antigen-binding fragments thereof; or epitope binding fragments of antibodies such as single-chain, Fv, sFv, scFv, Fab, Fab', and F(ab')2 (Parham, J. Immunol. 131:2895-2902 (1983); Spring et al, J. Immunol. 113:470-478 (1974); Nisonoff et al, Arch. Biochem. Biophys. 89:230-244 (1960)).

[0079] Particularly useful EGFR antibodies for generation of EGFR immunoconjugates are described in co-pending US Appl. Pub. No. 2012/0156217. One such antibody, huEGFR-7R is a humanized antibody that comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NOs: 2 or 3. In one embodiment, the EGFR immunoconjugate comprises a humanized EGFR-7 antibody or antigen binding fragment thereof that specifically binds EGFR comprising (a) an immunoglobulin heavy chain variable region comprising the heavy chain CDR1 sequence of TSYWMQ (SEQ ID NO:4); a heavy chain CDR2 sequence selected from the group consisting of: TIYPGDGDTT (SEQ ID NO:5), and $Xaa_1Xaa_2YPGDGDXaa_3Xaa_4$ (SEQ ID NO:7), wherein Xaa_1 is T or A, Xaa_2 is I or L, Xaa_3 is T or A, Xaa_4 is T, R, or S, Xaa_5 is Y, T, or I, and Xaa_6 is Q or K; and a heavy chain CDR3 sequence selected from the group consisting of: YDAPGYAMDY (SEQ ID NO:6) and $YDAPGYXaa_1MDY$ (SEQ ID NO:8), wherein Xaa1 is A or T; and (b) an immunoglobulin light chain variable region comprising a light chain CDR1 sequence selected from the group consisting of: KASQDINNYLA (SEQ ID NO:9), RASQDINNYLA (SEQ ID NO:12), and $Xaa_1ASQDINNYXaa_2A$ (SEQ ID NO:13), wherein Xaa_1 is K or R and Xaa_2 is L or I; the light chain CDR2 sequence of YTSTLHP (SEQ ID NO:10); and the light chain CDR3 sequence of LQYDNLLYT (SEQ ID NO:11).

huEGFR-7R V_H	QVQLVQSGAEVAKPGASVKLSCKASGYTFTSYWMQWVKQRPGQGLECIGTIYP GDGDTTYTQKFQGKATLTADKSSSTAYMQLSSLRSEDSAVYYCARYDAPGYAM DYWGQGTLVTVSS (SEQ ID NO:1)
huEGFR-7R VL v1.0	DIQMTQSPSSLSASVGDRVTITCRASQDINNYLAWYQHKPGKGPKLLIHYTSTLH P GIPSRFSGSGSGRDYSFSISSLEPEDIATYYCLQYDNLLYTFGQGTKLEIKR (SEQ ID NO:2)
huEGFR-7R VL v1.01	DIQMTQSPSSLSASVGDRVTITCKASQDINNYLAWYQHKPGKGPKLLIHYTSTLH P GIPSRFSGSGSGRDYSFSISSLEPEDIATYYCLQYDNLLYTFGQGTKLEIKR (SEQ ID NO:3)

[0080] Other EGFR antibodies are known in the art. These antibodies include necitumumab, cetixumab, panitumumab, nimotuzumab, zalutumumab, mAb 806 (*J Clin Invest.* 2007;117(2):346–352).

III. EGFR Immunoconjugates

[0081] The present invention is also directed to conjugates (also referred to herein as immunoconjugates), comprising the anti-EGFR antibodies, antibody fragments, and their functional equivalents as disclosed herein, linked or conjugated to a drug or prodrug. Suitable drugs or prodrugs

are known in the art. The drugs or prodrugs can be cytotoxic agents. The cytotoxic agent used in the cytotoxic conjugate of the present invention can be any compound that results in the death of a cell, or induces cell death, or in some manner decreases cell viability, and includes, for example, maytansinoids and maytansinoid analogs. Other suitable cytotoxic agents are for example benzodiazepines, taxoids, CC-1065 and CC-1065 analogs, duocarmycins and duocarmycin analogs, enediynes, such as calicheamicins, dolastatin and dolastatin analogs including auristatins, tomaymycin derivatives, leptomycin derivaties, methotrexate, cisplatin, carboplatin, daunorubicin, doxorubicin, vincristine, vinblastine, melphalan, mitomycin C, chlorambucil and morpholino doxorubicin.

[0082] Immunoconjugates can be prepared by using a linking group in order to link a drug or prodrug to the antibody or functional equivalent. Suitable linking groups are well known in the art

WHAT IS CLAIMED IS:

1. Use of an epidermal growth factor receptor (EGFR) antibody immunoconjugate in the manufacture of a medicament for the treatment of EGFR-expressing tumor cells that are resistant or refractory to EGFR therapy, wherein said medicament is to be contacted with said tumor cells in an amount effective for inhibiting the growth of said tumor cells.

