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(54) **Title:** DOSAGE AND ADMINISTRATION OF ANTI-ERBB3 ANTIBODIES IN COMBINATION WITH PACLITAXEL

(57) **Abstract:** Provided are methods and compositions for clinical treatment of breast cancer using anti-ErbB3 antibodies combined with paclitaxel.



DOSAGE AND ADMINISTRATION OF ANTI-ERBB3 ANTIBODIES IN COMBINATION WITH PACLITAXEL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority of U.S. Provisional Application No. 61/500,752 filed June 24, 2011, U.S. Provisional Application No. 61/596,102 filed February 7, 2012 and French Patent Application No. 1252652 filed March 23, 2012, all of which are incorporated herein by reference.

BACKGROUND

Despite improvements in breast cancer therapies and late-stage options, 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 kD transmembrane receptor belonging to the ErbB/EGFR receptor tyrosine kinase family although it is kinase dead. The ErbB receptors form homo- and heterodimeric complexes that impact the physiology of cells and organs by mediating ligand-dependent activation of multiple signal transduction pathways. 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), a physiological ligand for the ErbB3 receptor, ErbB3 dimerizes with other ErbB family members, predominantly 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 therefore 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, migration and survival.

Heregulin has been shown to be involved in several different types of cancer: 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 a therapeutic approach to controlling cancer cell growth.

SUMMARY

Provided are compositions and methods for treating breast cancer in a human patient, comprising administering to the patient a combination of an anti-ErbB3 antibody and paclitaxel, wherein the combination is administered (or is for administration) according to a particular clinical dosage regimen.

An exemplary anti-ErbB3 antibody is Antibody A, described below. 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.

Accordingly, in one aspect, compositions and methods for treatment (e.g., effective treatment) of breast cancer in a human patient are provided, the methods 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) paclitaxel, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the anti-ErbB3 antibody is administered at a weekly dose of 20 mg/kg and the paclitaxel is administered at a weekly dose of 80 mg/m². In one example, the anti-ErbB3 antibody is Antibody A.

In one embodiment, the effective amount comprises administering the anti-ErbB3 antibody as a monotherapy prior to said at least one cycle.

In another embodiment, the anti-ErbB3 antibody monotherapy is administered for two weeks, wherein the anti-ErbB3 antibody is administered at 40 mg/kg the first week and at 20 mg/kg the second week.

In one embodiment, the breast cancer is ER+, HER2 non-overexpressing invasive breast cancer.

In one embodiment, breast cancer is triple negative breast cancer.

In one embodiment, paclitaxel is administered immediately following the anti-ErbB3 antibody.

In one embodiment, the patient is pretreated with an agent that prevents hypersensitivity prior to paclitaxel administration.

In one embodiment, the agent that prevents hypersensitivity is selected from the group consisting of: 20 mg of dexamethasone; 50 mg of diphenhydramine; 300 mg of cimetidine; and 50 mg of ranitidine.

In another embodiment, the patient does not have metastatic disease.

In another embodiment, the method further comprises at least one additional cycle, wherein the additional cycle is a period of two weeks, and wherein for each additional cycle doxorubicin is administered at a dose of 60 mg/m² and cyclophosphamide is administered at a dose of 600 mg/m².

In another embodiment, the breast cancer is ER+, HER2 non-overexpressing invasive breast cancer.

In another embodiment, the breast cancer is triple negative breast cancer.

In another embodiment, the breast cancer tests positive for estrogen receptor and has a Ki-67 index of 10% or greater.

In another embodiment, the breast cancer is estrogen receptor positive and is a ductal or pleomorphic lobular cancer.

In another embodiment, the breast cancer is an estrogen receptor positive breast cancer that has greater than or equal to 1% of breast cancer cell nuclei that are immunoreactive with anti-estrogen receptor antibody.

In another embodiment, the breast cancer is ductal.

In another embodiment, the breast cancer is an estrogen receptor negative breast cancer that has less than 1% of breast cancer cell nuclei that are immunoreactive with anti-estrogen receptor antibody.

In another embodiment, the patient does not have metastatic disease.

In another embodiment, the method comprises four additional cycles.

In another embodiment, the patient is further treated with peg-filgrastim on day 2 of each additional cycle, following said administration of doxorubicin and cyclophosphamide.

