i) or ii).

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

the modified anti-EGFR antibody, or antigen-binding fragment thereof, exhibits a ratio of binding activity to human epidermal growth factor receptor (EGFR) or a soluble fragment thereof under conditions in a tumor environment compared to under conditions in a non-tumor environment of at least 2.0 or at least 3.0;

conditions in a tumor environment comprise one or both of pH between or about between 6.0 to 6.5 or lactate concentration between or about between 5 mM to 20 mM, and protein concentration of 10 mg/mL to 50 mg/mL;

conditions in a non-tumor environment comprise one or both of pH of about 7.4 or lactate concentration between or about between 0.5 mM to 5 mM, and protein concentration of 10 mg/mL to 50 mg/mL , whereby the anti-EGFR antibody or fragment thereof is conditionally active under conditions in a tumor microenvironment.

3. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 1 , wherein the anti-EGFR antibody, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions that exist in a tumor microenvironment that comprise a pH of between or about between 6.0 to 6.5 compared to under conditions that exist in a non-tumor microenvironment that comprise a pH of about 7.4.

4. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-3, wherein the anti-EGFR antibody or, or antigen-binding fragment thereof, exhibits the ratio of activity under conditions of a tumor microenvironment that comprise pH of 6.0 to 6.5 and lactate concentration of 10 mM to 20 mM compared to under condition of a non-tumor microenvironment that comprise pH of 7.0 to 7.4, inclusive, and lactate concentration of 0.5 mM to 2 mM.

5. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-4 , wherein the protein concentration under conditions in a tumor microenvironment and under conditions in a non-tumor microenvironment is substantially the same or is the same.

6. The anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-5, comprising:

a) a variable heavy (VH) chain comprising the sequence of amino acids set forth in SEQ ID NO:495, 1062, 1112, 1114-1117, 1124-1126, 1128-1130, 1134-1137, or 1146-1152, or a sequence of amino acids that exhibits at least 85% sequence identity to any of SEQ ID NOS: 495, 1062, 1112, 1114-1117, 1124-1126, 1128-1130, 1134-1137, or 1146-1152; and

b) a variable light (VL) chain comprising the sequence of amino acids set forth in SEQ ID NO:4, 10, 1138-1145, 1153-1159 or 1186, or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4, 10, 1138-1145, 1153-1159 or 1186.

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

a) the variable heavy chain set forth in SEQ ID NO:495 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:495, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

b) the variable heavy chain set forth in SEQ ID NO:1062 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1062, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

c) the variable heavy chain set forth in SEQ ID NO:1112 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1112, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

d) the variable heavy chain set forth in SEQ ID NO:1114 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1114, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

e) the variable heavy chain set forth in SEQ ID NO:1115 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1115, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

f) the variable heavy chain set forth in SEQ ID NO:1116 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1116, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

g) the variable heavy chain set forth in SEQ ID NO:1117 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1117, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

h) the variable heavy chain set forth in SEQ ID NO:1124 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1124, and the variable light chain set forth

in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

i) the variable heavy chain set forth in SEQ ID NO:1125 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1125, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

j) the variable heavy chain set forth in SEQ ID NO:1126 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1126, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

k) the variable heavy chain set forth in SEQ ID NO:1128 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1128, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

l) the variable heavy chain set forth in SEQ ID NO:1129 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1129, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

m) the variable heavy chain set forth in SEQ ID NO:1130 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1130, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10;

n) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

o) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1139 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1139;

p) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1138 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1138;

q) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1140 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1140;

r) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1141 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1141;

s) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth

in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

t) the variable heavy chain set forth in SEQ ID NO:1135 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1135, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

u) the variable heavy chain set forth in SEQ ID NO:1134 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1134, and the variable light chain set forth in SEQ ID NO:1143 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1143;

v) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1142 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1142;

w) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

x) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1144 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1144;

y) the variable heavy chain set forth in SEQ ID NO:1137 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1137, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

z) the variable heavy chain set forth in SEQ ID NO:1136 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1136, and the variable light chain set forth in SEQ ID NO:1145 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1145;

aa) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

bb) the variable heavy chain set forth in SEQ ID NO:1147 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1147, and the variable light chain set forth in SEQ ID NO:1153 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1153;

cc) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

dd) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth

in SEQ ID NO:1154 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1154;

ee) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1155 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1155;

ff) the variable heavy chain set forth in SEQ ID NO:1151 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1151, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

gg) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

hh) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1156 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1156;

ii) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

jj) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

kk) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

ll) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

mm) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

nn) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

oo) the variable heavy chain set forth in SEQ ID NO:1148 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1148, and the variable light chain set forth

in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

pp) the variable heavy chain set forth in SEQ ID NO:1149 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1149, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186;

qq) the variable heavy chain set forth in SEQ ID NO:1150 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1150, and the variable light chain set forth in SEQ ID NO:1158 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1158;

rr) the variable heavy chain set forth in SEQ ID NO:1152 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1152, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

ss) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1159 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1159;

tt) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1157 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1157;

uu) the variable heavy chain set forth in SEQ ID NO:1146 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1146, and the variable light chain set forth in SEQ ID NO:1186 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1186; and

vv) the variable heavy chain set forth in SEQ ID NO:1118 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:1118, and the variable light chain set forth in SEQ ID NO:4 or 10 or a sequence of amino acids that exhibits at least 85% sequence identity to SEQ ID NO:4 or 10.

8. The anti-EGFR antibody, or antigen-binding fragment thereof, of claim 6 or claim 7, wherein sequence identity is at least 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 98%, 99% or more.

