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(54) Title: DOSAGE AND ADMINISTRATION OF ANTI-ERBB3 ANTIBODIES IN COMBINATION WITH TYROSINE KINASE INHIBITORS

(57) Abstract: Provided are methods and compositions for clinical treatment of NSCLC using anti- ErbB3 antibodies combined with use of TKIs such as erlotinib or gefitinib.



DOSAGE AND ADMINISTRATION OF ANTI-ERBB3 ANTIBODIES IN COMBINATION WITH TYROSINE KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application No. 61/497,834 filed June 16, 2011, U.S. Provisional Application No. 61/555,141 filed November 3, 2011, U.S. Provisional Application No. 61/596,097 filed February 7, 2012, U.S. Provisional Application No. 61/602,365 filed February 23, 2012, and U.S. Provisional Application No. 61/616,912 filed March 28, 2012, all of which are incorporated herein by reference.

BACKGROUND

Despite improvements in lung cancer therapies and late-stage options, more people die from lung cancer than any other type of cancer. Lung cancer claims more lives than breast cancer, prostate cancer and colon cancer, combined. There remains a critical need to optimize established therapies and develop new, promising therapies which prolong patients' lives while maintaining a high quality of life.

The ErbB3 receptor is 148 kilodalton (kD) transmembrane receptor tyrosine kinase belonging to the ErbB/EGFR family and is known to be kinase dead. The ErbB family of transmembrane receptor tyrosine kinases impacts the physiology of cells and organs by eliciting ligand-dependent activation of multiple signal transduction pathways. However, ErbB3-containing heterodimers (such as ErbB2/ErbB3) in tumor cells have been shown to be the most mitogenic and oncogenic receptor complex within the ErbB family. Upon binding of heregulin (HRG), the physiological ligand for the ErbB3 receptor, ErbB3 dimerizes with other ErbB family members, preferentially ErbB2. ErbB3/ErbB2 dimerization results in transphosphorylation of ErbB3 on tyrosine residues contained within the cytoplasmic tail of the protein. Phosphorylation of these sites creates SH2 docking sites for SH2-containing proteins, including PI3-kinase. ErbB3-containing heterodimeric complexes are potent activators of AKT as ErbB3 possesses six tyrosine phosphorylation sites with YXXM motifs that, when phosphorylated, serve as excellent binding sites for phosphoinositol-3-kinase (PI3K) the action of which results in

subsequent downstream activation of the AKT pathway. These six PI3K sites serve as a strong amplifier of ErbB3 signaling. Activation of this pathway further elicits several important biological processes involved in tumorigenesis, such as cell growth and survival.

Heregulin, a cognate ligand of ErbB2/ErbB3 heterodimers, has been shown to be involved in several different types of cancer, including breast, ovarian, endometrial colon, gastric, lung, thyroid, glioma, medulloblastoma, melanoma as well as head and neck squamous cell carcinoma. In most of these tumor types, HRG regulates growth, invasion and angiogenesis through either over expression or the activation of an autocrine or paracrine loop. Disruption of the heregulin autocrine loop by blocking HRG binding or disruption of the ErbB2/ErbB3 dimer may provide an important therapeutic measure to control growth in certain cancers.

SUMMARY

Provided are compositions and methods for treating non-small-cell lung cancer (NSCLC) in a human patient, comprising administering to the patient a combination of an anti-ErbB3 antibody and a small molecule tyrosine kinase inhibitor (TKI), wherein the combination is administered according to a particular clinical dosage regimen (i.e., at a particular dose amount and according to a specific dosing schedule).

An exemplary anti-ErbB3 antibody is Antibody A (including antigen binding fragments and variants thereof). In one embodiment, the anti-ErbB3 antibody comprises variable heavy (VH) and/or variable light (VL) regions encoded by the nucleic acid sequences set forth in SEQ ID NOs:1 and 3, respectively. In another embodiment, the antibody comprises VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs 2 and 4, respectively. In another embodiment, the antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and/or CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3). In another embodiment, an antibody is used that competes for binding with and/or binds to the same epitope on human ErbB3 as the above-mentioned antibodies. In a particular embodiment, the

epitope comprises residues 92-104 of human ErbB3 (SEQ ID NO: 11). In another embodiment, the antibody competes with Antibody A for binding to human ErbB3 and has at least 90% variable region amino acid sequence identity with the above-mentioned anti-ErbB3 antibodies.

Small molecule TKIs useful in the methods disclosed herein include erlotinib, gefitinib, vandetanib, lapatinib, afatinib and neratinib.

Accordingly, in one aspect, compositions and methods for treating non-small-cell lung cancer (NSCLC) in a human patient are provided, the methods comprising administering the composition in combination with erlotinib, the composition comprising: an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) for treatment of the patient in combination with erlotinib according to one or more of the following Dose Schedules 1, 2, 3, 3a, 4a, 4b, or 4c of Table 1. In one embodiment, the anti-ErbB3 antibody is Antibody A.

Table 1

Dose Schedule	Antibody Dose (mg/kg, i.v.)	Erlotinib Dose (mg, q.d., p.o.)	Antibody dosing schedule
1	6	100	6 mg/kg weekly dose
2	6	150	6 mg/kg weekly dose
3	12	150	12 mg/kg weekly dose
3a	12	100	12 mg/kg weekly dose
4a	20	100, 125 or 150	20 mg/kg weekly dose
4b	20	100, 125 or 150	20 mg/kg every other week
4c	20	100, 125 or 150	20mg/kg every third week

In one embodiment, the dose schedule is Dose Schedule 1, wherein the antibody is administered (or is for administration) intravenously at a dose of 6 mg/kg weekly with erlotinib administered orally at a dose of 100 mg per day.

In another embodiment, the dose schedule is Dose Schedule 2, wherein the antibody is administered (or is for administration) intravenously at a dose of 6 mg/kg weekly with erlotinib administered orally at a dose of 150 mg per day.

In yet another embodiment, the dose schedule is Dose Schedule 3, wherein the antibody is administered (or is for administration) intravenously at a dose of 12 mg/kg weekly with erlotinib administered orally at a dose of 150 mg per day.

In yet another embodiment, the dose schedule is Dose Schedule 3a, wherein the antibody is administered (or is for administration) intravenously at a dose of 12 mg/kg weekly with erlotinib administered orally at a dose of 100 mg per day.

In yet another embodiment, the dose schedule is Dose Schedule 4a, wherein the antibody is administered (or is for administration) intravenously at a dose of 20 mg/kg weekly with erlotinib administered orally at a dose of 100 or 150 mg per day.

In yet another embodiment, the dose schedule is Dose Schedule 4b, wherein the antibody is administered (or is for administration) intravenously at a dose of 20 mg/kg every other week with erlotinib administered orally at a dose of 100 or 150 mg per day.

In yet another embodiment, the dose schedule is Dose Schedule 4c, wherein the antibody is administered (or is for administration) intravenously at a dose of 20 mg/kg every third week with erlotinib administered orally at a dose of 100 or 150 mg per day.

In another aspect, methods of treating non-small-cell lung cancer (NSCLC) in a human patient are provided, the methods comprising: administering combination therapy to the patient comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), in combination with

gefitinib, according to one or more of the following Dose Schedules 5, 6, 7, 7a, 8a, 8b, or 8c of Table 2. In one embodiment, the anti-ErbB3 antibody is Antibody A.

Table 2

Dose Schedule	Antibody Dose (mg/kg, i.v.)	Gefitinib Dose (mg, q.d., p.o.)	Antibody dosing schedule
5	6	125	6 mg/kg weekly dose
6	6	250	6 mg/kg weekly dose
7	12	250	12 mg/kg weekly dose
7a	12	125	12 mg/kg weekly dose
8a	20	125 or 250	20 mg/kg weekly dose
8b	20	125 or 250	20 mg/kg every other week
8c	20	125 or 250	20mg/kg every third week

In another aspect, methods of treating non-small-cell lung cancer (NSCLC) in a human patient are provided, the methods comprising: administering combination therapy to the patient comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), in combination with vandetanib, according to one or more of the following Dose Schedules 9, 10, 11, 11a, 12a, 12b, or 12c of Table 3. In one embodiment, the anti-ErbB3 antibody is Antibody A.

Table 3

Dose Schedule	Antibody Dose (mg/kg, i.v.)	Vandetanib Dose (mg, q.d., p.o.)	Antibody dosing schedule
9	6	100 or 200	6 mg/kg weekly dose
10	6	300	6 mg/kg weekly dose
11	12	300	12 mg/kg weekly dose
11a	12	100 or 200	12 mg/kg weekly dose
12a	20	100, 200 or 300	20 mg/kg weekly dose
12b	20	100, 200 or 300	20 mg/kg every other week
12c	20	100, 200 or 300	20mg/kg every third week

In another aspect, methods of treating non-small-cell lung cancer (NSCLC) in a human patient are provided, the methods comprising: administering combination therapy to the patient comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), in combination with neratinib, according to one or more of the following Dose Schedules 13, 14, 15, 15a, 16a, 16b, or 16c of Table 4. In one embodiment, the anti-ErbB3 antibody is Antibody A.

Table 4

Dose Schedule	Antibody (mg/kg, i.v.)	Dose Neratinib Dose (mg, q.d., p.o.)	Antibody dosing schedule
13	6	about 120	6 mg/kg weekly dose
14	6	about 240	6 mg/kg weekly dose
15	12	about 240	12 mg/kg weekly dose
15a	12	about 120	12 mg/kg weekly dose
16a	20	about 120 or about 240	20 mg/kg weekly dose
16b	20	about 120 or about 240	20 mg/kg every other week
16c	20	about 120 or about 240	20mg/kg every third week

In another aspect, methods of treating non-small-cell lung cancer (NSCLC) in a human patient are provided, the methods comprising: administering combination therapy to the patient comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), in combination with lapatinib, according to one or more of the following Dose Schedules 17, 18, 19, 19a, 20a, 20b, or 20c of Table 5. In one embodiment, the anti-ErbB3 antibody is Antibody A.

Table 5

Dose Schedule	Antibody Dose (mg/kg, i.v.)	Lapatinib Dose (mg, q.d., p.o.)	Antibody dosing schedule
17	6	125	6 mg/kg weekly dose
18	6	250	6 mg/kg weekly dose
19	12	250	12 mg/kg weekly dose
19a	12	125	12 mg/kg weekly dose
20a	20	125 or 250	20 mg/kg weekly dose
20b	20	125 or 250	20 mg/kg every other week
20c	20	125 or 250	20mg/kg every third week

In additional embodiments (including embodiments comprising those involving Tables 1-5, above), the patient (i.e., a human subject) has locally advanced or metastatic NSCLC. In yet another embodiment, the patient has a NSCLC tumor in which the EGFR tyrosine kinase domain is wild-type, and the subject has previously undergone at least one chemotherapy-containing regimen. In yet another embodiment, the patient has a NSCLC tumor that has demonstrated acquired resistance to EGFR TKIs. In yet another embodiment, the patient has a NSCLC tumor in which the EGFR tyrosine kinase domain comprises an activating mutation, and the subject has not received any prior EGFR TKI therapy. In yet another embodiment, the patient has NSCLC that is characterized as having a mutation in the tyrosine kinase domain of EGFR that sensitizes the NSCLC to TKI treatment. In yet another embodiment, the patient has NSCLC that is characterized as having a mutation in the tyrosine kinase domain of EGFR (SEQ ID NO: 15) that is an exon 19 deletion of fewer than 10 contiguous amino acids comprising the deletion of amino acids R748 and E749 of the tyrosine kinase domain of EGFR (SEQ ID NO: 15). Patients can be tested or selected for one or more of the above described clinical attributes prior to, during or after treatment.

In another aspect, methods of selecting therapy for a patient having NSCLC are provided, wherein the method comprises: (a) determining whether the patient's cancer comprises an activating mutation of the EGFR tyrosine kinase domain; and (b) if so, administering to the patient an effective amount of (1) an anti-ErbB3 antibody comprising

CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (2) erlotinib. In one embodiment, the activating mutation of the EGFR tyrosine kinase domain is a deletion of residues E746-A750 of the EGFR tyrosine kinase domain (SEQ ID NO: 15). In another embodiment, the anti-ErbB3 antibody is Antibody A.

In another aspect, compositions for use in the treatment of a human patient diagnosed with NSCLC (non-small-cell lung cancer) in combination with treatment with a TKI (e.g., erlotinib, gefitinib, vandetanib or neratinib) are provided, the compositions comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), formulated for intravenous administration at a dose of 6 mg/kg. In one embodiment, the anti-ErbB3 antibody is Antibody A.

In still another aspect, compositions for use in the treatment of a human patient diagnosed with NSCLC in combination with treatment with a TKI (e.g., erlotinib, gefitinib, vandetanib or neratinib) are provided, the compositions comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), formulated for intravenous administration at a dose of 12 mg/kg. In one embodiment, the anti-ErbB3 antibody is Antibody A.

In yet another aspect, compositions for use in the treatment (e.g., effective treatment) of a human patient diagnosed with NSCLC in combination with treatment with a TKI (e.g., erlotinib, gefitinib, vandetanib or neratinib) are provided, said compositions comprising an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO:

6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), formulated for intravenous administration at a dose of 20 mg/kg.

In one embodiment, the antibody is for administration intravenously at a dose of 6 mg/kg weekly and the TKI is erlotinib, which is for administration orally daily at a dose of 100 mg per day, or the TKI is gefitinib, which is for administration orally daily at a dose of 125 mg per day, or with vandetanib administration orally daily at a dose of 150 mg per day, or with neratinib administration orally daily at a dose of 120 mg per day.

In another embodiment, the antibody is for administration intravenously at a dose of 6 mg/kg weekly in conjunction with erlotinib administration orally daily at a dose of 150 mg per day, or with gefitinib administration orally daily at a dose of 250 mg per day, or with vandetanib administration orally daily at a dose of 300 mg per day, or with neratinib administration orally daily at a dose of 240 mg per day.

In still another embodiment, the antibody is for administration intravenously at a dose of 12 mg/kg weekly in conjunction with erlotinib administration orally daily at a dose of 150 mg per day, or with gefitinib administration orally daily at a dose of 250 mg per day, or with vandetanib administration orally daily at a dose of 300 mg per day, or with neratinib administration orally daily at a dose of 240 mg per day.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a schematic diagram of the phase 2 clinical trial.

Figure 2 provides data from phase 1 clinical trial employing the combination of Antibody A and erlotinib. Cohort 1 includes patients treated with 6 mg/kg of Antibody A and erlotinib 100 mg/day. Cohort 2 includes patients treated with 6 mg/kg of Antibody A and erlotinib 150 mg/day. Cohort 3 includes patients treated with 12 mg/kg of Antibody A and erlotinib 150 mg/day. Cohort 3A includes patients treated with 12 mg/kg of Antibody A and erlotinib 100 mg/day. Cohort 4A includes patients treated with 20 mg/kg QW of Antibody A and erlotinib 100 mg/day. Cohort 4B includes patients treated with 20 mg/kg QOW of Antibody A and erlotinib 100 mg/day. Cohort 4C includes

patients treated with 20 mg/kg Q3W of Antibody A and erlotinib 100 mg/day. The heading of the right-hand column reads "Reason for Study Discontinuation."

Figure 3, panel A, shows the Phase 1 3+3 design which evaluated patients for toxicity, with escalating doses of Antibody A and erlotinib until maximum tolerated dose or maximum target dose was identified. Panel B shows history information on the 33 patients in the study.