In another embodiment, the patient subsequently undergoes surgery to remove cancerous tissue.

In yet another embodiment, the treatment produces at least one therapeutic effect selected from the group consisting of reduction in size of a breast cancer tumor, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.

In another aspect, the invention pertains to a combination for use in treating breast cancer in a human patient, the combination 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), (b) paclitaxel, (c) doxorubicin and (d) cyclophosphamide.

In one embodiment, the anti-ErbB3 antibody is Antibody A.

In another embodiment, the antibody is formulated for intravenous administration at a dose of 20 mg/kg. In one embodiment, the antibody is formulated for administration intravenously at a dose, which results in an average target serum concentration of approximately 300-350 (e.g., about 324) mcg/ml in a patient.

In another aspect, the invention pertains to a kit comprising a dose of an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth, respectively, 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, respectively, in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), and instructions for using the anti-ErbB3 antibody in the method of claim 1. In one embodiment, the anti-ErbB3 antibody is Antibody A.

In another, the kit comprises at least 500 mg of the antibody.

In another embodiment, the kit comprises at least 1 mg of paclitaxel.

In another aspect, the invention pertains to an antiErbB3 antibody comprising SEQ ID NO: 5 (CDRH1), SEQ ID NO: 6 (CDRH2), SEQ ID NO: 7 (CDRH3), SEQ ID NO: 8 (CDRL1), SEQ ID NO: 9 (CDRL2), and SEQ ID NO: 10 (CDRL3), for co-administration with paclitaxel in at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the anti-ErbB3 antibody is administered at a weekly dose of 20 mg/kg and the paclitaxel is administered at a weekly dose of 80 mg/m².

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the response of cancer patients receiving combination therapy of Antibody A and paclitaxel. Cohort 1: MM-121 20mg/kg (loading), 12 mg/qw QW; paclitaxel 80 mg/m². Cohort 2: MM-121 40mg/kg (loading), 20 mg/qw QW; paclitaxel 80 mg/m². Exp. Cohort 1: MM-121 40mg/kg (loading), 20 mg/qw QW; paclitaxel 80 mg/m². Exp. Cohort 2: MM-121 20mg/kg (loading), 12 mg/qw QW; paclitaxel 80 mg/m². Exp. Cohort 3: MM-121 40mg/kg QOW; paclitaxel 80 mg/m².

Figure 2 shows the response of cancer patients receiving combination therapy of Antibody A and paclitaxel presented in terms of sum diameters (%).

Figure 3 shows a schematic diagram of the phase 2 clinical trial.

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 breast cancer. Effective treatment may refer to alleviation of at least one symptom of breast 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 breast cancer tumor, and/or may slow growth of a breast cancer tumor.

The terms "effective amount" refers to an amount of an agent that provides 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 paclitaxel required to provide a clinically significant decrease in breast cancer or slowing of progression of breast cancer.

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 patient. The term antibody variant also includes artificial polypeptide constructs which comprise at least one antibody-derived binding site.

As used herein, the term Ki-67 index refers to the fraction of tumor cells exhibiting immunoreactivity with an antibody (e.g., MIB-1) that specifically binds to Ki-67 (also known as MKI67), a nuclear nonhistone protein that is found in growing, dividing cells but is absent in the resting phase of cell growth.

Paclitaxel is a natural product with antitumor activity. The drug is produced via a semi-synthetic process from *Taxus baccata*. The chemical name for Paclitaxel is (5 β ,20-Epoxy-1,2 α ,4,7 β ,10 β ,13 α -hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S) -N-benzoyl-3-phenylisoserine. Paclitaxel is sold under the trade name Taxol®.

The term doxorubicin refers to the drug with the chemical name (8S,10S)-10-(4-amino-5 hydroxy-6-methyl-tetrahydro-2H-pyran-2-yloxy)-6,8,11-trihydroxy-8-(2-hydroxyacetyl)-1-methoxy-7,8,9,10-tetrahydrotetracene-5,12-dione. It is marketed under the trade names Adriamycin PFS®, Adriamycin RDF®, or Rubex®. Doxorubicin is an anthracycline antibiotic, closely related to the natural product daunomycin, and like all anthracyclines, it works by intercalating DNA. Typically, the drug is administered intravenously, in the form of hydrochloride salt. Doxorubicin is photosensitive, and containers are often covered by an aluminum bag and/or brown wax paper to prevent light from affecting it.