2. The use of claim 1, wherein said therapy comprised administration of an EGFR antibody or an EGFR kinase inhibitor.

3. The use of claims 1 or 2, wherein the EGFR therapy to which the cells are resistant is selected from the group consisting of: erlotinib, gefitinib, lapatinib, BIB2992, cetuximab, panitumumab, zalutumumab, necitumumab, and nimotuzumab.

4. The use of any of claims 1-3, wherein at least one of the tumor cells: (1) contains one or more mutations in an EGFR-encoding gene; (2) contains one or more mutations in a PIK3CA, RAS, or PTEN encoding gene; (3) has an activated MET or IGF1R pathway; (4) has mesenchymal histology or has undergone epithelial-mesenchymal transition; or (5) has ERBB2 gene amplification or increased production of HER2 protein.

5. The use of claim 4, wherein the mutated EGFR gene comprises a EGFRvIII or T790M mutation.

6. The use of claim 4, wherein said at least one tumor cell contains one or more mutations in a PIK3CA, RAS, or PTEN encoding genes.

7. The use of claim 4, wherein the MET or IGF1R pathway is activated.

8. Use of an EGFR antibody immunoconjugate in the manufacture of a medicament for the treatment of cancer in a subject, wherein said medicament is to be administered to said subject in an amount effective for inhibiting the growth of tumor cells in said subject, wherein at least one of the tumor cells: (1) contains one or more mutations in an EGFR-

encoding gene; (2) contains one or more mutations in a PIK3CA, RAS, or PTEN encoding gene; (3) has an activated MET or IGF1R pathway; (4) has mesenchymal histology or has undergone epithelial-mesenchymal transition; or (5) has ERBB2 gene amplification or increased production of HER2 protein.

9. Use of an EGFR antibody immunoconjugate in the manufacture of a medicament for the treatment of cancer in a subject, wherein tumor cells from said subject have been identified that (1) contain one or more mutations in an EGFR-encoding gene; (2) contain one or more mutations in a PIK3CA, RAS, or PTEN encoding gene; (3) have an activated MET or IGF1R pathway; or (4) have mesenchymal histology or have undergone epithelial-mesenchymal transition; and wherein said medicament is to be administered to said subject in an amount effective for inhibiting the growth of said tumor cells in said subject.

10. The use of claims 8 or 9, wherein said cancer is a squamous cell cancer, lung cancer, head and neck cancer, or an EGFR-positive cancer.

11. The use of claims 1-4, or 7-9, wherein said MET activation is caused by MET gene amplification.

12. The use of any of claims 8-11, wherein said subject previously failed or is currently failing an EGFR therapy.

13. The use of claim 12, wherein said therapy comprised administration of an EGFR antibody or an EGFR kinase inhibitor.

14. The use of claim 13, wherein said EGFR antibody is cetuximab or panitumumab.

15. The use of claim 13, wherein said EGFR kinase inhibitor is erlotinib or gefitinib.

16. Use of an EGFR antibody immunoconjugate in the manufacture of a medicament for the treatment of cancer in a subject, wherein said medicament is to be administered to said

subject in an amount effective for inhibiting the growth of tumor cells in said subject, wherein at least one of the tumor cells is resistant to therapy comprising an anaplastic lymphoma kinase (ALK) inhibitor.

17. Use of an EGFR antibody immunoconjugate in the manufacture of a medicament for the treatment of cancer in a subject, wherein tumor cells from said subject have been identified that are resistant to at least one ALK inhibitor; and wherein said medicament is to be administered to said subject in an amount effective for inhibiting the growth of said tumor cells in said subject.

18. The use of claims 16 or 17, wherein at least one of the tumor cells contains an EML4-ALK translocation.

19. The use of any one of claims 16-18, wherein the cancer is non-small cell lung cancer.

20. The use of any of claims 16-19, wherein the ALK inhibitor is crizotinib.

21. The use of any of claims 1-20, wherein said immunoconjugate has the formula (A) - (L) - (C), wherein:
(A) is an antibody or antigen binding fragment thereof that specifically binds EGFR;
(L) is a linker; and
(C) is a cytotoxic agent; and
wherein said linker (L) links (A) to (C).

22. The use of claim 21, wherein said EGFR antibody comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NOs:2 or 3.

23. The use of claim 22, wherein said linker is selected from the group consisting of a cleavable linker, a non-cleavable linker, a hydrophilic linker, and a dicarboxylic acid based linker.