9. The modified anti-EGFR antibody or fragment thereof of claim 1, wherein:

a) the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among V24E, V24I, V24L, S25C, S25H, S25R, S25A, S25D, S25G, S25M, S25Q, S25V, S25L, S28C, L29H, N31H, G54D, G54S, F63R, F63C, F63M, F63P, F63S, T64V, L67G, D72L, D72P, D72W, N73Q, K75H, K75G, K75P, K75W, S76I, S76V, Q77E, T100P, Y104S, Y104V, Q111I and Q111V, with reference to amino acid positions set forth in SEQ ID NO:3, wherein:

corresponding amino acid positions are identified by alignment of the VH chain of the antibody with the VH chain set forth in SEQ ID NO:3; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement; and/or

b) the variable light chain, or portion thereof, of the modified anti-EGFR antibody contains an amino acid replacement corresponding to an amino acid replacement selected from among L4F, L4V, T5P and R24G, with reference to amino acid positions set forth in SEQ ID NO:4, wherein:

corresponding amino acid positions are identified by alignment of the VL chain of the antibody with the VL chain set forth in SEQ ID NO:4; and

the portion thereof is sufficient to form an antigen binding site and contains the amino acid replacement.

10. The modified anti-EGFR antibody of claim 9, wherein:

the variable heavy chain, or portion thereof, of the modified anti-EGFR antibody contains a further amino acid replacement selected from among V24E, S25C, S25V, F27R, T30F, S53G, D72L, R97H, Y104D and Q111P.

11. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-10, wherein the unmodified cetuximab antibody, antigen-binding fragment thereof or variant thereof comprises:

a heavy chain having a sequence of amino acids set forth in SEQ ID NO:1 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:1 and a light chain having a sequence of amino acids set forth SEQ ID NO:2 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:2; or

a heavy chain having a having a sequence of amino acids set forth in SEQ ID NO: 8 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:8 and a light chain having a sequence of amino acids set forth SEQ ID NO:9 or a sequence of amino acids that exhibits at least 85% sequence identity to the sequence of amino acids set forth in SEQ ID NO:9.

12. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-11, wherein the unmodified anti-EGFR antibody is humanized.

13. The modified anti-EGFR antibody, or antigen-binding fragment thereof, of claim 12 wherein the unmodified anti-EGFR antibody comprises the variable heavy chain set forth in SEQ ID NO:28 and the variable light chain set forth in SEQ ID NO:29.

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

the unmodified anti-EGFR antibody is an antigen-binding fragment; and

the antigen-binding fragment is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

15. The modified anti-EGFR antibody or antigen binding fragment of any of claims 1-14 that is a full-length IgG antibody or is an antigen-binding fragment selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, diabody, Fd and Fd' fragments.

16. A conjugate, comprising a modified anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15 linked directly or indirectly to a targeted agent.

17. The conjugate of claim 16, wherein the targeted agent is a therapeutic moiety.

18. The conjugate of claim 17, wherein the therapeutic moiety is a cytotoxic moiety, a radioisotope, a chemotherapeutic agent, a lytic peptide or a cytokine.

19. The conjugate of claim 18, wherein the therapeutic moiety is selected from among taxol; cytochalasin B; gramicidin D; ethidium bromide; emetine; mitomycin; etoposide; tenoposide; vincristine; vinblastine; colchicin; 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 analogue 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,l-c][l, 4]-benzodiazepines (PDB); a toxin; ribonuclease (RNase); DNase I, Staphylococcal enterotoxin A; and pokeweed antiviral protein.

20. The conjugate of claim 18 or claim 19, wherein the therapeutic moiety is a maytansine derivative that is a maytansinoids selected from among ansamitocin or mertansine (DM1) or is an auristatin or a functional peptide analog or derivative thereof that is monomethyl auristatin E (MMAE) or F (MMAF); or isis an antimetabolite selected from among methotrexate, 6 mercaptopurine, 6 thioguanine, cytarabine, fludarabin, 5 fluorouracil, decarbazine, hydroxyurea, asparaginase, gemcitabine, and cladribine; or is

an alkylating agent selected from among mechlorethamine, thioepa, chlorambucil, melphalan, carmustine (BSNU), lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, dacarbazine (DTIC), procarbazine and mitomycin C; or is a platinum derivative that is cisplatin or carboplatin or is an antibiotic selected from among dactinomycin, bleomycin, daunorubicin, doxorubicin, idarubicin, mithramycin, mitomycin, mitoxantrone, plicamycin and anthramycin (AMC); or 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, mitogellin, restrictocin, phenomycin, and enomycin toxins.

21. 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 1-15; and/or

a nucleic acid molecule, comprising a sequence of nucleotides encoding the light chain of any of the anti-EGFR antibody, or antigen-binding fragment thereof, of any of claims 1-15.

22. A vector, comprising the nucleic acid molecule(s) of claim 21.

23. A cell, comprising a vector or vectors of claim 22.

24. A method of making a modified anti-EGFR antibody, or antigen-binding fragment thereof, comprising expressing the heavy chain or light chain encoded from a vector or vectors of claim 22 encoding the heavy chain and the light chain in a suitable host cells and recovering the antibody.

25. A pharmaceutical composition comprising:

a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-15 or a conjugate of any of claims 16-20; and

a pharmaceutically acceptable carrier or excipient.

26. The pharmaceutical composition claim 25 for treating a tumor, cancer or metastasis.

27. Use of a modified anti-EGFR antibody or antigen-binding fragment of any of claims 1-15 or a conjugate of any of claims 16-20 for preparation of a medicament for treating a tumor, cancer or metastasis.