The term cyclophosphamide refers to the drug having the chemical name *N,N*-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2-oxide. It is marketed under the tradenames Endoxan®, Cytosan®, Neosar®, Procytox®, or Revimmune®. Cyclophosphamide is a nitrogen mustard alkylating agent from the oxazaphorines group. Alkylating agents add an alkyl group (C_nH_{2n+1}) to DNA. It attaches the alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the imidazole ring.

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. Pharmaceutical Compositions

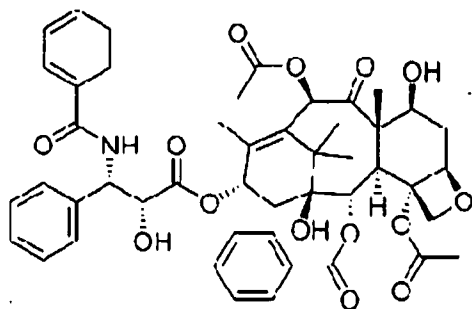
Pharmaceutical compositions suitable for administration to a patient are preferably in liquid form for intravenous administration.

In general, compositions typically comprise a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable" means approved by a government regulatory agency 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 solution saline and aqueous dextrose and glycerol solutions may be employed as carriers, particularly for injectable solutions (e.g., comprising an anti-ErbB3 antibody and/or paclitaxel). Liquid compositions for parenteral administration can be formulated for administration by injection or continuous infusion. Routes of administration by injection or infusion include intravenous, intraperitoneal, intramuscular, intrathecal and subcutaneous. In one embodiment, both anti-ErbB3 antibody and paclitaxel are administered intravenously (e.g., separately or together over the course of one hour).

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.

Paclitaxel injection, USP is a clear colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg Paclitaxel, 527 mg of polyoxyl 35 castor oil, NF1 and 49.7% (v/v) dehydrated alcohol, USP.

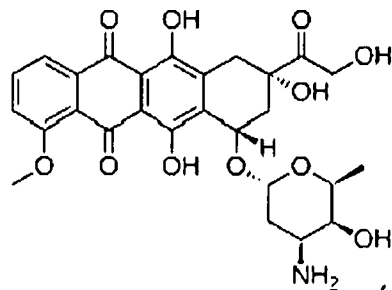
Paclitaxel has the following structural formula:



Paclitaxel is a white to off-white crystalline powder with the molecular formula $C_{47}H_{51}NO_{14}$ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216 °C to 217 °C.

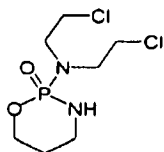
Doxorubicin is supplied in the hydrochloride form as a sterile red-orange lyophilized powder containing lactose and as a sterile parenteral, isotonic solution with sodium chloride and is also supplied as a sterile red-orange aqueous solution containing sodium chloride 0.9%. Doxorubicin is for IV use only.

Doxorubicin has the following structural formula:



CYTOXAN® (cyclophosphamide for injection, USP) is a sterile white powder containing cyclophosphamide monohydrate. CYTOXAN Tablets (cyclophosphamide tablets, USP) are for oral use and contain 25 mg or 50 mg cyclophosphamide (anhydrous). Inactive ingredients in CYTOXAN Tablets are: acacia, FD&C Blue No. 1, D&C Yellow No. 10 Aluminum Lake, lactose, magnesium stearate, starch, stearic acid, and talc.

Cyclophosphamide has the following structural formula:



IV. Patient Populations

Provided herein are effective methods for treating patients with HER2 negative breast cancer (having breast cancer tumors that test negative for HER2). In one aspect, a patient has ER+ (estrogen receptor positive), HER2 non-overexpressing invasive breast cancer. In another, the patient has triple negative breast cancer (TNBC).