Figure 4A provides a summary of adverse events by grade occurring in >10% of patients (n=33). Figure 4B provides a summary of number of adverse events >10% patients (n=33) by dosing cohorts. Cohort 1 = 6 mg/kg Antibody A, 100 mg erlotinib. Cohort 2 = 6 mg/kg Antibody A, 150 mg erlotinib. Cohort 3 = 12 mg/kg Antibody A, 150 mg erlotinib. Cohort 3A = 12 mg/kg Antibody A, 100 mg erlotinib. Cohort 4a = 20 mg/kg Antibody A administered weekly, 100 mg erlotinib. Cohort 4b = 20 mg/kg Antibody A administered every other week, 100 mg erlotinib. Cohort 4c = 20 mg/kg Antibody A administered every 3 weeks, 100 mg erlotinib.

Figure 5 shows Progression Free Survival (PFS) for all patients in the Phase I study as well as for patients in Groups A and Groups C.

Figure 6 provides a waterfall plot of overall survival data from the Phase I.

Figure 7 provides a cell viability plot and demonstrates that treating cancer cells having an activating mutation of the EGFR tyrosine kinase domain with a combination of Antibody A and erlotinib has a synergistic effect on cell viability.

Figure 8 shows the synergistic effects of Antibody A in combination with erlotinib in ACHN and HCC827 cells.

DETAILED DESCRIPTION

I. Definitions

As used herein, the term "subject" or "patient" is a human cancer patient.

As used herein, "effective treatment" refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder. A beneficial effect can take the form of an improvement over baseline, i.e., an improvement over a

measurement or observation made prior to initiation of therapy according to the method. A beneficial effect can also take the form of arresting, slowing, retarding, or stabilizing of a deleterious progression of a marker of NSCLC. Effective treatment may refer to alleviation of at least one symptom of non-small cell lung cancer. Such effective treatment may, e.g., reduce patient pain, reduce the size and/or number of lesions, may reduce or prevent metastasis of a tumor, and/or may slow tumor growth.

The term "effective amount" refers to an amount of an agent clinically proven to provide the desired biological, therapeutic, and/or prophylactic result. That result can be reduction, amelioration, palliation, lessening, delaying, and/or alleviation of one or more of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. In reference to cancers, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation. In some embodiments, an effective amount is an amount sufficient to delay tumor development. In some embodiments, an effective amount is an amount sufficient to prevent or delay tumor recurrence. An effective amount can be administered in one or more administrations. The effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and may stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and may stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer. In one example, an "effective amount" for therapeutic uses is the amount of Antibody A and the amount of erlotinib, gefitinib, neratinib, lapatinib or vandetanib required to provide a clinically significant decrease in NSCLC or slowing of progression of the NSCLC.

The term "antibody" includes antibodies and antibody variants comprising at least one antibody-derived antigen binding site (e.g., VH/VL region or Fv) that specifically binds to ErbB3. Antibodies include known forms of antibodies. For example, the antibody can be a human antibody, a humanized antibody, a bispecific antibody, or a chimeric antibody. The antibody also can be a Fab, Fab'2, ScFv, SMIP, AFFIBODY®,

nanobody, or a domain antibody. The antibody also can be of any of the following isotypes: IgG1, IgG2, IgG3, IgG4, IgM, IgA1, IgA2, IgAsec, IgD, and IgE.

As used herein, the term antibody variant includes naturally occurring antibodies which have been altered (e.g., by mutation, deletion, substitution, conjugation to a non-antibody moiety) to include at least one variant amino acid which changes a property of the antibody. For example, numerous such alterations are known in the art which affect, e.g., half-life, effector function, and/or immune responses to the antibody in a subject. The term antibody variant also includes artificial polypeptide constructs which comprise at least one antibody-derived antigen binding site.

The terms “tyrosine kinase inhibitor” or “TKI” refers to a small molecule (under 900 AMU) compound which selectively inhibits kinase activity mediated by one or more receptor tyrosine kinases. Examples of TKIs include erlotinib, gefitinib, imatinib, lapatinib, neratinib, nilotinib, sunitinib, and vandetanib.

II. Anti-ErbB3 Antibodies

Useful anti-ErbB3 antibodies (or VH/VL domains derived therefrom) can be made using methods well known in the art. Alternatively, art recognized anti-ErbB3 antibodies can be used. For example, Ab#3, Ab #14, Ab #17, Ab # 19, described in U.S. 7,846,440, can be used. Antibodies that compete with any of these antibodies for binding to ErbB3 also can be used. Additional art-recognized anti-ErbB3 antibodies which can be used include those disclosed in US 7,285,649; US20200310557; US20100255010, as well as antibodies IB4C3 and 2D1D12 (U3 Pharma Ag), both of which are described in e.g., US2004/0197332; anti-ErbB3 antibody referred to as AMG888 (U3-1287 – U3 Pharma Ag and Amgen); and monoclonal antibody 8B8, described in US 5,968,511. Other useful anti-ErbB3 antibodies are disclosed in the art in the context of a bispecific antibody (see e.g., B2B3-1 or B2B3-2 in WO/2009/126920 and those described in US 7,846,440 and US 2010/0266584, the entire contents of which are incorporated by reference herein. One example of such an antibody is Antibody A having heavy and light chains comprising the amino acid sequences set forth in SEQ ID NOs 12 and 13, respectively. Antibody A is referred to as “Ab #6” in US 7,846,440.

In one embodiment, the anti-ErbB3 antibody comprises variable heavy (VH) and/or variable light (VL) regions encoded by the nucleic acid sequences set forth in SEQ ID NOs: 1 and 3, respectively. In another embodiment, the antibody comprises VH and/or VL regions comprising the amino acid sequences set forth in SEQ ID NOs 2 and 4, respectively.

In another embodiment, the antibody comprises CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and/or CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3). In another embodiment, the antibody competes for binding with and/or binds to the same epitope on human ErbB3 as the above-mentioned antibodies. In a particular embodiment, the epitope comprises residues 92-104 of human ErbB3 (SEQ ID NO: 11). In another embodiment, the antibody binds to human ErbB3 and has at least 90% variable region sequence identity with the above-mentioned antibodies.

In other embodiments, the antibody is a fully human monoclonal antibody, such as an IgG2, that binds to ErbB3 and prevents the HRG and EGF-like ligand-induced phosphorylation of ErbB3.

Anti-ErbB3 antibodies, such as Antibody A, can be generated, e.g., in prokaryotic or eukaryotic cells, using methods well known in the art. In one embodiment, the antibody is produced in a cell line capable of glycosylating proteins such as CHO cells.

III. TKIs

TKIs that target intracellular ErbB signaling pathways include, for example, erlotinib, gefitinib, neratinib, lapatinib or vandetanib.

In one embodiment, the TKI specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase, which is highly expressed and occasionally mutated in various forms of cancer. Such TKIs include neratinib, afatinib, dacomitinb, vandetanib, lapatinib, erlotinib and gefitinib. Some TKIs binds in a reversible fashion, to the adenosine triphosphate (ATP) binding site of the receptor.

For a signal to be transmitted by an ErbB receptor, two EGFR family member molecules need to associate together to form a homodimer (other than an ErbB3/ErbB3 homodimer) or a heterodimer. These then use a molecule of ATP to autophosphorylate or to phosphorylate the associated dimerized molecule. Phosphorylation may expose binding sites on the cytoplasmic domain of the receptor for binding cell proteins that, when bound to the phosphorylated receptor, initiate a signaling cascade transmitting mitogenic stimuli to the nucleus. In one embodiment, the TKI acts by inhibiting phosphorylation so that signal transduction to the nucleus is reduced or stopped.

IV. Pharmaceutical Compositions

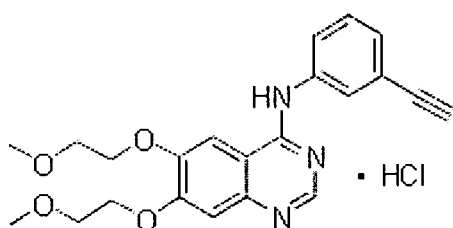
Pharmaceutical compositions suitable for administration to a subject can be in the form of tablets, capsules, pills, lozenges, powders or granules, or solutions or dispersions in a liquid.

In general, compositions typically comprise a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable" means approved by a government regulatory agency or listed in the U.S. Pharmacopeia or another generally recognized pharmacopeia for use in animals, particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the compound is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water or aqueous saline solutions and aqueous dextrose and glycerol solutions may be employed as carriers, particularly for injectable solutions (e.g., comprising an anti-ErbB3 antibody). Liquid compositions for parenteral administration (e.g., comprising an antibody) can be formulated for administration by injection or continuous infusion. Routes of administration by injection or infusion include intravenous, intraperitoneal, intramuscular, intrathecal and subcutaneous.

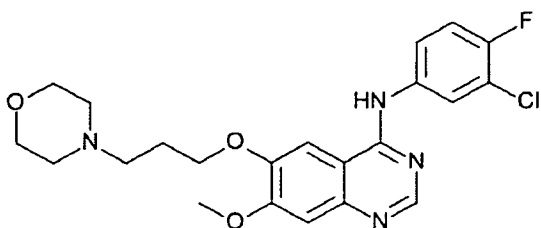
For oral administration (e.g., of a TKI) a composition in the form of a tablet can be prepared employing pharmaceutical excipients known in the art for that purpose and conventionally used for the preparation of solid pharmaceutical compositions.

Erlotinib (TARCEVA®) tablets for oral administration are commercially available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg

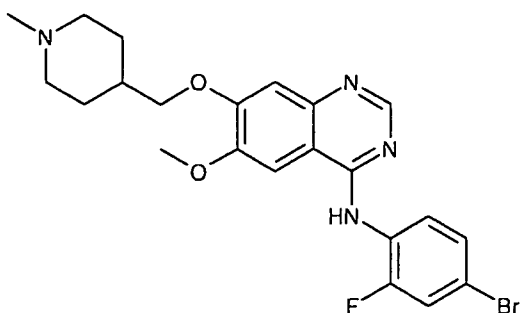
and 163.9 mg) equivalent to 25 mg, 100 mg and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives for product identification, including (for 25 mg only) FD&C Yellow #6. Erlotinib has the formula:



Gefitinib (IRESSA®) tablets for oral administration are commercially available in one dosage strength (250 mg) containing a tablet core comprising gefitinib, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate and magnesium stearate, which core is coated with a coating comprising hypromellose, polyethylene glycol 300, titanium dioxide, red ferric oxide and yellow ferric oxide. Gefitinib has the formula:

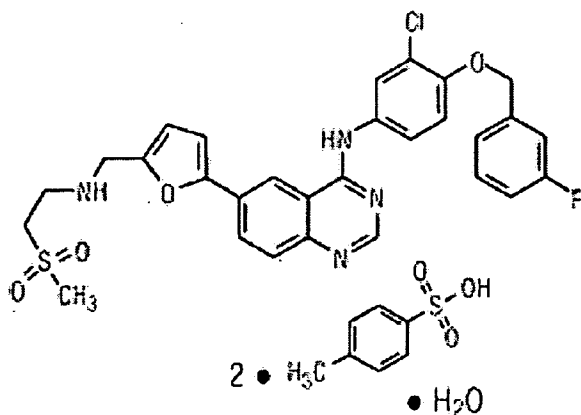


Vandetanib (CAPRELSA®) tablets for oral administration are commercially available in 100 and 300 mg dosage strength tablets containing a tablet core comprising vandetanib (calcium hydrogen phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone and magnesium stearate; and a film-coat comprising hypromellose 2910, macrogol 300, and titanium dioxide E171. Vandetanib has the formula:

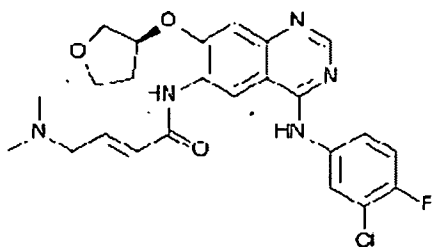


Lapatinib (TYKERB®) tablets for oral administration are commercially available in one dosage strength (250 mg) containing a tablet core comprising lapatinib ditosylate monohydrate, 405 mg, equivalent to 398 mg of lapatinib ditosylate or 250 mg lapatinib free base, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, and an orange film-coat comprising FD&C yellow No.6/sunset yellow FCF aluminum lake, hypromellose, macrogol/PEG 400, polysorbate 80, titanium dioxide.

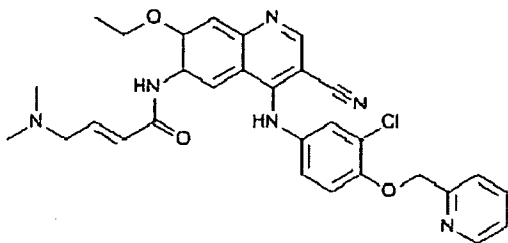
Lapatinib has the formula:



Afatinib has the formula:



Neratinib has the formula:



Antibody A for intravenous infusion (e.g., over the course of one hour) is, supplied as a clear liquid solution in sterile, single-use vials containing 10.1 ml of Antibody A at a concentration of 25 mg/ml in 20mM histidine, 150mM sodium chloride, pH 6.5, which should be stored at 2-8°C

V. Patient Populations

Provided herein are effective methods for treating patients having NSCLC using a combination of an anti-ErbB3 antibody and a TKI. In a particular embodiment, the subject has histologically or cytologically confirmed NSCLC that is locally advanced or metastatic.

In one embodiment, the mutation status of the EGFR tyrosine kinase domain of the patient's NSCLC tumor is determined, e.g., using art recognized techniques. For example, the tumor can be biopsied and the mutation status of the EGFR tyrosine kinase domain determined using PCR with known primers or hybridization with known probes. In one embodiment, the mutation status of the EGFR tyrosine kinase domain is wild-type, i.e., not-mutated.

In another embodiment, the patient's cancer has recurred or progressed following at least one chemotherapy-containing regimen in the metastatic setting that is considered standard of care for NSCLC.

In yet another embodiment, the patient is tested or selected, prior to treatment, for one or more of the above characteristics. For example, the subject can be tested for histologically or cytologically confirmed locally advanced or metastatic NSCLC; a mutation status of the EGFR tyrosine kinase domain of the tumor that is wild-type; and/or cancer that has recurred or progressed following at least one chemotherapy-containing regimen in the metastatic setting that is considered standard of care for NSCLC.

In a particular embodiment, the patient is tested or selected as having a tumor characterized as EGFR wild-type after receiving one or more prior regimen(s) of standard chemotherapy.

In yet another embodiment, the patient is tested or selected as having a tumor with a known activating mutation of the EGFR tyrosine kinase domain.

In yet another embodiment, the patient is tested or selected as having not received any prior EGFR TKI therapy in the metastatic setting for NSCLC.

In yet another embodiment, the patient is tested or selected as having a tumor with a known activating mutation of the EGFR tyrosine kinase domain, and having not received any prior EGFR TKI therapy in the metastatic setting for NSCLC.

In yet another embodiment, the patient is tested or selected as having a NSCLC that has demonstrated acquired resistance to EGFR TKIs such as erlotinib or gefitinib. Drug sensitivity can be measured using techniques well known in the art. For example, drug sensitivity can be determined by measuring the response of cells derived from the tumor to the drug. In another embodiment, drug sensitivity/resistance can be demonstrated by the presence or absence of an EGFR mutation or another mutation known to be associated with drug sensitivity/resistance (e.g., G719X, exon 19 deletion, L858R, L861Q, T790M, L747S, D761Y, amplification of the MET receptor and activation of IGFR signaling, or a K-RAS mutation).

In a particular embodiment, the patient has previously received EGFR TKI therapy and had a response to treatment, but has subsequently progressed and become resistant to this therapy.

In yet another embodiment, the patient has NSCLC that is characterized as having a mutation in the tyrosine kinase domain of EGFR that sensitizes the NSCLC to TKI treatment.