24. The use of claim 23, wherein said linker is a non-cleavable linker.

25. The use of claim 21, wherein said linker is selected from the group consisting: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB) or N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB); N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC); N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfoSMCC); N-succinimidyl-4-(iodoacetyl)-aminobenzoate (SIAB); N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide); N-(beta-maleimidopropyloxy)succinimide ester (BMPS); and gamma-maleimidobutyric acid N-succinimidyl ester (GMBS).

26. The use of claim 21, wherein said cytotoxic agent is selected from the group consisting of a maytansinoid, maytansinoid analog, doxorubicin, a modified doxorubicin, benzodiazepine, taxoid, CC-1065, CC-1065 analog, duocarmycin, duocarmycin analog, calicheamicin, dolastatin, dolastatin analog, auristatin, tomaymycin derivative, and leptomycin derivative or a prodrug of the agent.

27. The use of claim 26, wherein said cytotoxic agent is a maytansinoid.

28. The use of claim 27, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1) or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

29. The use of any of claims 1-28, wherein the EGFR antibody immunoconjugate comprises an antibody which comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NOs:2 or 3; the linker SMCC; and the maytansinoid DM1.

30. The use of any of claims 1-29, wherein the EGFR antibody immunoconjugate is administered with an anti-neoplastic agent.

31. The use of claim 30, wherein the EGFR antibody immunoconjugate is administered simultaneously with the anti-neoplastic agent.

32. The use of claim 30, wherein the EGFR antibody immunoconjugate and anti-neoplastic agent are administered in any temporal order.

33. The use of any of claims 8-32, wherein said subject is a human.

WHAT IS CLAIMED IS:

1. Use of an epidermal growth factor receptor (EGFR) antibody immunoconjugate in the manufacture of a medicament for inhibiting the growth of EGFR-expressing tumor cells that are resistant or refractory to an EGFR antibody therapy, wherein said medicament is to be contacted with said tumor cells in an amount effective for inhibiting the growth of said tumor cells; wherein the immunoconjugate has the formula (A) - (L) - (C), wherein:

(A) is an antibody or antigen binding fragment thereof that specifically binds EGFR and comprises a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO:4, a CDR2 sequence of SEQ ID NO: 5 or 7, and a CDR3 sequence of SEQ ID NO: 6 or 8; and a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 9, 12, or 13, a CDR2 sequence of SEQ ID NO:10, and a CDR3 sequence of SEQ ID NO:11;

(L) is a linker selected from the group consisting of: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB); N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC); N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfoSMCC); N-succinimidyl-4-(iodoacetyl)-aminobenzoate (SIAB); N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide); N-(beta-maleimidopropyloxy)succinimide ester (BMPS); and gamma-maleimidobutyric acid N-succinimidyl ester (GMBS); and

(C) is a cytotoxic agent; and

wherein said linker (L) links (A) to (C).

2. The use of claim 1, wherein said therapy comprised administration of an EGFR antibody.

3. The use of claim 1 or 2, wherein the EGFR therapy to which the cells are resistant is selected from the group consisting of: cetuximab, panitumumab, zalutumumab, necitumumab, and nimotuzumab.

4. The use of any one of claims 1-3, wherein at least one of the tumor cells: (1) contains one or more mutations in an EGFR-encoding gene; (2) contains one or more mutations in a PIK3CA, RAS, or PTEN encoding gene; (3) has an activated MET pathway; (4) has mesenchymal histology or has undergone epithelial-mesenchymal transition; or (5) has ERBB2 gene amplification or increased production of HER2 protein.

5. The use of claim 4, wherein at least one of the tumor cells contains one or more mutations in an EGFR-encoding gene.

6. The use of claim 5, wherein the mutated EGFR gene comprises a EGFRvIII mutation.

7. The use of claim 4, wherein said at least one of the tumor cells contains one or more mutations in a PIK3CA, RAS, or PTEN encoding genes.

8. The use of claim 4, wherein at least one of the tumor cells has an activated MET pathway.

9. The use of claim 8, wherein said MET pathway activation is caused by MET gene amplification.

10. Use of an EGFR antibody immunoconjugate in the manufacture of a medicament for the treatment of cancer in a subject with a tumor comprising tumor cells that are resistant or refractory to an EGFR antibody therapy, wherein said medicament is to be administered to said subject in an amount effective for inhibiting the growth of tumor cells in said subject, and wherein the immunoconjugate has the formula (A) - (L) - (C), wherein:

(A) is an antibody or antigen binding fragment thereof that specifically binds EGFR and comprises a heavy chain variable region comprising a CDR1 sequence of SEQ ID NO:4, a CDR2 sequence of SEQ ID NO: 5 or 7, and a CDR3 sequence of SEQ ID NO: 6 or 8; and a light chain variable region comprising a CDR1 sequence of SEQ ID NO: 9, 12, or 13, a CDR2 sequence of SEQ ID NO:10, and a CDR3 sequence of SEQ ID NO:11;