ER+, HER2 non-overexpressing invasive breast cancer is characterized as:

(A) HER2 non-overexpressing, as documented by one of the following:

Negative by immunohistochemistry (IHC) staining of 0 or 1+, **OR**

Fluorescence in situ hybridization (FISH) result of less than 4.0 Her2 gene copies per nucleus, **OR**

FISH ratio of less than 1.8; and

(B) ER+, as defined having/being:

Ki-67 index of 10% or greater

Ductal or pleomorphic lobular cancers

ER+ tumors defined as $\geq 1\%$ of tumor nuclei that are immunoreactive.

Meanwhile, TNBC is characterized as:

(A) HER2 non-overexpressing, as documented by one of the following:

Negative by immunohistochemistry (IHC) staining of 0 or 1+, **OR**

Fluorescence in situ hybridization (FISH) result of less than 4.0 Her2 gene copies per nucleus, **OR**

FISH ratio of less than 1.8; and

(B) Ductal cancers; and

(C) ER negative, PR negative tumors defined as $< 1\%$ of tumor nuclei that are immunoreactive for ER and/or PR.

In yet another embodiment, the patient does not have metastatic disease.

Patients can be tested or selected for one or more of the above described clinical attributes prior to, during or after treatment.

V. Combination Therapy

As herein provided, anti-ErbB3 antibodies are administered adjunctively with paclitaxel in combination with doxorubicin and cyclophosphamide to effect improvement in subjects having breast cancer. In one embodiment, the anti-ErbB3 antibody is Antibody A.

As used herein, adjunctive or combined administration (co-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 paclitaxel, wherein both the antibody and paclitaxel are formulated together. Alternatively, the antibody can be administered in combination with the paclitaxel, wherein both the antibody and paclitaxel 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 paclitaxel, or vice versa. Such concurrent or sequential administration preferably results in both Antibody A and paclitaxel being simultaneously present in treated patients.

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. In one embodiment, the dose of antibody is 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 is initially administered at a low dose and increased over time. In another embodiment, a dose of 40 mg/kg of Antibody A antibody is administered once per week for two weeks, followed by a dose of 20 mg/kg of Antibody A antibody in combination with Paclitaxel.

VI. Treatment Protocols

Suitable treatment protocols include, for example, those wherein (A) the anti-ErbB3 antibody is administered to a patient (i.e., human subject) once per week over a course of fourteen weeks (at a dose of 40 mg/kg in the first two weeks and at a dose of 20 mg/kg over the following 12 weeks), and (B) the paclitaxel is administered to a patient once per week over the last 12 weeks of the anti-ErbB3 treatment.

In one embodiment, paclitaxel is administered in combination with an amount of Antibody A at an interval measured of at least seven days. A suitable weekly dosage of paclitaxel is 80 mg/m².

In another embodiment, a total of fourteen doses of Antibody A are administered fourteen times in a 14-week cycle, i.e., one dose per week. The administration cycle can be repeated, as necessary.

In another embodiment, the amount of Antibody A antibody 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.

In one embodiment, an anti-ErbB3 antibody is administered as a monotherapy prior to at least one cycle of anti-ErbB3 antibody/paclitaxel combination therapy. In one embodiment, anti-ErbB3 antibody monotherapy is administered for two weeks, wherein the anti-ErbB3 antibody is administered at 40 mg/kg the first week and at 20 mg/kg the second week.

VII. Outcomes

Responses to therapy may include:

Pathologic complete response (pCR)- absence of invasive cancer in the breast and lymph nodes following primary systemic treatment.

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) which has reduction in short axis to <10 mm;

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

Meanwhile, non-CR/Non-PD denotes a persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD) denotes 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 exemplary outcomes, patients treated according to the methods disclosed herein may experience improvement in at least one sign of breast cancer.

In one embodiment the patient so treated exhibits pCR, CR, PR, or SD.

In another embodiment, the patient so treated experiences tumor shrinkage 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.

In some embodiments, administration of effective amounts of the anti-ErbB3 antibody and paclitaxel according to any of the methods provided herein produce at least one therapeutic effect selected from the group consisting of reduction in size of a breast tumor, reduction in number of metastatic lesions appearing over time, complete remission, partial remission, stable disease, increase in overall response rate, or a pathologic complete response. In some embodiments, the provided methods of treatment produce a comparable clinical benefit rate ($CBR = CR + PR + SD \geq 6 \text{ months}$) better than that achieved by paclitaxel alone. In other embodiments, the improvement of clinical benefit rate is about 20%, 30%, 40%, 50%, 60%, 70%, 80% or more compared to paclitaxel alone.