In yet another embodiment, the patient has NSCLC that is characterized as having a mutation in the tyrosine kinase domain of EGFR (SEQ ID NO: 15) that is an exon 19 deletion of fewer than 10 contiguous amino acids comprising the deletion of amino acids R748 and E749 of the tyrosine kinase domain of EGFR (SEQ ID NO: 15).

In another embodiment, the patient meets one or more of the following clinical criteria: 1) no history of smoking; 2) female gender; 3) adenocarcinoma subtype of NSCLC or its bronchoalveolar variant, 4) Asian ethnicity; and/or 5) one EGFR mutation selected from the group consisting of: tyrosine kinase domain mutations and truncating mutations involving exons 2 to 7.

VI. Combination Therapy

As herein provided, anti-ErbB3 antibodies are administered adjunctively with a TKI, e.g., erlotinib or gefitinib, to effect improvement in subjects having NSCLC. In one embodiment, the anti-ErbB3 antibody is Antibody A and the TKI is erlotinib. In another embodiment the NSCLC is characterized as having an activating mutation in the tyrosine kinase domain of EGFR (SEQ ID NO: 15). Preferably the mutation sensitizes the NSCLC to TKI treatment. In one such embodiment the EGFR mutation results in a deletion of amino acids in exon 19 of the EGFR gene. In another such embodiment the mutation is an E746-A750 deletion of the tyrosine kinase domain of EGFR (i.e., residues 743-750 of SEQ ID NO: 15). In other such embodiments the mutation is an L747-T751 deletion, an L747-P753 deletion, an L747-E749 deletion, an E746-A750 deletion, an E746-T751 deletion or an exon 19 deletion of fewer than 10 contiguous amino acids comprising the deletion of amino acids R748 and E749 of the tyrosine kinase domain of EGFR (SEQ ID NO: 15). In other such embodiment the NSCLC has a point mutation in exon 18, such as a G719A mutation, a G719C mutation or a G719S mutation. In another embodiment the NSCLC has a point mutation in exon 21, such as an L858R mutation, an L858M mutation, or an L861Q mutation. In other embodiments the EGFR gene does not comprise a mutation conferring resistance to TKI treatment such as an L747S mutation, a D761Y mutation, a T790M mutation, a D770-N771insNPG insertion mutation, a D770-N771insSVD insertion mutation, an A767-V769dup ASV insertion mutation, or another such mutation in exon 20 of the EGFR gene. The full length EGFR sequence is shown in SEQ ID NO: 14.

As used herein, adjunctive or combined administration includes simultaneous administration of the compounds in the same or different dosage form, or separate administration of the compounds (e.g., sequential administration). For example, the

antibody can be simultaneously administered with the TKI, wherein both the antibody and TKI are formulated together. Alternatively, the antibody can be administered in combination with the TKI, wherein both the antibody and TKI are formulated for separate administration and are administered concurrently or sequentially. For example, the antibody can be administered first followed by the administration of the TKI, or vice versa.

In one embodiment, the TKI is formulated for oral administration. In particular embodiments the TKI is erlotinib, and is administered at a dose selected from 150 mg/day, 100 mg/day, 80 mg/day and/or 50 mg/day. In another embodiment, the TKI is administered at its maximum tolerated dose. The dose of TKI may be varied over time. For example, the TKI may be initially administered at a relatively high dose and may be lowered over time. In another embodiment, the TKI may be initially administered at a relatively low dose and may be increased over time.

In another embodiment, anti-ErbB3 antibody is formulated for intravenous administration. In particular embodiments the anti-ErbB3 antibody is administered at a dose selected from: of 40 mg/kg, 20 mg/kg, 12 mg/kg, 10 mg/kg, 6 mg/kg, and/or 3.2 mg/kg. The dose of antibody may be varied over time. For example, the antibody may be initially administered at a high dose and may be lowered over time. In another embodiment, the antibody may be initially administered at a low dose and may be increased over time. For example, the antibody may be initially administered at a high dose and may be lowered over time. In another embodiment, the antibody may be initially administered at a low dose and may be increased over time. In one embodiment, a dose of 3.2, 6, 10, 12, 15, 20, or 40 mg/kg of Antibody A antibody is administered.

VII. Treatment Protocols

Suitable treatment protocols include, for example, those wherein (A) the TKI is administered to a patient (i.e., human subject) daily, and (B) the anti-ErbB3 antibody is administered to the patient once per week, every other week, or every three weeks.

In one embodiment, erlotinib is administered in combination with an amount of Antibody A at an interval measured in days. Suitable daily dosages of erlotinib include, for example, 100, 125 or 150 mg/day. In another embodiment, the method comprises

coadministering to the patient a dose of Antibody A, followed at least one seven day interval by at least one further administration of a dose of Antibody A. In another embodiment, four doses of Antibody A are administered four times in a 4-week cycle, i.e., one dose is administered per week. In another embodiment, two doses of Antibody A are administered in each 4 week cycle, i.e., one dose is administered every other week. In yet another embodiment, one dose of Antibody A is administered every three weeks. In one embodiment, the administration cycle is repeated, as necessary.

In another embodiment, the amount of Antibody A administered is constant for each dose. In another embodiment, the amount of antibody administered varies with each dose. For example, the maintenance (or follow-on) dose of the antibody can be higher or the same as the loading dose which is first administered. In another embodiment, the maintenance dose of the antibody can be lower or the same as the loading dose. Exemplary doses include 3.2, 6, 10, 15, 20, and 40mg/kg.

In particular embodiments, the subject is treated with a combination of Antibody A and erlotinib according to the dosages set forth in the Table 6 below.

Table 6

Antibody A Dose (mg/kg)	Erlotinib Dose (mg)
3.2	100
3.2	125
3.2	150
6	100
6	125
6	150
10	100
10	125
10	150
12	100
12	125
12	150
15	100
15	125
15	150
20	100
20	125
20	150
40	100
40	125
40	150

In other particular embodiments, Antibody A is administered at 6 mg/kg once per week, once per two weeks or once per 3 weeks in combination with daily administration of 100, 125, or 150 mg of erlotinib. In other embodiments, Antibody A is administered at 12 mg/kg once per week, once per two weeks or once per 3 weeks, in combination with daily administration of 100, 125, or 150 mg of erlotinib. In still other embodiments, Antibody A is

administered at 20 mg/kg once per week, once per two weeks or once per 3 weeks in combination with daily administration of 100, 125, or 150 mg of erlotinib.

VIII. Exemplary Outcomes

Subjects treated according to the methods disclosed herein may experience improvement in at least one sign or symptom associated with NSCLC.

In one embodiment, the subject experiences tumor shrinking and/or decrease in growth rate, i.e., suppression of tumor growth. In another embodiment, unwanted cell proliferation is reduced or inhibited. In yet another embodiment, one or more of the following can occur: the number of cancer cells can be reduced; tumor size can be reduced; cancer cell infiltration into peripheral organs can be inhibited, retarded, slowed, or stopped; tumor metastasis can be slowed or inhibited; tumor growth can be inhibited; recurrence of tumor can be prevented or delayed; one or more of the symptoms associated with cancer can be relieved to some extent.

In other embodiments, such improvement is measured by a reduction in the quantity and/or size of measurable tumor lesions. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter is to be recorded) as ≥ 10 mm by CT scan (CT scan slice thickness no greater than 5 mm), 10 mm caliper measurement by clinical exam or >20 mm by chest X-ray. The size of non-target lesions, e.g., pathological lymph nodes can also be measured for improvement. In one embodiment, lesions can be measured on chest x-rays or CT or MRI films.

In other embodiments, cytology or histology can be used to evaluate responsiveness to a therapy. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease can be considered to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Exemplary therapeutic responses to therapy may include:

Partial Response (PR): At least a 30% decrease in the sum of dimensions of target lesions, taking as reference the baseline sum diameters;

Stable Disease (SD): Neither sufficient shrinkage to qualify for partial response, nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study; or

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD refers to a response presenting a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD) refers to a response presenting at least a 20% increase in the sum of dimensions of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. The appearance of one or more new lesions is also considered progression.

In some embodiments, an effective amount of the compositions provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a lung tumor, reduction in metastasis, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, an effective amount produces a comparable clinical benefit rate (CBR = CR + PR + SD $\geq$ 6 months) similar to that achieved by erlotinib alone. In other embodiments, the improvement of clinical benefit rate is about 20%, 30%, 40%, 50%, 60%, 70%, 80% or more.

IX. Kits and Unit Dosage Forms

Also provided are kits that include a pharmaceutical composition containing an anti-ErbB3 antibody, such as Antibody A, and a pharmaceutically-acceptable carrier, in a therapeutically effective amount adapted for use in the preceding methods. The kits can optionally also include instructions, e.g., comprising administration schedules, to allow a practitioner (e.g., a physician, nurse, or patient) to administer the composition contained therein to administer the composition to a subject having cancer, e.g., NSCLC. In one

embodiment, the kit further comprises a TKI. In another embodiment the kit includes a syringe.

Optionally, the kits include multiple packages of the single-dose pharmaceutical composition(s) containing an effective amount of the antibody (e.g., Antibody A) for a single administration in accordance with the methods provided above. Optionally, instruments or devices necessary for administering the pharmaceutical composition(s) may be included in the kits. For instance, a kit may provide one or more pre-filled syringes containing an amount of Antibody A that is about 100 times the dose in mg/kg indicated for administration in the above methods. Optionally, the kit may further comprise a TKI, e.g., erlotinib or gefitinib in a desired unit dosage form (e.g., a unit dosage form distributed by the manufacturer of the TKI) for administration.

It will be apparent to those skilled in the art that various modifications and variations can be made in the compositions, methods, and kits provided herein without departing from the spirit or scope of the present invention, which includes modifications and variations that fall within the scope of the appended claims and their equivalents.

X. Methods for Selecting Therapy for a Patient Having NSCLC

Also provided are methods of selecting therapy for a patient having NSCLC, wherein the method comprises: (a) determining whether the patient's cancer comprises an activating mutation of the EGFR tyrosine kinase domain; and (b) if so, administering to the patient an effective amount of (1) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (2) erlotinib. In one embodiment, the activating mutation of the EGFR tyrosine kinase domain is a deletion of residues E746-A750 of the EGFR tyrosine kinase domain (SEQ ID NO: 15). In one embodiment, the anti-ErbB3 antibody is Antibody A.

The following examples are merely illustrative and should not be construed as limiting the scope of this disclosure in any way as many variations and equivalents will become apparent to those skilled in the art upon reading the present disclosure.

EXAMPLES

Example 1: Clinical Trials in Humans

A Phase 1-2 trial of Antibody A in combination with erlotinib is conducted in patients with Non-Small Cell Lung Cancer (NSCLC).

Phase 1

Objectives and Subject Selection

The primary objective in Phase 1 is to determine the safety of the Antibody A + erlotinib combination and to determine the recommended Phase 2 doses of the Antibody A + erlotinib combination.

The secondary objectives of this study are:

- to describe the dose limiting toxicity of the Antibody A/erlotinib combination;
- to determine the adverse event profile of the Antibody A/erlotinib combination;
- to determine the pharmacokinetic parameters and immunogenicity of Antibody A when administered in combination with erlotinib;
- to obtain an initial estimate of other key efficacy endpoints (disease control rate, OS and ORR) in this population for use in planning a subsequent randomized phase 2/3 trials;
- to gather exploratory clinical data on a potentially predictive set of biomarkers to be measured in serum and tumor tissue

Study Design

The study is an open-label Phase 1/2 trial of the Antibody A/erlotinib combination. Antibody A is administered as a one hour intravenous infusion either once per week, every other week or every three weeks, depending on the cohort assignment. Erlotinib is administered orally once per day. The Antibody A dose is escalated in this study only if the ongoing study of single-agent Antibody A has shown the planned

Antibody A dose to be safe and if the DLT (dose-limiting toxicity) evaluation period is successfully cleared.

An initial protocol for Phase 1 (version 1.1) utilized single-patient cohorts for Cohort 1. The protocol was revised to version 2.1 per which the Phase 1 portion of this study employed a standard 3 + 3 design. The protocol was revised to the current version to incorporate additional dosing cohorts, alternate dosing schedule, and a modified 3+3 design, according to which 6 patients are enrolled in each of the cohorts 4a, 4b and 4c. Cohorts 4b and 4c may be enrolled in parallel. Doses of the Antibody A + erlotinib combination in this study will escalate until either the maximum tolerated dose (MTD) is identified or the combination is shown to be tolerable at the highest planned doses of Antibody A and erlotinib.

Four doses of Antibody A are administered in each 4-week cycle in cohorts 1 to 4a. In cohort 4b, two doses of Antibody A are administered in each 4 week cycle (dosing is every other week) and in cohort 4c, 1 dose of Antibody A is administered every 3 weeks (cycle duration is 3 weeks). The safety assessment period for purposes of DLT evaluation, and dose escalation decisions is 4 weeks after the first dose. If no DLT is observed in 3 patients in a cohort, the next subject may be dosed at the next consecutive dose level.

As cohorts 4b and 4c explore alternate dosing schedules (every two weeks and every three weeks, respectively), but do not explore escalating dose levels, the DLT evaluation period is 4 weeks after the first dose for each of the first three patients in cohort 4b and 4c. Safety will continue to be assessed in patients 4 through 6 of each cohort, however, the intention of enrolling these additional three patient per cohort is to collect additional PK data to make a determination regarding dosing schedule for Phase 2.

Patients in cohorts 4b and 4c are randomly assigned to a cohort at the time of enrollment to minimize bias between these concurrently enrolling cohorts.

Rate of Enrollment

During Phase 1, enrollment can proceed to the next cohort after the dose limiting toxicity (DLT) evaluation period has elapsed and the safety data is reviewed. However, in Cohort 4, cohorts 4b and 4c may be enrolled in parallel and patients are randomly assigned between these cohorts to allow unbiased evaluation of both the dosing schedules. Enrollment in Phase 2 is opened as soon as the last subject in the final cohort completes the DLT evaluation period and a Phase 2 dose is determined.

Duration of Treatment

Subjects are treated until disease progression. Subjects are re-assessed for evidence of disease progression in accordance with current RECIST criteria [56 Eisenhauer EA, Therasse P, Bogaerts, et al., *New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1)*. European Journal of Cancer, 2009. 45(228-247)] every 8 weeks from the date of first dose (Cycle 1 Day 1). In the absence of disease progression, a subject may continue treatment for additional cycles.

Following discontinuation from study treatment, all subjects are followed via phone contact every 4 months (+/- 2 weeks) from the date of the 30 day follow up visit for Overall Survival (OS). This follow up is completed until the subject expires or until 1 year has elapsed since the enrollment of the last subject within the respective cohort, whichever occurs first.

Dose Levels

The proposed starting dose levels for Antibody A and erlotinib are presented in the Table 8 below.

Table 8

Dose Level ²	Antibody A Dose (mg/kg)	erlotinib Dose (mg)	Comment
1 ¹	6	100	Starting Dose
2	6	150	
3	12	150	
3a	12	100	

4	4a	20	100 ⁴	20 mg/kg weekly dose
	4b ³	20	100 ⁴	20 mg/kg every other week
	4c ³	20	100 ⁴	20mg/kg every 3 weeks

¹Dose level 1, as described in protocol v1.1, is a single-subject cohort in which the cohort is only expanded to 6 if the one subject experiences a DLT. In the event the Cohort 1 subject is ongoing at the successful completion of Dose level 2 DLT evaluation period, the subject may elect to receive the higher dose of erlotinib (150 mg).

²Intermediate Antibody A and erlotinib doses (between Cohorts 2, 3 and 4) and alternate dosing schedules may be explored following evaluation of safety profile and PK data. This would include decreased doses of Antibody A or decreased doses of erlotinib in the event that a DLT is experienced at a higher dose or PK data suggests adequate concentration levels may be achieved at lower doses.