(L) is a linker selected from the group consisting of: N-succinimidyl 4-(2-pyridyldithio)pentanoate (SPP); N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB); N-succinimidyl 4-(2-pyridyldithio)-2-sulfobutanoate (sulfo-SPDB); N-succinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (SMCC); N-sulfosuccinimidyl 4-(maleimidomethyl) cyclohexanecarboxylate (sulfoSMCC); N-succinimidyl-4-(iodoacetyl)-aminobenzoate (SIAB); N-succinimidyl-[(N-maleimidopropionamido)-tetraethyleneglycol] ester (NHS-PEG4-maleimide); N-(beta-maleimidopropyloxy)succinimide ester (BMPS); and gamma-maleimidobutyric acid N-succinimidyl ester (GMBS); and

(C) is a cytotoxic agent; and

wherein said linker (L) links (A) to (C).

11. The use of claim 10, wherein at least one of the tumor cells: (1) contains one or more mutations in an EGFR-encoding gene; (2) contains one or more mutations in a PIK3CA, RAS, or PTEN encoding gene; (3) has an activated MET pathway; (4) has mesenchymal histology or has undergone epithelial-mesenchymal transition; or (5) has ERBB2 gene amplification or increased production of HER2 protein.

12. The use of claim 10 or 11, wherein said cancer is a squamous cell cancer, lung cancer, head and neck cancer, or an EGFR-positive cancer.

13. The use of any one of claims 10-12, wherein the at least one of the tumor cells contains one or more mutations in an EGFR-encoding gene.

14. The use of claim 13, wherein the mutated EGFR gene comprises a EGFRvIII mutation.

15. The use of any one of claims 10-12, wherein the at least one of the tumor cells contains one or more mutations in a PIK3CA, RAS, or PTEN encoding gene.

16. The use of any one of claims 10-12, wherein the at least one of the tumor cells has an activated MET pathway, wherein said MET activation is caused by MET gene amplification.

17. The use of any one of claims 10-16, wherein said subject previously failed or is currently failing an EGFR antibody therapy.

18. The use of claim 17, wherein said EGFR antibody therapy comprises administration of an EGFR antibody selected from the group consisting of cetuximab, panitumumab, zalutumumab, necitumumab, and nimotuzumab.

19. The use of any one of claims 10-18, wherein the tumor further comprises at least one tumor cell that is resistant to therapy comprising an anaplastic lymphoma kinase (ALK) inhibitor.

20. The use of claim 19, wherein tumor cells from said subject have been identified that are resistant to at least one ALK inhibitor.

21. The use of claim 19 or 20, wherein the at least one tumor cell that is resistant to therapy comprising an ALK inhibitor contains an EML4-ALK translocation.

22. The use of any one of claims 19-21, wherein the cancer is non-small cell lung cancer.

23. The use of any one of claims 19-22, wherein the ALK inhibitor is crizotinib.

24. The use of any one of claims 1-23, wherein said antibody or antigen binding fragment thereof that specifically binds EGFR comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NO: 2 or 3.

25. The use of any one of claims 1-24, wherein said cytotoxic agent is selected from the group consisting of: a maytansinoid, maytansinoid analog, doxorubicin, a modified doxorubicin, benzodiazepine, taxoid, CC-1065, CC-1065 analog, duocarmycin, duocarmycin analog, calicheamicin, dolastatin, dolastatin analog, auristatin, tomaymycin derivative, and leptomycin derivative or a prodrug of the cytotoxic agent.

26. The use of claim 25, wherein said cytotoxic agent is a maytansinoid.

27. The use of claim 26, wherein said cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1) or N(2')-deacetyl-N(2')-(4-mercapto-4-methyl-1-oxopentyl)-maytansine (DM4).

28. The use of any one of claims 1-27, wherein the antibody or antigen binding fragment thereof that specifically binds EGFR comprises the heavy chain variable region of SEQ ID NO:1 and the light chain variable region of SEQ ID NO: 2 or 3; wherein the linker is SMCC; and wherein the cytotoxic agent is N(2')-deacetyl-N(2')-(3-mercapto-1-oxopropyl)-maytansine (DM1).

29. The use of any one of claims 10-28, wherein said subject is a human.

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His Tyr Thr Ser Thr Leu His Pro Gly Ile Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Arg Asp Tyr Ser Phe Ser Ile Ser Ser Leu Glu Pro
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SEQUENCE LISTING

<110> IMMUNOGEN, INC.

<120> METHOD OF TREATMENT OF TUMORS THAT ARE RESISTANT TO EGFR THERAPIES BY EGFR ANTIBODY CYTOTOXIC AGENT CONJUGATE

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His Tyr Thr Ser Thr Leu His Pro Gly Ile Pro Ser Arg Phe Ser Gly
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