VIII. 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 patient having breast cancer. In one embodiment, the kit further comprises paclitaxel. 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 paclitaxel in a desired unit dosage form (e.g., a unit dosage form distributed by the manufacturer of paclitaxel) for administration. In another embodiment, a kit may further comprise doxorubicin and cyclophosphamide.

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. Phase 1 Trial in Certain Gynecological and Breast Cancers

A phase 1 trial of Antibody A in combination with paclitaxel was conducted in patients with certain gynecological and breast cancers to evaluate the safety and tolerability of escalating doses of Antibody A antibody and paclitaxel, as well as to determine the maximum tolerated dose of Antibody A in combination with paclitaxel and to characterize dose-limiting toxicities associated with the combination.

In the study each of paclitaxel and Antibody A antibody were administered once per week. A fixed dose of paclitaxel was administered (80 mg/m² once per week) in combination with Antibody A at a dose of either i) 12 mg/kg the first week followed by 6 mg/kg weekly thereafter, ii) 20 mg/kg the first week followed by 12 mg/kg weekly thereafter, or iii) 40 mg/kg the first week followed by 20 mg/kg weekly thereafter. One treatment cycle in the study consisted of weekly treatments for four weeks. Cycles were repeated every four weeks.

To participate in the phase 1 study, patients with locally advanced/metastatic or recurrent epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, endometrial cancer, or cytological or histological confirmation of locally advanced/metastatic Her2 non-overexpressing breast cancer were identified. Those

patients with ovarian, fallopian, primary peritoneal or endometrial cancer had evidence of recurrent or persistent disease following primary chemotherapy and had received at least one prior platinum based chemotherapy regimen (or high dose therapy, consolidation treatment, or extended therapy delivered after surgical or non-surgical assessment). Those patients with ovarian, fallopian or primary peritoneal cancer were confirmed as having platinum-resistant or refractory cancer as described herein. Those patients with Her2 non-overexpressing breast cancer had evidence of recurrent or persistent disease following at least one prior therapy in the locally advanced or metastatic setting and were documented as having non Her2 overexpressing cancer (as demonstrated using methods known in the art e.g., negative by IHC staining of 0 or 1+, a FISH result of less than 4.0 Her2 gene copies per nucleus, or a FISH ratio of less than 1.8).

Summaries of preliminary responses are provided in Figures 1-2. As shown in Figure 1 patients with ovarian cancer who received combination therapy, 13 displayed a clinical benefit, as demonstrated by stable disease or partial response.

Alternate dosing schedules will be examined in an expansion cohort of 24 patients, as described below in Table 2. Dose level 1 will be enrolled first. Once all six patients have been enrolled, dose level 2 can begin enrollment, followed by dose levels 3 and 4.

Table 2: Dosing Schedule of Antibody A/Paclitaxel for Expansion Cohort

	Antibody A Dose	Paclitaxel Dose	# Patients
1	40 mg/kg loading dose x 1 (Cycle 1 Week 1) followed by 20 mg/kg weekly maintenance dose thereafter	80mg/kg paclitaxel QW	6 patients
2	20 mg/kg loading dose x 1 (Cycle 1 Week 1) followed by 12 mg/kg weekly maintenance dose thereafter	80mg/kg paclitaxel QW	6 patients
3	40mg/kg QOW of Antibody A	80mg/kg paclitaxel QW	6 patients
4	20mg/kg QOW of Antibody A	80mg/kg paclitaxel QW	6 patients

Patients receiving QOW (every other week) dosing of Antibody A will not receive Antibody A on weeks 2 and 4 of each cycle.

Example 2. Phase 2 Trial in HER2 Negative Breast Cancer

A phase 2 trial of Antibody A in combination with paclitaxel is conducted in patients with HER2 negative breast cancer to demonstrate the efficacy of administering Antibody A as part of a neoadjuvant treatment comprising paclitaxel.

Objectives

The primary objective of the study is to determine the pathologic Complete Response (pCR) rates associated with weekly treatment of Antibody A plus paclitaxel followed by the combination treatment of doxorubicin plus cyclophosphamide compared with weekly paclitaxel alone followed by the combination treatment of doxorubicin + cyclophosphamide in patients with human epidermal growth factor receptor 2 (HER2)-negative primary breast cancer.