³ Cohort 4b and 4c are enrolled in parallel and patients are randomly assigned between the two cohorts to allow unbiased evaluation of both the dosing schedules.

⁴ Upon completion of the DLT evaluation period, the erlotinib dose may be increased, in increments of 25 mg daily per week, up to 150 mg.

Cohorts utilizing Antibody A doses > 20 mg/kg or alternate dosing schedules may be evaluated upon successful completion of the Cohort 4 DLT evaluation period.

Each subject will complete a four week DLT evaluation period prior to evaluating dose escalation. In the event a subject experiences a DLT and the cohort expands to 6 subjects, all 6 subjects will complete the 4 week evaluation period. In the event that 2 or more subjects experience a DLT in either of the cohorts, no further dose escalation will take place. Cohorts 4b and 4c are enrolled as expanded cohorts of 6 subjects each, and in parallel. Subjects are randomly assigned between these cohorts 4b and 4c to allow unbiased evaluation of the dosing schedules. In addition, as cohorts 4b and 4c explore alternate dosing schedules (every two weeks and every three weeks, respectively), but do not explore escalating dose levels, the DLT evaluation period is 4 weeks after the first dose for each of the first three patients in cohort 4b and 4c. However, in the event a DLT is experienced by any one patient within these cohorts, all 6 patients must complete the 4 week DLT evaluation period in order to determine the dose level to be safe.

Decision Process for Dose Escalations

Decisions to escalate the dose to the next cohort is made by one skilled in the art. For cohorts that are utilizing an Antibody A dose > 20 mg/kg or an alternate dosing schedule, prior cohort PK data and safety data, as well as available data from the ongoing Phase 1 Solid Tumor study, are analyzed.

In Phase 1, the dose will escalate to the next level only after the safety data have been evaluated at the current dose level for all subjects enrolled at the dose level and the criteria for MTD have not been met. In addition, any drug-related toxicities of Grade 3 or higher that arise after the 4 week DLT evaluation period are assessed for their potential relationship to cumulative Antibody A+erlotinib dose and considered in the decision to escalate dose. The Antibody A dose is escalated only if the ongoing study of single-agent Antibody A has shown the Antibody A dose to be safe in ≥ 3 subjects.

Dose Limiting Toxicity Definition (Phase 1)

During the Phase 1 portion of the study, any drug-related Grade 3-4 hematologic or non-hematologic toxicity, including Grade 3-4 infusion reactions related to Antibody A are considered dose limiting. Nausea, vomiting and diarrhea are dose-limiting when Grade 3-4 toxicity occurs despite use of standard anti-emetic or anti-diarrheal agents. Grade 3 rash is considered dose limiting only if it lasts longer than 14 days despite optimal rash management. In addition, inability to deliver at least three of the planned doses over the first cycle of treatment due to drug-related toxicities is considered a dose-limiting effect.

All events qualifying as a DLT, regardless of seriousness, are reported.

Retreatment after Dose Limiting Toxicity in Phase 1

Ordinarily a subject who experiences a drug related dose-limiting toxicity may not receive additional doses of Antibody A and is removed from the study. Such a subject may continue on study at the next lower dose level if the consensus judgment is that continued treatment is in the subject's best interest. Subjects should have recovered from toxicity to baseline or Grade 1 (except alopecia) prior to re-treatment. For DLTs due to low hemoglobin, subjects' hemoglobin concentrations should have returned to their

baseline grade before re-treatment. FDA is notified if there are any instances of retreatment following a DLT.

Definition of Maximum Tolerated Dose within Phase 1 and Recommended Phase 2 Dose

The Maximum Tolerated Dose (MTD) is defined as the highest dose level of both Antibody A and erlotinib in which a DLT is experienced by fewer than two subjects in a cohort of 3 - 6 subjects. When a DLT is observed in at least two subjects in a cohort of 3 - 6 subjects, the MTD is determined to have been exceeded and additional subjects (up to a total of six) may be treated at the next lower dose level. The recommended Phase 2 dose of the Antibody A and erlotinib combination is 20 mg/kg of Antibody A and 100 mg of erlotinib; single agent erlotinib dose is 150 mg daily.

In the event that the MTD is based on DLTs of abnormal AST (aspartate aminotransferase), ALT (alanine aminotransferase) or Alkaline Phosphatase of Grade 3 that are observed in subjects who have Grade 2 abnormalities and known liver metastases at baseline, escalation may continue per inclusion criteria in subjects who at baseline have $\leq 2 \times$ ULN (upper limit of normal) in these enzyme levels (i.e. separate MTDs may be defined for populations with elevated liver enzyme levels due to liver metastases). In this case, if two different MTD's are defined for the two groups, Phase 2 will proceed with the higher MTD in subjects with baseline AST, ALT or Alkaline Phosphatase of $\leq 2 \times$ ULN.

Subject Selection and Discontinuation

In Phase 1, approximately 25 to 37 subjects are enrolled, depending on the number of expansions and additional cohorts required. In Phase 2, approximately 229 evaluable subjects are enrolled.

Three separate groups of NSCLC subjects will be enrolled concurrently into parallel cohorts. These cohorts are further defined below.

Group A includes subjects with NSCLC that have received at least one chemotherapy-containing regimen that is considered standard of care for NSCLC and a tumor with a mutation status of the EGFR tyrosine kinase domain that is wild-type. This

includes chemotherapy regimens that also contain biologic agents such as bevacizumab or cetuximab.

Group B includes subjects that have not received any prior EGFR TKI therapy for their cancer in the metastatic setting for NSCLC; however, such subjects must have a known activating mutation of the EGFR tyrosine kinase domain.

Group C includes subjects that have previously received EGFR TKI therapy and had a response to treatment but have subsequently progressed and become resistant to this therapy. Such subjects must meet the first 2 following criteria and one additional criterion (3a or 3b) as adapted from Jackman, et al. [Jackman D, Pao W, Riely GJ, et al. *Clinical Definition of Acquired Resistance to Epidermal Growth Factor Receptor TKIs in Non-Small-Cell Lung Cancer*. J Clin Oncol, 2009. (Epub ahead of print) doi: 10.1200/JCO.2009.25.8574] and Mok [70 Mok TS. *Living with Imperfection*. J Clin Oncol, 2009. (Epub ahead of print) doi:10.1200/JCO.2009.24.7049]:

1. Previously received treatment with a single-agent EGFR kinase inhibitor (e.g. gefitinib or erlotinib);
2. Subsequent systemic progression of disease while on continuous treatment with gefitinib or erlotinib for minimum of 30 days; AND,
3. Either of the following:
 - a. A tumor that harbors an EGFR mutation known to be associated with drug sensitivity (i.e., G719X, exon 19 deletion, L858R, L861Q); OR,
 - b. The subject's tumor is characterized as EGFR wild-type or EGFR unknown status; however, the subject has documented response to a prior EGFR kinase inhibitor therapy lasting at least 12 weeks.

The classification of EGFR (wild type or mutation status) is based upon information available to the investigative sites at the time of enrollment. However, samples obtained at baseline is subsequently evaluated to confirm the EGFR status. Any discrepancies are reconciled at the time of analysis.

Inclusion Criteria

For both Phase 1 and 2, the three groups of NSCLC patients that are eligible for this study must meet the criteria of one of these groups:

Group A: The subject must have a tumor with a mutation status of the EGFR tyrosine kinase domain that is wild-type. The subject's cancer have recurred or progressed following at least one chemotherapy-containing regimen that is considered standard of care for NSCLC. This would include chemotherapy regimens that also contain biologic agents such as bevacizumab or cetuximab; **OR,**

Group B: The subject must not have received any prior EGFR TKI therapy for NSCLC and have a tumor that has a known activating mutation of the EGFR tyrosine kinase (TKI) domain; **OR,**

Group C: The subject's cancer must have demonstrated acquired resistance to EGFR TKI, as outlined in above. For such subjects, any number of prior therapies is permitted.

Subjects must have histologically or cytologically confirmed locally advanced or metastatic non-small cell lung cancer

Subjects being considered for the phase II portion of the study must have a lesion amenable to biopsy and must be willing to undergo a pre-treatment biopsy, unless both of the following conditions are met:

- Subject underwent a biopsy within 2 months prior to enrollment and has sufficient tumor tissue available; and
- Subject has not had any intervening treatment since this biopsy.

Subjects must be ≥ 18 years of age. Subjects or their legal representatives must be able to understand and sign an informed consent. Subjects must have non-measurable or measurable tumor(s) for the phase 1 portion of the trial and must have measurable disease for the phase 2 portion in accordance with RECIST v 1.1. Subjects must have archived tumor samples available for analysis. Approximately 125 μ m of tumor sample is required (as FFPE blocks or prepared as slides). During the Phase 1 portion of the study, if the subject does not have archived tumor tissue available, they must be willing to undergo a biopsy prior to treatment initiation. Subjects must have an ECOG Performance Score (PS) of 0, 1 or 2. Subjects must have adequate bone marrow reserves as evidenced

by: ANC $> 1,500/\mu\text{l}$ and Platelet count $> 100,000/\mu\text{l}$ and Hemoglobin $> 9 \text{ g/dL}$. Subjects must have adequate hepatic function as evidenced by: Serum total bilirubin $\leq 1.5 \times \text{ULN}$ and AST, ALT and alkaline phosphatase $\leq 2 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ is acceptable if liver metastases are present, and $\leq 5 \times \text{ULN}$ of alkaline phosphatase is acceptable if bone metastases are present). Subjects must have adequate renal function as evidenced by a serum creatinine $\leq 1.5 \times \text{ULN}$. Subjects must be recovered from clinically significant effects of any prior surgery, radiotherapy or other antineoplastic therapy. Up to CTCAE Grade 1 is acceptable for subjects with known peripheral neuropathy. Women of childbearing potential as well as fertile men and their partners must agree to abstain from sexual intercourse or to use an effective form of contraception during the study and for 90 days following the last dose of study drugs (an effective form of contraception is an oral contraceptive or a double barrier method).

Exclusion Criteria

For both Phase 1 and 2, subjects are excluded based on one or more of: history of any second malignancy (recurrence or initial diagnosis) in the last 5 years (subjects with prior history of in-situ cancer or basal or squamous cell skin cancer are eligible); subjects with other malignancies are eligible if they have been continuously disease free for at least 5 years; subjects who are pregnant or lactating; subjects with an active infection or with an unexplained fever $> 38.5^{\circ}\text{C}$ during screening visits or on the first scheduled day of dosing (subjects with tumor fever may be enrolled); subjects with untreated and/or symptomatic CNS malignancies (primary or metastatic); subjects with CNS metastases who have undergone surgery or radiotherapy, whose disease is stable, and who have been on a stable dose or tapering of corticosteroids for at least 2 weeks prior to the first scheduled day of dosing are eligible for the trial; subjects with known hypersensitivity to any of the components of Antibody A or who have had hypersensitivity reactions to fully human monoclonal antibodies; subjects who have received other recent antitumor therapy (including investigational therapy administered within the 30 days prior to the first scheduled day of dosing in this study or any standard chemotherapy or radiation within 14 days prior to the first scheduled dose in this study; adequate time must have passed from last treatment to first scheduled dose in this study to clear the timeframe for actual or anticipated toxicities of such treatment); subjects having NYHA (New York Heart

Association Functional Classification) Class III or IV congestive heart failure or LVEF (left ventricular ejection fraction) of < 55%; subjects with a significant history of cardiac disease (i.e. uncontrolled blood pressure, unstable angina, myocardial infarction within 1 year or ventricular arrhythmias requiring medication) are also excluded; subjects with a recent (within 1 year) cerebrovascular accident; subjects with clinically significant ophthalmologic or gastrointestinal abnormalities (including: severe dry eye syndrome; keratoconjunctivitis sicca; Sjogren's syndrome; severe exposure keratopathy); subjects having disorders that might increase the risk for epithelium-related complications (e.g. bullous keratopathy, aniridia, severe chemical burns, neutrophilic keratitis); subjects having uncontrolled inflammatory gastrointestinal diseases (Crohn's disease, ulcerative colitis, etc.); subjects having a history of allogeneic transplant (subjects with a history of autologous bone marrow or stem cell transplant may be enrolled); subjects having a history of allergic reactions attributed to compounds of similar chemical or biologic composition as erlotinib; known HIV, hepatitis B or C (active, previously treated or both); subjects having any other medical condition deemed to be likely to interfere with a subject's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results.

Management of Toxicity

Therapy may be withheld for up to 28 consecutive days to allow for recovery from toxicity, especially for patients who are benefiting from study treatment. If a patient does not recover within 28 days from a toxicity, which is unrelated to study drug, then their continuation in the study is evaluated.

Subjects that experience toxicities that are less than dose-limiting may continue to receive daily erlotinib.

Dosing Adjustments of erlotinib in Phase 1 and Phase 2

If a subject experiences any of the following grade 2+ events, in addition to withholding Antibody A treatment, erlotinib dosing should be modified as indicated

below, per guidelines established during previous clinical trials of erlotinib [57 FDA Medical Review; Tarceva® (erlotinib); OSI Pharmaceuticals Inc. NDA Application No. 021743].

Table 9

Observed Toxicity	Grade	erlotinib Dose Modifications	Suggested Intervention
Keratitis	$2 \geq 3$	For grade 2 with ≥ 2 weeks in duration, withhold until $<$ grade 1 and then reduce by 50 mg. For grade ≥ 3 withhold until $<$ grade 1 and then reduce by 50 mg.	Preservative-free artificial tears, ointments, and other therapies see appendix. Follow up examination within two weeks
Diarrhea	$2 \geq 3$ (despite use of medication)	None Withhold until $<$ grade 1 and then reduce by 50 mg.	Loperamide (4mg at first onset followed by 2mg every 2-4 hours until diarrhea free for 12 hours. Maximum loperamide dose in 24 hours not to exceed 12mg) Treat severe diarrhea as above and as dictated by clinical condition i.e.: IV fluid and electrolyte supplementation as needed
Rash	$2 \geq 3$	None Withhold until $<$ grade 1 and then reduce by 50 mg.	Consider topical preventive treatment ¹
Suspected Interstitial Lung Disease (ILD); or unexplained acute onset of new or progressive pulmonary symptoms	--	Withhold both Antibody A and erlotinib pending diagnosis. Discontinue both erlotinib and Antibody A if diagnosis of ILD is confirmed.	Treat as indicated for ILD

¹ It is recommended that cutaneous toxicity be managed in accordance with guidelines established by medical advisors to Genentech, Inc. and OSI Pharmaceuticals, Inc.

Mode of Administration of Antibody A

Antibody A is supplied in sterile, single-use vials containing 10.1 mL of Antibody A at a concentration of 25 mg/ml in 20 mM histidine, 150 mM sodium chloride, pH 6.5. Antibody A appears as a colorless liquid solution and may contain a small amount of visible, white, amorphous, Antibody A particulates. Antibody A drug product should be stored at 2-8°C (36 to 46°F) with protection from light. Light protection is not required during infusion. Antibody A must not be frozen. Antibody A has been shown to be compatible with Alaris®, Paclitaxel, Lifeshield® and Kawasumi infusion sets that utilize an in-line 0.2 micron filter.

In phase I, Antibody A is administered weekly in cohorts 1 to 4a, every other week in cohort 4b and every 3 weeks in cohort 4c (+/- 2 days). Dose levels are determined by the cohort in which the subject is enrolled. In Phase II portion of the study, the Antibody A dose to be given in combination with erlotinib is determined by the MTD identified in the phase I portion of the study or the target optimal dose of Antibody A as determined by pharmacokinetic findings and safety data.

The pharmacy is provided with expiration dates for stored Antibody A. Stability is generated on a continual basis and the expiration date is continually updated via a Sponsor notification to the pharmacy or via direct printing on the MM-12 vial, as required by local regulation.

Antibody A should be brought to room temperature prior to administration. Vials of Antibody A should not be shaken. The appropriate quantity of Antibody A is removed from the vial, diluted in 250 mLs of 0.9% normal saline and administered as an IV infusion over 90 minutes (for the first infusion) or 60 minutes (for subsequent infusions in the absence of infusion reactions) using a low protein binding 0.22 micrometer in-line filter.

Mode of Administration of Erlotinib

Erlotinib dosing begins the day after the first dose of Antibody A (i.e. Cycle 1 Day 2). Dose levels should be determined by the cohort in which the subject is enrolled. In the Phase II portion of the study, the erlotinib dose to be given in combination with Antibody A is determined either by the MTD identified in the phase I portion of the study or the target optimal dose of erlotinib as determined by pharmacokinetic findings and

safety data. Patients randomized to receive erlotinib alone will receive erlotinib 150 mg daily.

Erlotinib is to be taken orally (PO) at least one hour before or two hours after the ingestion of food. It should be taken at the same time each day. On days which the subject is to receive the Antibody A infusion, the subject should take the erlotinib just prior to Antibody A dose administration (e.g. within a few minutes of starting the infusion).

Pharmacokinetic Assessments

Serum levels of Antibody A and erlotinib are measured at a central analytical lab using an ELISA based assay. In order to better understand the PK and safety profile of Antibody A and erlotinib combination, additional analytes may also be measured.

Tumor Samples

Tumor samples are fixed in formalin and subsequently embedded in paraffin blocks. These samples are used to identify the subject's EGFR mutation status, evaluate potentially predictive biomarkers and complete other correlative studies. Other mutations may also be evaluated, as required. Archived paraffin blocks may be used if available. Approximately 125µl of tumor sample is required for this purpose.

In the Phase II portion of the study, tumor samples are collected from all patients through biopsies performed prior to the first dose administration and, if possible, at the time of disease progression (post treatment biopsies are optional). Tumor samples collected through these biopsies are compared with the historical samples and will also be analyzed to explore the biomarkers that could predict response to the Antibody A and erlotinib combination.

RESULTS

From February 2010 – July 2011 33 patients entered phase I of the study (median age 63y; 49% male; 18% ECOG 0, 82% ECOG 1). 64% of patients had adenocarcinoma, and 27% received 3 or more lines of prior therapies (range 0-7), with 91% having had prior platinum. 45% of patients had wild-type EGFR status and were never treated or never responded to EGFR-TKIs (EGFRwt). 28% had acquired resistance to erlotinib

treatment (EGFRresist). The most common toxicities observed were diarrhea (82%), rash (64%), and fatigue (64%). DLTs observed in different cohorts were diarrhea, mucositis, rash and failure to thrive. Clinical activity was observed including 1 PR (an EGFR TKI naïve EGFR mutant) and 14 SD. Average duration of disease stabilization was 21.6 wks (range 7.1 -89.3 wks). Median PFS was 7.9 weeks, and the 16 week PFS rate was 41% in the overall population. For EGFRwt and EGFRresist patients, the median PFS was 7.6 weeks and 15 weeks, and the 16 week PFS rates were 32% and 44%, respectively. 7/20 EGFRwt patients and 5/9 EGFRresist patients achieved SD. Overall survival (OS) for all 33 patients in the phase 1 study was 9.8mos (6.5 – inf). In EGFRwt patients, median OS was 9.8mos (6.5 – inf), while in EGFR resistant patients OS was 11.0 months (4.0 – inf). By comparison, in published studies conducted in a comparable patient population, median OS for erlotinib was 5.3mos (TITAN Study) and 6.3mos (BR.21 Study).

Figure 2 provides data from phase 1 clinical trial employing the combination of Antibody A and erlotinib.

Figure 3 shows the Phase 1 3+3 design which evaluated patients for toxicity, with escalating doses of Antibody A and erlotinib until maximum tolerated dose or maximum target dose was identified. Panel B provides history information on the 33 patients in the study.

Figure 4A shows adverse events reported, and Figure 4B provides a summary of number of adverse events by dosing cohorts. These events are similar to known erlotinib toxicities with a trend towards a higher frequency, but not higher severity, when combined with Antibody A.

A summary of the key results are set forth in Table 10:

Table 10

Population	Group A (n=20)	Group C (n=9)	Overall (n=32)
Age (median)			63 yrs
Gender (%)			
Male			49%
Female			51%

ECOG (%)			
0			18%
1			82%
Lines of Prior Therapy			Ranges: (0-7)
2 or less			70%
3 or more			30%
Prior platinum (%)			91%
Prior Taxane (%)			50%
Overall response of PR or SD (1 PR & 14 SD)	7/20 (35%)	5/9 (56%)	15/32 (47%)
Duration of SD or PR	N=7, range (7.4-89.3)	N=5, range (7.1-24.7)	N=15, Range (7.1 - 89.3)
Median (Mean)	Median=15.4 weeks Mean=25.2 weeks	Median=13.4 weeks Mean=13.9 weeks	Median=15.4 Weeks Mean=21.6 weeks
Median PFS	7.7 weeks	15.1 weeks	8.1 weeks
PFS rate at week 16 (%)	32%	44%	41%

Figure 5 shows Progression Free Survival (PFS) for all patients in the Phase 1 study as well as for patients in Groups A and Groups C. Median PFS overall was 7.9 weeks (95% CI: 7.6 – 20.1). Median PFS for Group A (EGFRwt) was 7.6 weeks (7.3 – 23). Median PFS for Group C (EGFRresist) was 15 weeks (7.6 - inf).

Figure 6 provides a waterfall plot of overall survival data from the phase I. Overall survival (overall) was 9.8 months (6.5 – inf). Overall survival for Group A (EGFRwt) was 9.8 months (6.5 – inf). Overall survival for Group C (EGFRresist) was 11.0 months (4.0 – inf).

Phase 2

In Phase 2, the trial will evaluate the combination of Antibody A and erlotinib in three different populations of approximately 229 NSCLC patients. See Figure 1..

The primary objective in Phase 2 is to estimate the Progression Free Survival of the Antibody A plus erlotinib combination in these three distinct groups of patients, defined as follows:

Group A (n= 120): The subject must have a tumor with a mutation status of the EGFR tyrosine kinase domain that is wild-type. Subjects that have received at least one chemotherapy-containing regimen in the metastatic setting that is considered standard of care for NSCLC. Group A subjects are randomized in a 2:1 ratio to receive either Antibody A plus erlotinib or erlotinib alone.

Group B (n=66): The subject must have a tumor with a known activating mutation of the EGFR tyrosine kinase domain. Subjects that have not received any prior EGFR TKI therapy in the NSCLC metastatic setting. Group B subjects are randomized in a 2:1 ratio to receive either Antibody A plus erlotinib or erlotinib alone.

Group C (n=43): Subjects in which the cancer has demonstrated acquired resistance to EGFR TKI, as outlined in above. For such subjects, any number of prior therapies is permitted. All subjects in this group will receive Antibody A plus erlotinib.

Recommended Phase 2 Dose

The recommended Phase 2 dose is 100 mg/day of erlotinib and 20 mg/kg Antibody A either every other week.

Dosing Adjustments for Antibody A in Phase 2

During the Phase 2 portion, in the event of Grade 1 or 2 toxicities that are possibly related to Antibody A treatment, whether to continue treatment is decided. In the event that a subject experiences a toxicity $\geq$ Grade 3 that is possibly related to Antibody A treatment, further treatment with Antibody A should be held until the toxicity resolves to Grade 1 or baseline. In the event that Antibody A treatment is withheld for 28 consecutive days without resolution of the toxicity (to baseline or Grade 1), the subject is discontinued from the study.

Based on the toxicity, the Antibody A dose for future dose(s) may be reduced.

Dosing Adjustments for erlotinib in Phase 2

Any adjustments in erlotinib dosing will follow the process described above for Phase 1.

Statistical Analyses

Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).

Safety analyses will be performed using the Intent-to-Treat (ITT) population (all subjects who received at least one infusion of study drug). Efficacy analyses will be performed using the ITT population and the Evaluable Subject population (subjects receiving ≥ 6 doses of Antibody A). Results from EGFR testing completed on baseline subject samples will be compared to initial enrollment classification (Group A, Group B, Group C). If any discrepancies are noted, an additional efficacy analysis will be completed to incorporate the correct classification. These results will be reported in addition to the primary efficacy analysis based on Investigator classification of subject subgroup. In addition, subanalyses will be completed to further explore key prognostic factors and the impact of the presence/absence of key biomarkers.

The following tumor assessment-related efficacy endpoints will be evaluated: overall PFS (progression-free survival) and PFS rate; Objective Response Rate (confirmed CR and PR); Confirmed CR rate; Disease control rate (DCR=proportion of subjects with SD, PR or CR) response at first tumor assessment (week 8); Duration of objective response; Change in tumor burden from baseline (Best change in Sum of Longest Diameters from baseline for target lesions); and Overall Survival. In addition, change from baseline in PS (performance scores) over time will be summarized.

Example 6: Combination treatment with Antibody A and erlotinib on cancer cells with an activating mutation of the EGFR tyrosine kinase domain

Cells of the HCC827 non-small cell lung adenocarcinoma cell line (ATCC CRL-2868™) have an acquired E746-A750 deletion in the tyrosine kinase domain-encoding region of the gene encoding EGFR (SEQ ID NO: 15). This mutation renders HCC827 cells responsive to erlotinib treatment.

HCC827 cells were maintained in RPMI-1640 medium (Lonza) supplemented with 10%FBS (Hyclone), 100 units/ml penicillin, and 100mg/ml streptomycin (Gibco). Cells were seeded in 96-well black-masked tissue culture plates (1000 cells per well), grown overnight, then switched to low-serum medium (0.5% FBS) for 24 hours. To

measure growth response, cells were treated with several concentrations of Antibody A, erlotinib, or an equimolar combination of Antibody A and erlotinib (erl+MM). Concentrations of Antibody A were 0.0073, 3, 40, 120, 200, and 1000 nM. Cells were grown for 3 days. Then, ATP levels were measured using CellTitre-Glo® Cell Viability Assay (Promega) as follows: cells were lysed at room temperature with CellTitre Glo® reagent for 5 minutes on a shaker, then equilibrated for an additional 10 minutes; luminescent signal was measured using an Envision Plate Reader (Perkin Elmer); and raw luminescent signal for each treatment was normalized to medium only control and plotted using Prism software (GraphPad Software, Inc.).

As shown in Figure 7, the combination of Antibody A and erlotinib yielded a synergistic effect on cell viability.

Example 7: Co-inhibition of ErbB3 Ligand Activation with an anti-ErbB3 ligand-blocking antibody and EGFR Signaling with an EGFR tyrosine kinase inhibitor

ACHN renal carcinoma cells were seeded at 1000 cells/well in 96-well culture plates, and HCC827 NSCLC cells were seeded at 2000 cells/well in 96-well culture plates. Cells were grown overnight, then switched to low serum media (0.5% FBS) for 24 hours before treating with multiple doses of the Antibody A (an anti-ErbB3 ligand-blocking antibody), erlotinib (an EGFR tyrosine kinase inhibitor), or Antibody A + erlotinib, for 3 days. ATP levels were measured using CellTitre Glo® (Promega Corp.) assay and then normalized to a vehicle control. Bliss synergy/additivity analysis was then performed. Per the Bliss analysis, the fractional response if two drugs are exactly additive was calculated by taking the product of control normalized data for each drug alone. Then the difference between the observed and calculated fractional response was divided by the calculated fractional response to get a bliss index value that is negative (synergy), close to zero (additive), or positive (antagonism).

The results are provided in Figure 8, which shows that Antibody A-erlotinib combinations synergistically inhibit cell growth, as assessed by Bliss additivity-synergy analysis (Fitzgerald, JB, *et al.*, Nat Chem Biol.2006 (9):458-66).

Those skilled in the art will recognize, and will be able to ascertain and implement using no more than routine experimentation, many equivalents of the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims. Any combinations of the embodiments disclosed in the dependent claims are within the scope of the disclosure.

Table of Sequences

SEQ ID NO:	DESIGNATION	SOURCE OR FORMAT	TYPE	SEQUENCE
1	Heavy Chain Variable Region (VH) of Antibody A	Human VH	DNA	gaggtgcagc tgctggagag cggcggaggg ctggtccagc caggcggcag cctgaggctg tcttgccg ccagcggctt caccctcagc cactacgtga tggcctgggt gcggcaggcc ccaggcaagg gcttgaatg ggtgtccagc atcagcagca gcggcggctg gaccctgtac gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgtac ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcac caggggcctg aagatggcca ccatcttcga ctactggggc cagggcaccc tggtgaccgt gaggcagc
2	Heavy Chain Variable Region (VH) of Antibody A	Human VH	PROTEIN	Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser His Tyr Val Met Ala Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ser Ile Ser Ser Ser Gly Gly Trp Thr Leu Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Thr Arg Gly Leu Lys Met Ala Thr Ile Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
3	Light Chain Variable Region (VL) of Antibody A	Human VL	DNA	cagtcgcgcc tgaccagacc cgccagcgtg agcggcagcc caggccagag catcaccatc agctgcaccg gcaccagcag cgacgtgggc agctacaacg tgggtgcctg gtatcagcag caccgccgga agggcccca gctgatcatc tacgaggtgt ccagagggcc cagcggcgtg agcaacaggt tcagcggcag caagagcggc aacaccgcca gcctgaccat cagcggcctg cagaccgagg acgaggccga ctactactgc tgcagctacg ccggcagcag catcttcgtg atcttcggcg gagggaccaa ggtgaccgtc cta
4	Light Chain Variable Region (VL) of Antibody A	Human VL	PROTEIN	Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Val Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu Ile Ile Tyr Glu Val Ser Gln Arg Pro Ser Gly Val Ser Asn Arg Phe Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu Gln Thr Glu Asp Glu Ala Asp Tyr Tyr Cys Cys Ser Tyr Ala Gly Ser Ser Ile Phe Val Ile Phe Gly Gly Gly Thr Lys Val Thr Val Leu
5	Heavy Chain CDR1 (CDRH1) of Antibody A	Human CDRH1	PROTEIN	His Tyr Val Met Ala