The secondary objectives of the study are: to characterize the toxicity of the treatment arms; to determine the clinical activity of the treatment arms at tumor resection based on residual cancer burden index; to evaluate the change in Ki-67 tumor marker in residual disease at surgery; to characterize the pharmacokinetics of Antibody A and paclitaxel; to characterize the immunogenicity of Antibody A; to assess if a biomarker profile (based on one or a composite set of pre-specified biomarkers) can predict a sub-population which can benefit from treatment as measured by improvement in pCR; and to assess changes in the following pharmacodynamic biomarkers and investigate the relationship between these changes, Antibody A exposure and anti-tumor activity: tErb3, pErbB3, pAKT, and pERK in pre-treatment and post-treatment tumor tissue.

Additional objectives of the study include assessing the pharmacodynamic changes associated with Antibody A and/or paclitaxel on additional downstream targets of key prosurvival pathways and assessing if additional biomarkers from serum or tumor tissue samples can be utilized to predict for response/ resistance to Antibody A as measured by pCR and RCB index.

Study Design

This is a multicenter, open-label, randomized, Phase II study of preoperative Antibody A with chemotherapy in HER2-negative breast cancer patients. See Figure 3.

Patients are randomized to receive paclitaxel with or without Antibody A for 12 weeks followed by 4 cycles of doxorubicin plus cyclophosphamide and surgery. The trial is designed to demonstrate whether addition of Antibody A to paclitaxel is more effective than treatment with paclitaxel alone, when administered as part of neoadjuvant treatment in Her2 negative locally advanced operable breast cancer patients.

Two groups of patients will participate in this study:

Group 1: Patients with ER+, HER2 non-overexpressing invasive breast cancer (ER+ tumors defined as $\geq 1\%$ of tumor nuclei that are immunoreactive);

Group 2: Patients with Triple Negative disease (ER- tumors defined as $< 1\%$ of tumor nuclei that are immunoreactive).

A total of 200 patients are enrolled in the study, with 100 patients in each group. Patients will participate in up to 28 days of screening, during which time they will complete all screening procedures. Patients who are eligible for the study are randomized using a computerized IVR system, in a 2:1 ratio, to receive the following therapies (1 cycle = 3 weeks):

- Arm A: 2 week run-in of Antibody A followed by 4 cycles of paclitaxel plus Antibody A followed by 4 cycles of doxorubicin and cyclophosphamide
- Arm B: 4 cycles of paclitaxel followed by 4 cycles of doxorubicin and cyclophosphamide

One treatment cycle with paclitaxel or paclitaxel plus Antibody A consists of weekly treatments for 3 weeks. Treatment with doxorubicin and cyclophosphamide consists of one administration every 2 weeks. Patients may discontinue study therapy prior to completion of the required number of cycles with therapy if they have documented radiological or clinical progression of disease or intolerable toxicity. Once the patient completes study therapy, they are followed up at 30 days (± 15 days) post treatment discontinuation.

Core biopsies are collected during screening and after week 3 of paclitaxel treatment (patients in Arm A [Antibody A Arm] may decline the biopsy after week 3 of paclitaxel plus Antibody A treatment). Patients randomized to Arm A, undergo an additional core biopsy after the 2 week run-in with Antibody A.

Treatment and Safety Assessments

Antibody A plus paclitaxel or paclitaxel alone is administered as a 1-hour IV infusion once per week (± 2 days) for 12 weeks. Doxorubicin plus cyclophosphamide are administered as a 1-hour IV infusion once every 2 weeks for 4 cycles. Post tumor resection, additional chemotherapy and/or radiation therapy may be given at the physician's discretion.

Patients are treated until they undergo surgery.

Inclusion Criteria

Patients will have had no prior treatment for this cancer including chemotherapy, surgery (except for diagnostic biopsy), radiotherapy, hormonal therapy, or investigational product. Clinically or radiologically measurable disease in the breast after diagnostic biopsy defined as longest diameter greater than or equal to 2cm (T2, T3, or T4).