6	Heavy Chain CDR2 (CDRH2) of Antibody A	Human CDRH2	PROTEIN	Ser Ile Ser Ser Ser Gly Gly Trp Thr Leu Tyr Ala Asp Ser Val Lys Gly
7	Heavy Chain CDR3 (CDRH3) of Antibody A	Human CDRH3	PROTEIN	Gly Leu Lys Met Ala Thr Ile Phe Asp Tyr
8	Light Chain CDR1 (CDRL1) of Antibody A	Human CDRL1	PROTEIN	Thr Gly Thr Ser Ser Asp Val Gly Ser Tyr Asn Val Val Ser
9	Light Chain CDR2 (CDRL2) of Antibody A	Human CDRL2	PROTEIN	Glu Val Ser Gln Arg Pro Ser
10	Light Chain CDR3 (CDRL3) of Antibody A	Human CDRL3	PROTEIN	Cys Ser Tyr Ala Gly Ser Ser Ile Phe Val Ile
11	Human ErbB3	Human	PROTEIN	Ser Glu Val Gly Asn Ser Gln Ala Val Cys Pro Gly Thr Leu Asn Gly Leu Ser Val Thr Gly Asp Ala Glu Asn Gln Tyr Gln Thr Leu Tyr Lys Leu Tyr Glu Arg Cys Glu Val Val Met Gly Asn Leu Glu Ile Val Leu Thr Gly His Asn Ala Asp Leu Ser Phe Leu Gln Trp Ile Arg Glu Val Thr Gly Tyr Val Leu Val Ala Met Asn Glu Phe Ser Thr Leu Pro Leu Pro Asn Leu Arg Val Val Arg Gly Thr Gln Val Tyr Asp Gly Lys Phe Ala Ile Phe Val Met Leu Asn Tyr Asn Thr Asn Ser Ser His Ala Leu Arg Gln Leu Arg Leu Thr Gln Leu Thr Glu Ile Leu Ser Gly Gly Val Tyr Ile Glu Lys Asn Asp Lys Leu Cys His Met Asp Thr Ile Asp Trp Arg Asp Ile Val Arg Asp Arg Asp Ala Glu Ile Val Val Lys Asp Asn Gly Arg Ser Cys Pro Pro Cys His Glu Val Cys Lys Gly Arg Cys Trp Gly Pro Gly Ser Glu Asp Cys Gln Thr Leu Thr Lys Thr Ile Cys Ala Pro Gln Cys Asn Gly His Cys Phe Gly Pro Asn Pro Asn Gln Cys Cys His Asp Glu Cys Ala Gly Gly Cys Ser Gly Pro Gln Asp Thr Asp Cys Phe Ala Cys Arg His Phe Asn Asp Ser Gly Ala Cys Val Pro Arg Cys Pro Gln Pro Leu Val Tyr Asn Lys Leu Thr Phe Gln Leu Glu Pro Asn Pro His Thr Lys Tyr Gln Tyr Gly Gly Val Cys Val Ala Ser Cys Pro His Asn Phe Val Val Asp Gln Thr Ser Cys Val Arg Ala Cys Pro Pro Asp Lys Met Glu Val Asp Lys Asn Gly Leu Lys Met Cys Glu Pro Cys Gly Gly Leu Cys Pro Lys Ala Cys Glu Gly Thr Gly Ser Gly Ser Arg Phe Gln Thr Val Asp Ser Ser Asn Ile Asp Gly Phe Val Asn Cys Thr Lys Ile Leu Gly Asn Leu Asp Phe Leu Ile Thr Gln Gly Asp Pro Trp His Lys Ile Pro Ala Leu Asp Pro Glu Lys Leu Asn Val Phe Arg Thr Val Arg

				Glu Ile Thr Gly Tyr Leu Asn Ile Gln Ser
				Trp Pro Pro His Met His Asn Phe Ser Val
				Phe Ser Asn Leu Thr Thr Ile Gly Gly Arg
				Ser Leu Tyr Asn Arg Gly Phe Ser Leu Leu
				Ile Met Lys Asn Leu Asn Val Thr Ser Leu
				Gly Phe Arg Ser Leu Lys Glu Ile Ser Ala
				Gly Arg Ile Tyr Ile Ser Ala Asn Arg Gln
				Leu Cys Tyr His His Ser Leu Asn Trp Thr
				Lys Val Leu Arg Gly Pro Thr Glu Glu Arg
				Leu Asp Ile Lys His Asn Arg Pro Arg Arg
				Asp Cys Val Ala Glu Gly Lys Val Cys Asp
				Pro Leu Cys Ser Ser Gly Gly Cys Trp Gly
				Pro Gly Pro Gly Gln Cys Leu Ser Cys Arg
				Asn Tyr Ser Arg Gly Gly Val Cys Val Thr
				His Cys Asn Phe Leu Asn Gly Glu Pro Arg
				Glu Phe Ala His Glu Ala Glu Cys Phe Ser
				Cys His Pro Glu Cys Gln Pro Met Glu Gly
				Thr Ala Thr Cys Asn Gly Ser Gly Ser Asp
				Thr Cys Ala Gln Cys Ala His Phe Arg Asp
				Gly Pro His Cys Val Ser Ser Cys Pro His
				Gly Val Leu Gly Ala Lys Gly Pro Ile Tyr
				Lys Tyr Pro Asp Val Gln Asn Glu Cys Arg
				Pro Cys His Glu Asn Cys Thr Gln Gly Cys
				Lys Gly Pro Glu Leu Gln Asp Cys Leu Gly
				Gln Thr Leu Val Leu Ile Gly Lys Thr His
				Leu Thr Met Ala Leu Thr Val Ile Ala Gly
				Leu Val Val Ile Phe Met Met Leu Gly Gly
				Thr Phe Leu Tyr Trp Arg Gly Arg Arg Ile
				Gln Asn Lys Arg Ala Met Arg Arg Tyr Leu
				Glu Arg Gly Glu Ser Ile Glu Pro Leu Asp
				Pro Ser Glu Lys Ala Asn Lys Val Leu Ala
				Arg Ile Phe Lys Glu Thr Glu Leu Arg Ser
				Leu Lys Val Leu Gly Ser Gly Val Phe Gly
				Thr Val His Lys Gly Val Trp Ile Pro Glu
				Gly Glu Ser Ile Lys Ile Pro Val Cys Ile
				Lys Val Ile Glu Asp Lys Ser Gly Arg Gln
				Ser Phe Gln Ala Val Thr Asp His Met Leu
				Ala Ile Gly Ser Leu Asp His Ala His Ile
				Val Arg Leu Leu Gly Leu Cys Pro Gly Ser
				Ser Leu Gln Leu Val Thr Gln Tyr Leu Pro
				Leu Gly Ser Leu Leu Asp His Val Arg Gln
				His Arg Gly Ala Leu Gly Pro Gln Leu Leu
				Leu Asn Trp Gly Val Gln Ile Ala Lys Gly
				Met Tyr Tyr Leu Glu Glu His Gly Met Val
				His Arg Asn Leu Ala Ala Arg Asn Val Leu
				Leu Lys Ser Pro Ser Gln Val Gln Val Ala
				Asp Phe Gly Val Ala Asp Leu Leu Pro Pro
				Asp Asp Lys Gln Leu Leu Tyr Ser Glu Ala
				Lys Thr Pro Ile Lys Trp Met Ala Leu Glu
				Ser Ile His Phe Gly Lys Tyr Thr His Gln
				Ser Asp Val Trp Ser Tyr Gly Val Thr Val
				Trp Glu Leu Met Thr Phe Gly Ala Glu Pro
				Tyr Ala Gly Leu Arg Leu Ala Glu Val Pro
				Asp Leu Leu Glu Lys Gly Glu Arg Leu Ala
				Gln Pro Gln Ile Cys Thr Ile Asp Val Tyr
				Met Val Met Val Lys Cys Trp Met Ile Asp
				Glu Asn Ile Arg Pro Thr Phe Lys Glu Leu

				Ala Asn Glu Phe Thr Arg Met Ala Arg Asp Pro Pro Arg Tyr Leu Val Ile Lys Arg Glu Ser Gly Pro Gly Ile Ala Pro Gly Pro Glu Pro His Gly Leu Thr Asn Lys Lys Leu Glu Glu Val Glu Leu Glu Pro Glu Leu Asp Leu Asp Leu Asp Leu Glu Ala Glu Glu Asp Asn Leu Ala Thr Thr Thr Leu Gly Ser Ala Leu Ser Leu Pro Val Gly Thr Leu Asn Arg Pro Arg Gly Ser Gln Ser Leu Leu Ser Pro Ser Ser Gly Tyr Met Pro Met Asn Gln Gly Asn Leu Gly Glu Ser Cys Gln Glu Ser Ala Val Ser Gly Ser Ser Glu Arg Cys Pro Arg Pro Val Ser Leu His Pro Met Pro Arg Gly Cys Leu Ala Ser Glu Ser Ser Glu Gly His Val Thr Gly Ser Glu Ala Glu Leu Gln Glu Lys Val Ser Met Cys Arg Ser Arg Ser Arg Ser Arg Ser Pro Arg Pro Arg Gly Asp Ser Ala Tyr His Ser Gln Arg His Ser Leu Leu Thr Pro Val Thr Pro Leu Ser Pro Pro Gly Leu Glu Glu Glu Asp Val Asn Gly Tyr Val Met Pro Asp Thr His Leu Lys Gly Thr Pro Ser Ser Arg Glu Gly Thr Leu Ser Ser Val Gly Leu Ser Ser Val Leu Gly Thr Glu Glu Glu Asp Glu Asp Glu Glu Tyr Glu Tyr Met Asn Arg Arg Arg Arg His Ser Pro Pro His Pro Pro Arg Pro Ser Ser Leu Glu Glu Leu Gly Tyr Glu Tyr Met Asp Val Gly Ser Asp Leu Ser Ala Ser Leu Gly Ser Thr Gln Ser Cys Pro Leu His Pro Val Pro Ile Met Pro Thr Ala Gly Thr Thr Pro Asp Glu Asp Tyr Glu Tyr Met Asn Arg Gln Arg Asp Gly Gly Gly Pro Gly Gly Asp Tyr Ala Ala Met Gly Ala Cys Pro Ala Ser Glu Gln Gly Tyr Glu Glu Met Arg Ala Phe Gln Gly Pro Gly His Gln Ala Pro His Val His Tyr Ala Arg Leu Lys Thr Leu Arg Ser Leu Glu Ala Thr Asp Ser Ala Phe Asp Asn Pro Asp Tyr Trp His Ser Arg Leu Phe Pro Lys Ala Asn Ala Gln Arg Thr
12	Heavy Chain of Antibody A	human heavy chain	PROTEIN	1 EVQLLESQGG LVQPGGSLRL SCAASGFTFS HYVMAWVRQA PGKGLEWVSS 51 ISSSGGWITLY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCTRGL 101 KMATIFDYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD 151 YFPEPVTVSW NSGALTSGVH TFPVAVLQSSG LYSLSSVVTV PSSNFGTQTY 201 TCNVDPKPSN TKVDKTVKRC CCVECPPCPA PPVAGPSVFL FPPKPKDTLM 251 ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV 301 VSVLTIVVHQA WLNGKEYKCK VSNKGLPAPI EKTISKTKGQ PREPQVYTLF 351 PSREEMTKNQ VSLTCLVKGK YPSDIAVEWE SNGQPENNYK TTPPMLDSG 401 SFFLYSKLTV DKSRWQQGNV FSCSVMEAL HNHYTQKSLS LSPGK

13	Light Chain of Antibody A	light heavy chain	PROTEIN	1 QSALTQPASV SGSPGQSITI SCTGTSSDVG SYNVVSWYQQ HPGKAPKLII 51 YEVSQRPSGV SNRFSGSKSG NTASLTISGL QTEDEADYYC CSYAGSSIFV 101 IFGGGTKVTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL VSDFYPGAVT 151 VAWKADGSPV KGVETTKPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCRV 201 THEGSTVEKT VAPAECS
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CLAIMS

We claim:

1. A method of treating non-small-cell lung cancer (NSCLC) in a human patient comprising administering to the patient an effective amount of (a) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (b) erlotinib, wherein the method comprises at least one cycle, wherein the cycle is a period of 28 days, and wherein said antibody and erlotinib are administered according to Dose Schedules 1, 2, 3, 3a, 4a, 4b, or 4c as follows:

Dose Schedule	Antibody Dose (mg/kg, i.v.)	Erlotinib Dose (mg, q.d., p.o.)	Antibody dosing schedule
1	6	100	6 mg/kg weekly dose
2	6	150	6 mg/kg weekly dose
3	12	150	12 mg/kg weekly dose
3a	12	100	12 mg/kg weekly dose
4a	20	100, 125 or 150	20 mg/kg weekly dose
4b	20	100, 125 or 150	20 mg/kg every other week
4c	20	100, 125 or 150	20mg/kg every third week

2. The method of claim 1, wherein the anti-ErbB3 antibody is Antibody A.

3. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 1, and wherein the antibody is administered intravenously at a dose of 6 mg/kg weekly and erlotinib is administered orally at a dose of 100 mg per day.

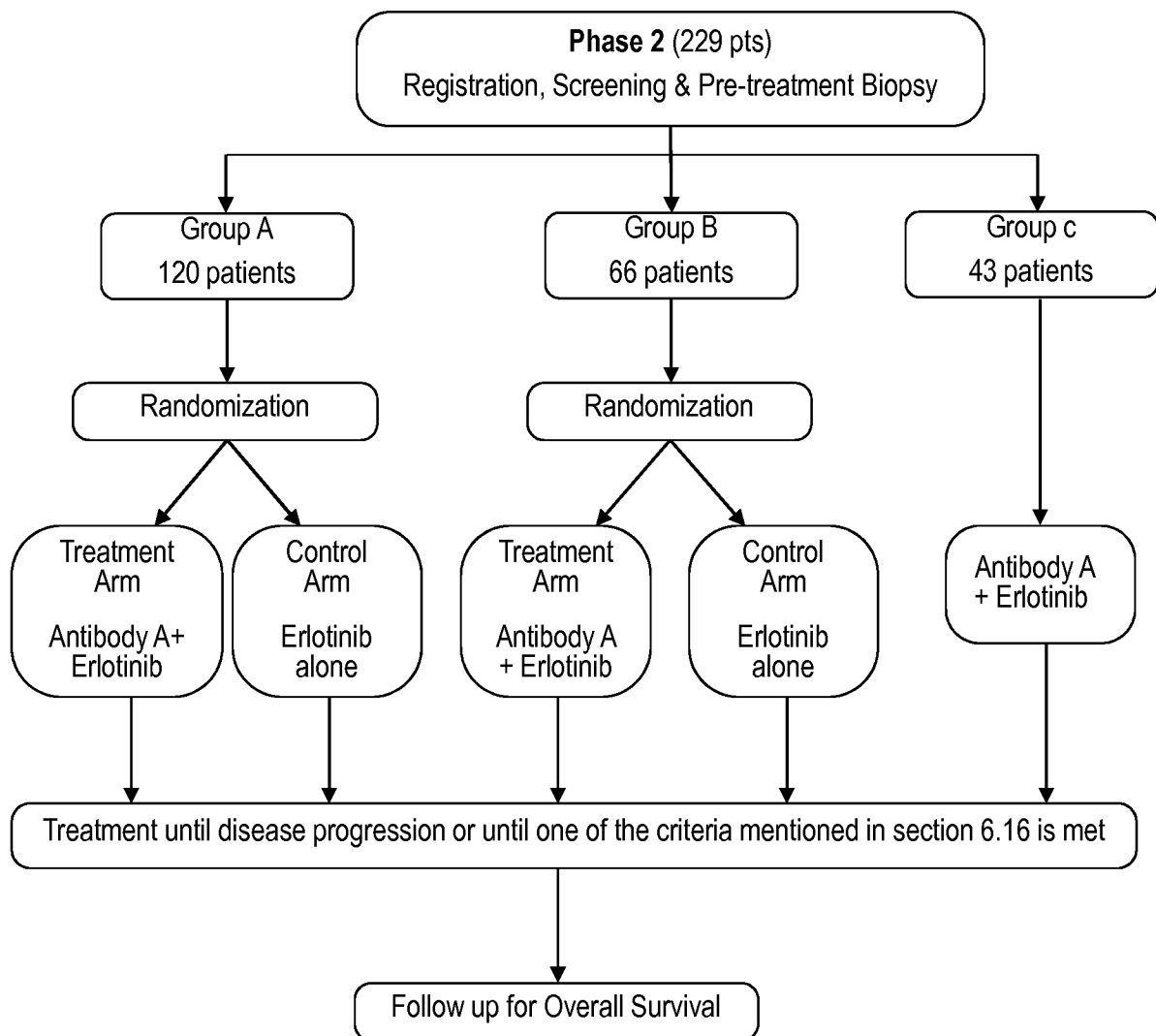
4. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 2, and wherein the antibody is administered intravenously at a dose of 6 mg/kg weekly and erlotinib is administered orally at a dose of 150 mg per day.
5. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 3, and wherein the antibody is administered intravenously at a dose of 12 mg/kg weekly and erlotinib is administered orally at a dose of 150 mg per day.
6. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 3a, and wherein the antibody is administered intravenously at a dose of 12 mg/kg weekly and erlotinib is administered orally at a dose of 100 mg per day.
7. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 4a, and wherein the antibody is administered intravenously at a dose of 20 mg/kg weekly and erlotinib is administered orally at a dose of 100 or 150 mg per day.
8. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 4b, and wherein the antibody is administered intravenously at a dose of 20 mg/kg every other week and erlotinib is administered orally at a dose of 100 or 150 mg per day.
9. The method of claim 1 or 2, wherein the dose schedule is Dose Schedule 4c, and wherein the antibody is administered intravenously at a dose of 20 mg/kg every third week and erlotinib is administered orally at a dose of 100 or 150 mg per day.
10. The method of any one of claims 1-9, wherein the effective amount produces at least one therapeutic effect selected from the group consisting of reduction in size of a tumor, reduction in metastasis, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response.
11. The method of any one of claims 1-9, wherein the NSCLC is locally advanced or metastatic.
12. The method of any one of claims 1-9, wherein the subject has a NSCLC tumor in which the EGFR tyrosine kinase domain is wild-type and the subject has previously undergone at least one chemotherapy-containing regimen.

13. The method of any one of claims 1-9, wherein the subject has a NSCLC tumor in which the EGFR tyrosine kinase domain comprises an activating mutation and the subject has not received any prior EGFR TKI therapy.
14. The method of any one of claims 1-9, wherein the subject has a NSCLC tumor that has demonstrated acquired resistance to EGFR TKIs.
15. The method of any one of claims 1-9, wherein the subject has NSCLC that is characterized as having a mutation in the tyrosine kinase domain of EGFR (SEQ ID NO: 15) that sensitizes the NSCLC to TKI treatment.
16. The method of any one of claims 1-9, wherein the subject has NSCLC that is characterized as having a mutation in the tyrosine kinase domain of EGFR that is an exon 19 deletion of fewer than 10 contiguous amino acids comprising the deletion of amino acids R748 and E749 of the tyrosine kinase domain of EGFR (SEQ ID NO: 15).
17. A method of selecting therapy for a patient having NSCLC, said method comprising: (a) determining whether said patient's cancer comprises an activating mutation of the EGFR tyrosine kinase domain (SEQ ID NO: 15); and (b) if so, administering to said patient an effective amount of (1) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (2) erlotinib.
18. The method of claim 17, wherein the activating mutation of the EGFR tyrosine kinase domain is a deletion of residues E746-A750 of SEQ ID NO: 15.
19. A composition for use in treating non-small-cell lung cancer (NSCLC) in a human patient, the composition comprising a clinically proven safe and effective amount (a) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (b) erlotinib.

20. The composition of claim 19, wherein the anti-ErbB3 antibody is Antibody A.
21. The composition of claim 19 or 20, wherein the antibody is formulated for intravenous administration at a dose of 6 mg/kg.
22. The composition of claim 19 or 20, wherein the antibody is formulated for intravenous administration at a dose of 12 mg/kg.
23. The composition of claim 19 or 20, wherein the antibody is formulated for intravenous administration at a dose of 20 mg/kg.
24. The composition of any one of claims 19 or 20 wherein the erlotinib is formulated for a daily oral dose of 100 mg per day.
25. The composition of any one of claims 19 or 20 wherein the erlotinib is formulated for a daily oral dose of 150 mg per day.
26. A kit comprising a dose of an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), and a dose of erlotinib, wherein the doses of antibody and erlotinib are in the amounts shown below for Dose Schedule 1, 2, 3, 3a, 4a, 4b, or 4c:

Dose Schedule	Antibody Dose (mg/kg, i.v.)	erlotinib Dose (mg, q.d., p.o.)	Antibody dosing schedule
1	6	100	6 mg/kg weekly dose
2	6	150	6 mg/kg weekly dose
3	12	150	12 mg/kg weekly dose
3a	12	100	12 mg/kg weekly dose
4a	20	100, 125 or 150	20 mg/kg weekly dose
4b	20	100, 125 or 150	20 mg/kg every other week
4c	20	100, 125 or 150	20mg/kg every third week

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**Fig. 1**



	N = 33
Median Age, yr (range)	63 (44 - 86)
Gender	
Female	17
Male	16
ECOG	
0	6
1	27
Histology	
Adenocarcinoma	21
Squamous Cell Carcinoma	8
Other, specify	3
Unclassified Carcinoma	1
Line of Therapy	
L0	1
L1	13
L2	10
L3	5
L4	0
L5	3
L6	0
L7	1
Smoking History	
Previous	18
Never	8
Current	6
Unknown	1
EGFR	
Negative / Wild Type	15
Positive	10
Unknown/Not Reported	8

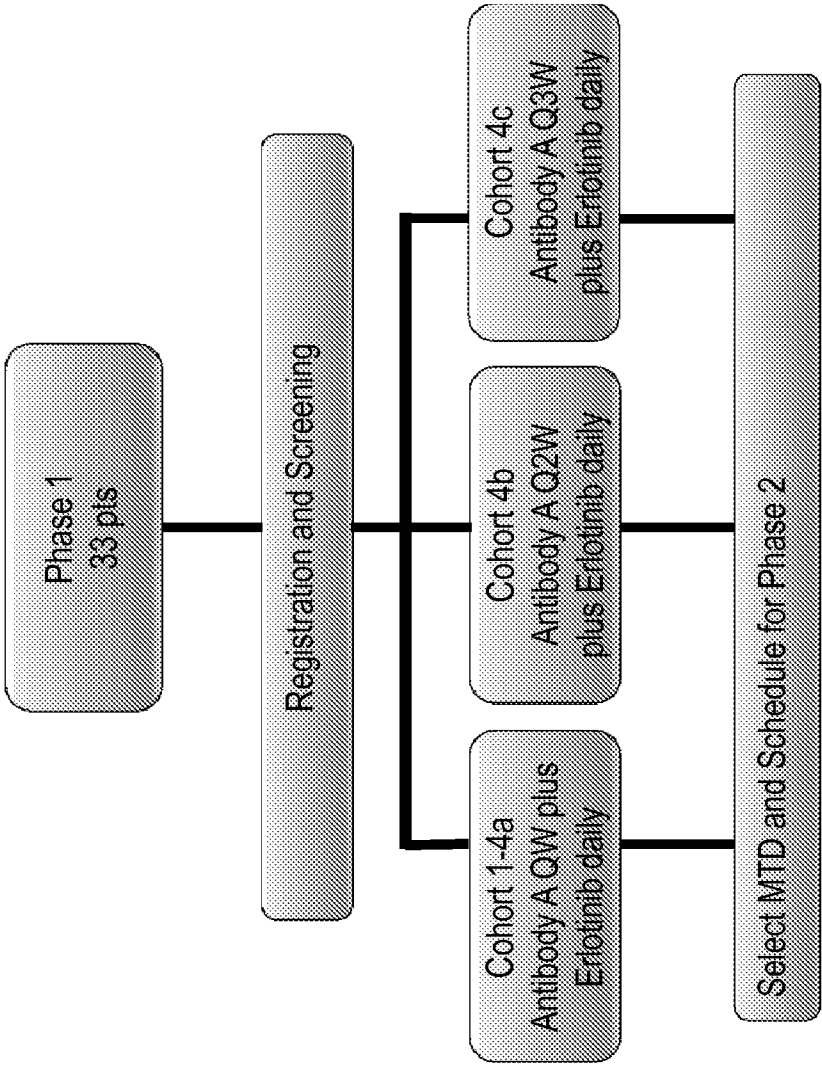


Fig. 3

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Summary of adverse events by grade occurring in >10% of patients (n=33).

Adverse Events (n=33)	Any n (%)	Grade 1 n	Grade 2 n	Grade 3 n	Grade 4 n	Grade 5 n
Diarrhea	27 (82)	16	8	3	.	.
Fatigue	21 (64)	7	9	5	.	.
Rash	21 (64)	12	7	2	.	.
Decreased appetite	11 (33)	3	7	1	.	.
Dehydration	11 (33)	6	3	2	.	.
Dry skin	11 (33)	8	3	.	.	.
Nausea	11 (33)	8	3	.	.	.
Cough	10 (30)	4	5	1	.	.
Insomnia	10 (30)	7	3	.	.	.
Mucosal inflammation	10 (30)	5	4	1	.	.
Hypokalaemia	9 (28)	7	.	2	.	.
Urinary tract infection	9 (28)	2	5	2	.	.
Vomiting	9 (28)	7	2	.	.	.
Weight decreased	8 (24)	4	4	.	.	.
Anaemia	7 (21)	2	5	.	.	.
Constipation	7 (21)	5	1	1	.	.
Dermatitis acneiform	7 (21)	4	1	2	.	.
Early satiety	7 (21)	5	2	.	.	.
Hypomagnesaemia	7 (21)	3	4	.	.	.
Stomatitis	7 (21)	3	4	.	.	.
Dysgeusia	6 (18)	4	2	.	.	.
Dyspnoea	6 (18)	5	.	.	1	.
Dyspnoea exertional	6 (18)	2	3	1	.	.
Paronychia	6 (18)	3	3	.	.	.
Back pain	5 (15)	2	3	.	.	.
Oropharyngeal pain	5 (15)	3	2	.	.	.
Pain	5 (15)	1	2	2	.	.
Pain in extremity	5 (15)	2	1	2	.	.
Arthralgia	4 (12)	2	1	1	.	.
Asthenia	4 (12)	1	2	1	.	.
Conjunctivitis	4 (12)	2	2	.	.	.
Dizziness	4 (12)	4	.	.	.	.
Dysuria	4 (12)	3	.	1	.	.
Epistaxis	4 (12)	4	.	.	.	.
Gastroesophageal reflux disease	4 (12)	1	3	.	.	.
Muscular weakness	4 (12)	2	1	1	.	.
Oedema peripheral	4 (12)	4	.	.	.	.
Wheezing	4 (12)	3	1	.	.	.

Fig. 4A

Adverse Event	Any (n=33) n(%)	Cohort 1 (n=1) n (%)	Cohort 2 (n=3) n (%)	Cohort 3 (n=3) n (%)	Cohort 3A (n=6) n (%)	Cohort 4A (n=6) n (%)	Cohort 4B (n=7) n (%)	Cohort 4C (n=7) n (%)
Diarrhoea	27 (82)	1 (100)	2 (67)	2 (67)	4 (67)	6 (100)	6 (86)	6 (86)
Fatigue	21 (64)	1 (100)	1 (33)	2 (67)	4 (67)	6 (100)	3 (43)	4 (57)
Rash	21 (64)	1 (100)	2 (67)	1 (33)	4 (67)	6 (100)	5 (71)	2 (29)
Decreased appetite	11 (33)	1 (100)	1 (33)	1 (33)	1 (17)	5 (83)	1 (14)	1 (14)
Dehydration	11 (33)			2 (67)	2 (33)	4 (67)	1 (14)	2 (29)
Dry skin	11 (33)		1 (33)	2 (67)	1 (17)	3 (50)	3 (43)	1 (14)
Nausea	11 (33)		2 (67)	1 (33)	2 (33)	4 (67)	1 (14)	1 (14)
Cough	10 (30)	1 (100)	1 (33)	1 (33)	1 (17)	2 (33)	4 (57)	
Insomnia	10 (30)		2 (67)	1 (33)	1 (17)	2 (33)	3 (43)	1 (14)
Mucosal inflammation	10 (30)		2 (67)	2 (67)	3 (50)	1 (17)	1 (14)	1 (14)
Hypokalaemia	9 (27)		2 (67)	1 (33)		3 (50)	3 (43)	
Urinary tract infection	9 (27)		1 (33)	1 (33)	4 (67)	3 (50)		
Vomiting	9 (27)	1 (100)	2 (67)	1 (33)	1 (17)	2 (33)		2 (29)
Weight decreased	8 (24)		1 (33)	2 (67)	1 (17)	2 (33)	1 (14)	1 (14)
Anaemia	7 (21)		1 (33)		2 (33)	1 (17)	1 (14)	2 (29)
Constipation	7 (21)		1 (33)	1 (33)	1 (17)	1 (17)	3 (43)	
Dermatitis acneiform	7 (21)			1 (33)	2 (33)	1 (17)	1 (14)	2 (29)
Early satiety	7 (21)		2 (67)		1 (17)	2 (33)	1 (14)	1 (14)
Hypomagnesaemia	7 (21)		2 (67)	2 (67)		1 (17)	1 (14)	1 (14)
Stomatitis	7 (21)		2 (67)	1 (33)	1 (17)	2 (33)	1 (14)	
Dysgeusia	6 (18)		1 (33)		2 (33)	2 (33)	1 (14)	
Dyspnoea	6 (18)		1 (33)	1 (33)	1 (17)	1 (17)	1 (14)	1 (14)
Dyspnoea exertional	6 (18)		2 (67)	1 (33)	1 (17)	1 (17)	1 (14)	
Paronychia	6 (18)				1 (17)	2 (33)	2 (29)	1 (14)
Back pain	5 (15)		1 (33)			2 (33)	1 (14)	1 (14)
Oropharyngeal pain	5 (15)		1 (33)	1 (33)		2 (33)	1 (14)	
Pain	5 (15)	1 (100)	1 (33)	1 (33)		1 (17)	1 (14)	
Pain in extremity	5 (15)		1 (33)		1 (17)	2 (33)		1 (14)
Arthralgia	4 (12)				1 (17)	3 (50)		
Asthenia	4 (12)			2 (67)		1 (17)	1 (14)	
Conjunctivitis	4 (12)		1 (33)		1 (17)	2 (33)		
Dizziness	4 (12)			1 (33)			1 (14)	2 (29)
Dysuria	4 (12)			1 (33)	1 (17)	2 (33)		
Epistaxis	4 (12)				2 (33)	1 (17)		1 (14)
Gastroesophageal reflux disease	4 (12)				1 (17)		2 (29)	1 (14)
Muscular weakness	4 (12)		1 (33)	1 (33)		2 (33)		
Oedema peripheral	4 (12)		1 (33)	1 (33)	1 (17)		1 (14)	
Wheezing	4 (12)	1 (100)			1 (17)	1 (17)		1 (14)