Patients are enrolled into 1 of 2 groups: those with TN breast cancer and those with ER+, HER2 non-overexpressing invasive breast cancer. It is to be noted that ER positivity is defined as $\geq 1\%$ tumor nuclei that are immunoreactive while ER negativity is defined as $< 1\%$ tumor nuclei that are immunoreactive (Hammond 2010).

Patients must have/be:

Histological confirmation of locally advanced ER+, HER2 non-overexpressing invasive breast cancer (Group 1) or invasive triple negative breast cancer (Group2).

Group 1: (ER+, HER2 non-overexpressing invasive breast cancer)

HER2 non-overexpressing status documented as one of the following:

Negative by immunohistochemistry (IHC) staining of 0 or 1+, OR
Fluorescence in situ hybridization (FISH) result of less than 4.0 Her2 gene copies per nucleus, OR
FISH ratio of less than 1.8

ER+ tumors should have/be:

Ki-67 index of 10% or greater
Ductal or pleomorphic lobular cancers
ER+ tumors defined as $\geq 1\%$ of tumor nuclei that are immunoreactive

Group 2: (Triple negative breast cancer)

HER2 non-overexpressing status documented as one of the following:

Negative by immunohistochemistry (IHC) staining of 0 or 1+, OR
Fluorescence in situ hybridization (FISH) result of less than 4.0 Her2 gene copies per nucleus, OR
FISH ratio of less than 1.8

In addition, TN tumors should be:

Ductal cancers

ER negative, PR negative tumors defined as < 1% of tumor nuclei that are immunoreactive for ER and/or PR.

Exclusion Criteria

Patients will not be entered in the study for any of the following reasons: have evidence of metastatic disease; active infection or an unexplained fever > 38.5°C during screening visits or on the first scheduled day of dosing, which in the Investigator's opinion, might compromise the patient's participation in the trial or affect the study outcome (at the discretion of the investigator, patients with tumor fever may be enrolled); have a known hypersensitivity to any of the components of Compound A or who have had hypersensitivity reactions to fully human monoclonal antibodies; have a New York Heart Association (NYHA) Class III or IV congestive heart failure or left ventricular ejection fraction (LVEF) < 55%; (Patients 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); have a history of severe allergic reactions to paclitaxel or other drugs formulated in Cremaphor® EL; are pregnant or breastfeeding; have any other medical condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate and participate in the study, or interfere with the interpretation of the results or have a need for chronic steroid therapy.

Dose Levels

Antibody A is administered weekly. Study drug should be brought to room temperature prior to administration. Vials of study drug should not be shaken. The appropriate quantity of study drug is removed from the vial, diluted in 250mL of 0.9% normal saline and administered over 90 minutes, for the first infusion, and over 60 minutes for all subsequent infusions, using compatible infusion sets with a low protein binding 0.22micrometer in-line filter.

A patient's body weight at the start of a cycle is to be used to calculate the dose used throughout the cycle. The first dose of Antibody A administered is 40mg/kg. Following this loading dose, the subsequent weekly dose of Antibody A is 20 mg/kg. Should a patient's body weight change by 10%, a new total dose should be calculated to reflect this change.

Paclitaxel is a clear, colorless to slightly yellow viscous solution. It is supplied as a non aqueous solution intended for dilution with a suitable parenteral fluid prior to IV infusion. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile non pyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Vials of paclitaxel should be stored in the original cartons between 20° to 25°C (68° to 77°F) and protected from light.

Paclitaxel is administered at the dose of 80 mg/m² weekly, as an IV infusion over 60 minutes. For patients also receiving Antibody A, paclitaxel should be administered immediately following the Antibody A dose. All patients should be pre-medicated prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Such premedication may consist of 20mg (orally) dexamethasone administered approximately 12 and 6 hours before paclitaxel, 50 mg (IV) diphenhydramine (or its equivalent) administered 30 to 60 minutes prior to paclitaxel, and 300 mg cimetidine (IV) or 50 mg ranitidine (IV) administered 30 to 60 minutes before paclitaxel.

Doxorubicin and Cyclophosphamide

Doxorubicin is supplied in the hydrochloride form as a sterile red-orange lyophilized powder containing lactose and as a sterile parenteral, isotonic solution with sodium chloride for IV use only. Lyophilized cyclophosphamide for injection is a sterile white lyophilized cake, or partially broken cake, containing 75 mg mannitol per 100 mg cyclophosphamide (anhydrous).