Fig. 4B

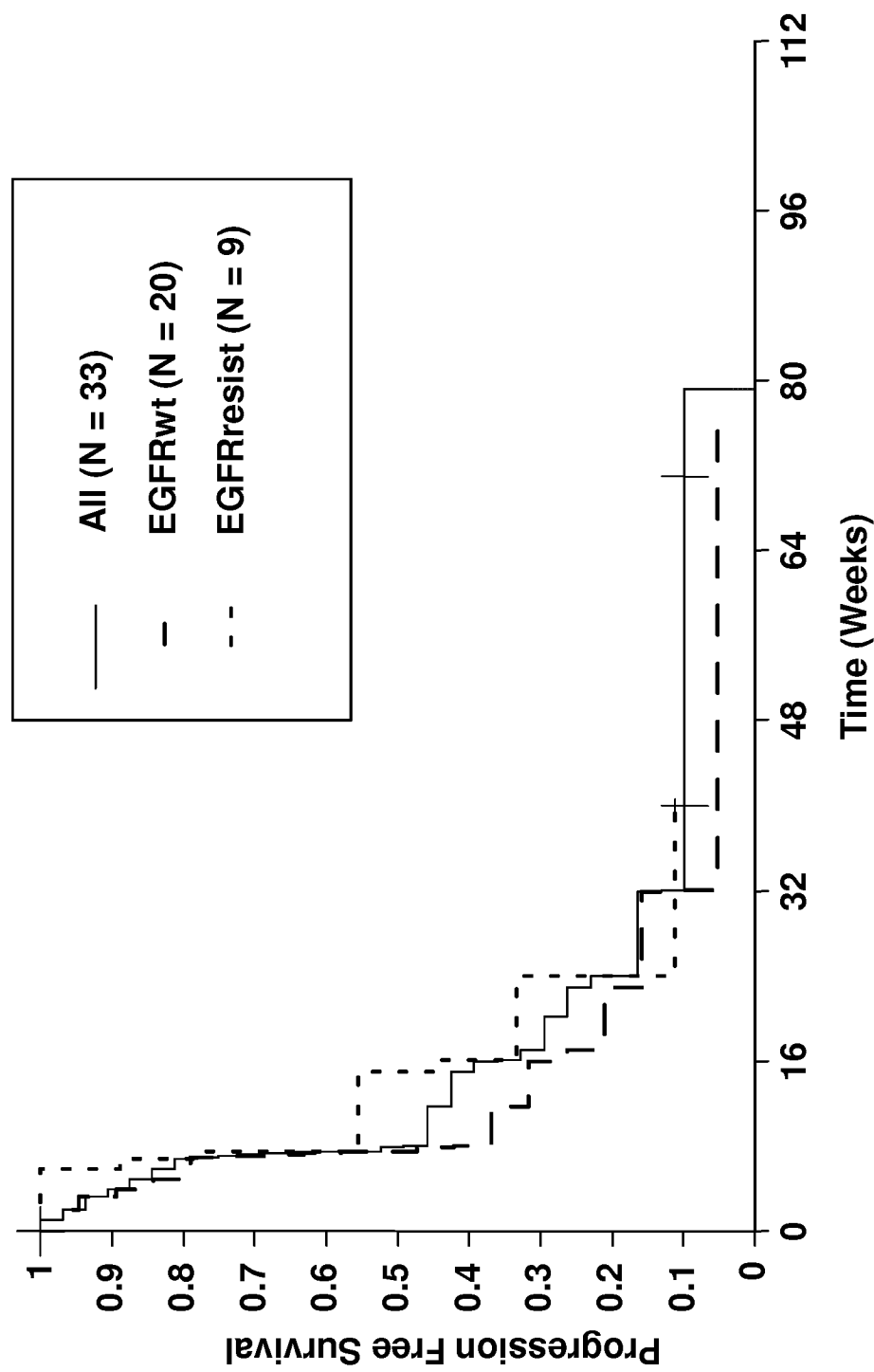


Fig. 5

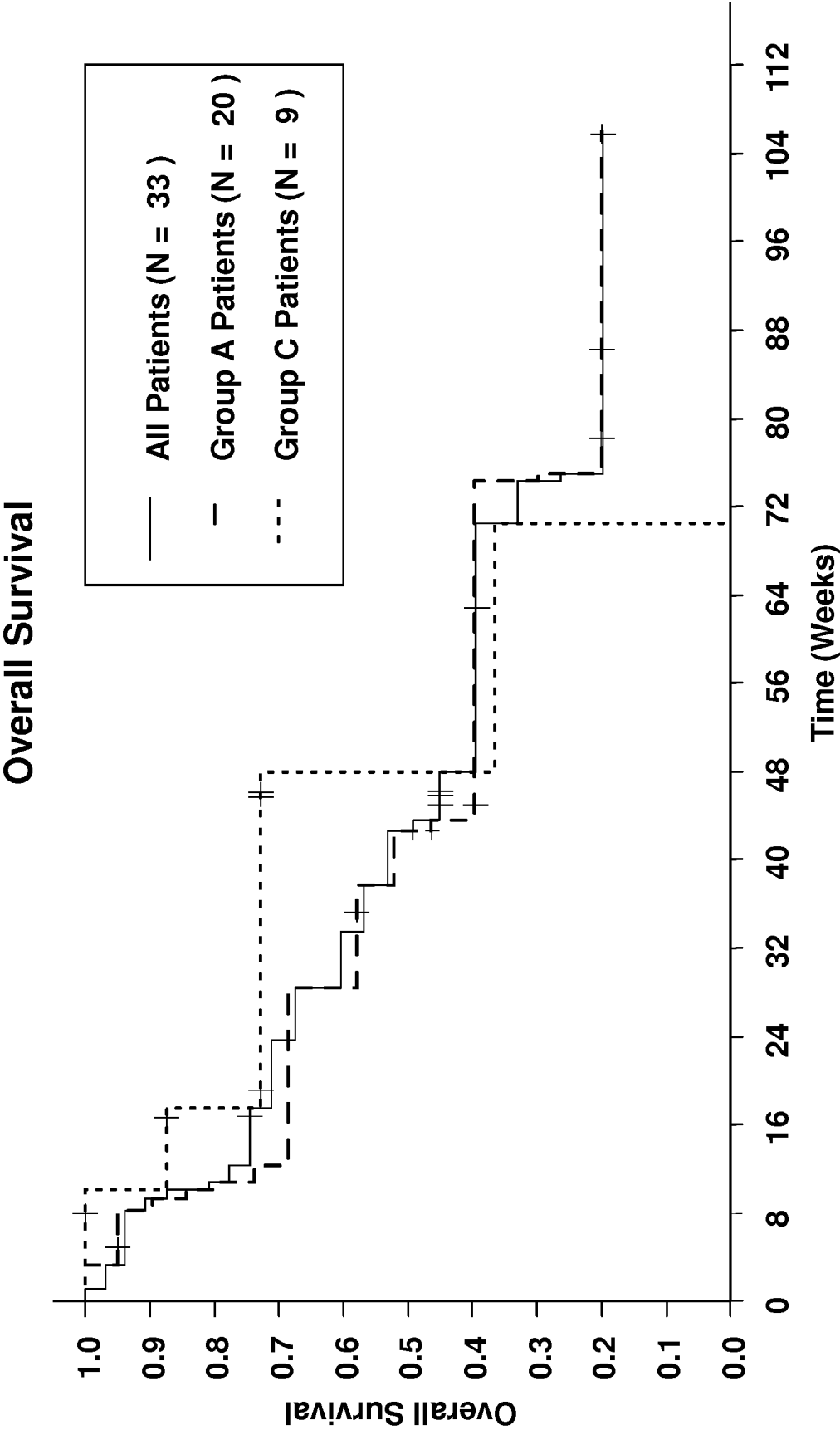
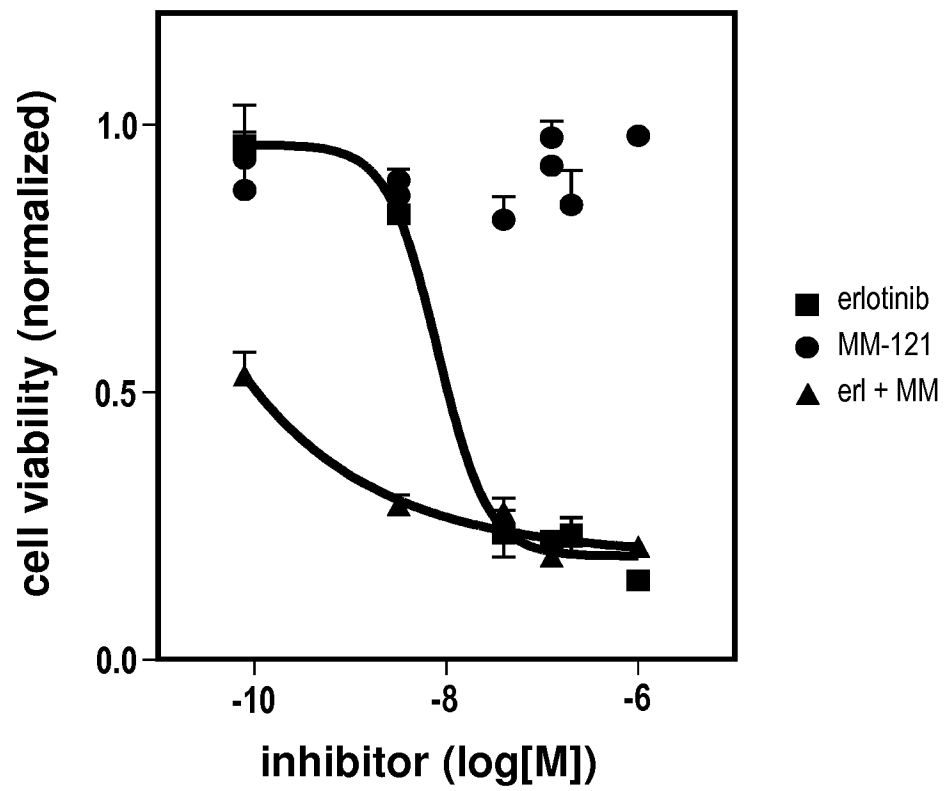


Fig. 6

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**Fig. 7**

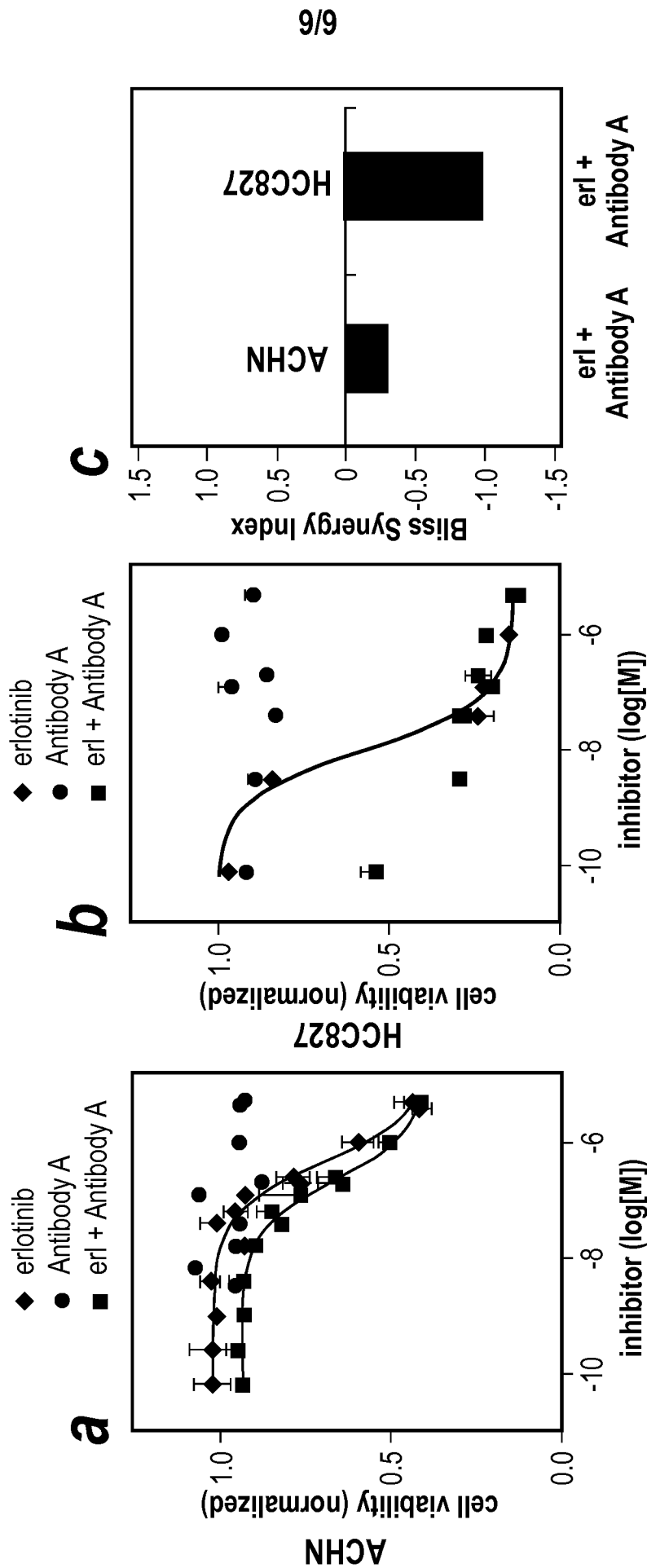


Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/41339

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395 (2012.01)
USPC - 514/19.2, 19.3; 424/143.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/395 (2012.01)
USPC - 514/19.2, 19.3; 424/143.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (PGPB, USPT, USOC, EPAB, JPAB); PatBase and Google Scholar.

Search Terms: erbb3, erb-b3, her3, antibody, mAb, cancer, non-small-cell lung cancer, NSCLC, erlotinib, cycle, day, week, regimen, treatment, therap\$, 100, month, 28 days, four weeks, 4 weeks.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/0123523 A1 (SCHOEBERL et al.) 26 May 2011 (26.05.2011) para [0004], [0021], [0123], [0128], [0182], [0188], [0202]	1-9 and 26
Y	US 2008/0221138 A1 (BUNN et al.) 11 September 2008 (11.09.2008) table 3; para [0013], [0024], [0041], [0173], [0253], [0256], [0262]	1-9 and 26
Y	US 7,846,440 B2 (SCHOEBERL et al.) 07 December 2010 (07.12.2010) entire document.	1-9 and 26

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

02 October 2012 (02.10.2012)

Date of mailing of the international search report

22 OCT 2012

Name and mailing address of the ISA/US

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Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/41339

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

a. (means)

☐

on paper

☒

in electronic form

b. (time)

☐

in the international application as filed

☒

together with the international application in electronic form

☐

subsequently to this Authority for the purposes of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

GenCore 6.4.1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/41339

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 10-16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: claims 1-9 and 26, directed to a method of treating non-small-cell lung cancer (NSCLC) in a human patient comprising administering to the patient an effective amount of (a) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (b) erlotinib, wherein the method comprises at least one cycle, wherein the cycle is a period of 28 days, and wherein said antibody and erlotinib are administered according to Dose Schedules 1, 2, 3, 3a, 4a, 4b, or 4c, as indicated.

- Please see extra sheet for continuation -

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9 and 26

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/41339

Continuation of Box III: Lack of Unity of Invention

Group II: claims 17-18, directed to a method of selecting therapy for a patient having NSCLC, said method comprising: (a) determining whether said patient's cancer comprises an activating mutation of the EGFR tyrosine kinase domain (SEQ ID NO: 15); and (b) if so, administering to said patient an effective amount of (1) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (2) erlotinib.

Group III: claims 19-25, directed to a composition for use in treating non-small-cell lung cancer (NSCLC) in a human patient, the composition comprising a clinically proven safe and effective amount (a) an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (b) erlotinib.

The inventions listed as Groups I - III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical feature of the claims of Groups I-III are indicated in the Group descriptions, above.

The common technical element shared by the above groups is that they are related to an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 5 (CDRH1) SEQ ID NO: 6 (CDRH2) and SEQ ID NO: 7 (CDRH3), and CDRL1, CDRL2, and CDRL3 sequences comprising the amino acid sequences set forth in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3) and (2) erlotinib for treatment of non-small cell lung cancer. These common technical elements do not represent an improvement over the prior art of US 2011/0027291 A1 to Schoeberl et al., which teaches antibodies to ErbB3 (abstract) comprising "particular antibodies and antigen binding portions thereof of the present invention include one or more CDR sequences selected from a heavy chain variable region CDR1 comprising SEQ ID NO: 7; a heavy chain variable region CDR2 comprising SEQ ID NO:8; a heavy chain variable region CDR3 comprising SEQ ID NO: 9; a light chain variable region CDR1 comprising SEQ ID NO:10; a light chain variable region CDR2 comprising SEQ ID NO:11; a light chain variable region CDR3 comprising SEQ ID NO: 12" para [0008]: Note - Applicants' SEQ ID NOS 5-10 are 100% identical to each of SEQ ID NOs: 7-12 of Schoeberl). Schoeberl further teaches treating (para [0004]) non-small cell lung cancer (para [0123]), by administration of the antibodies in combination with erlotinib (para [0021]).

Therefore, the inventions of Groups I-III lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.