Doxorubicin is stored at 15° to 30°C (59° to 86°F) and protected from light. All unused portions should be discarded.

Cyclophosphamide is stored at or below 25°C (77°F). The product will withstand brief exposure to temperatures up to 86°F (30°C) but should be protected from temperatures above 30°C (86°F).

Doxorubicin is administered at dose of 60mg/m² IV as a single IV injection. All patients will receive doxorubicin once every 2 weeks for 4 cycles.

Cyclophosphamide is administered at a dose of 600mg/m² IV. All patients will receive cyclophosphamide once every 2 weeks for 4 cycles

Group 2 patients (TNBC) are recommended to receive peg-filgrastim on day 2 following administration of doxorubicin and cyclophosphamide of every cycle.

Dose Modification

Infusion reactions are defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; Version 4.0) definition of an allergic reaction/hypersensitivity as outlined below:

Grade 1	Transient flushing or rash, drug fever < 38°C (< 100.4°F); intervention not indicated
Grade 2	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics); prophylactic medications indicated for ≤ 24 hrs
Grade 3	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension
Grade 4	Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines are used for the management of infusion reactions.

Grade 1	<ul style="list-style-type: none"> • Slow infusion rate by 50% • Monitor patient every 15 minutes for worsening of condition
Grade 2	<ul style="list-style-type: none"> • Stop infusion • Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen • Resume infusion at 50% of the prior rate once infusion reaction has resolved • Monitor patient every 15 minutes for worsening of condition • For all subsequent infusions, pre-medicate with diphenhydramine hydrochloride 25 to 50 mg IV

Grade 3	<ul style="list-style-type: none"> • Stop infusion and disconnect infusion tubing from patient • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary • No further treatment with Antibody A is permitted
Grade 4	<ul style="list-style-type: none"> • Stop the infusion and disconnect infusion tubing from patient • Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV • Consider hospital admission for observation • No further treatment with Antibody A is permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 90 minutes).

For patients who experience a second Grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. Subsequent infusions are premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

For patients randomized to the Antibody A arm who experience a Grade 3 or 4 infusion reaction, an anti-Antibody A antibody assay is taken as close to the onset of the infusion reaction as possible for any patient experiencing an infusion reaction to Antibody A. Anti-Antibody A antibody assays should also be obtained at the resolution of the event and 28 days ($\pm$ 2 days) following the event.

Management of Toxicities

In the event of Grade 1 or 2 toxicities that are possibly related to Antibody A treatment, it is decided whether to continue treatment. In the event that a patient experiences a toxicity $\geq$ Grade 3 that is possibly related to Antibody A treatment, further treatment with Antibody A is held until the toxicity resolves to Grade 1 or baseline. In the event that Antibody A treatment has been held for 28 consecutive days without resolution of the toxicity to baseline or Grade 1, the patient is discontinued from the study.

Based on the toxicity, the Antibody A dose may be to 15 mg/kg for future dose(s).

Patients should have an $ANC > 1000/mm^3$ prior to beginning treatment with paclitaxel. Weekly doses may be postponed if a patient experiences a grade 2, 3, or 4 toxicity or if $ANC < 1000/mm^3$. Paclitaxel dosing can be resumed once toxicities return to $\leq$ grade 1 and/or $ANC \geq 1000/mm^3$. Dose reductions are not recommended for paclitaxel.

For Doxorubicin and Cyclophosphamide, starting doses may be reduced, if necessary. Doxorubicin may be reduced from a starting dose of 60 mg/m² to 50 mg/m². Cyclophosphamide may be reduced from a starting dose of 600 mg/m² to 500 mg/m².

Patients not receiving G-CSF should have an $ANC > 1200/mm^3$ prior to beginning treatment with doxorubicin/cyclophosphamide. Patients who are receiving G-CSF should have an $ANC > 1000/mm^3$ to begin doxorubicin/cyclophosphamide treatment. Patients who experience a grade 3 or 4 non-hematologic toxicity or febrile neutropenia (in spite of G-CSF) should be dose reduced to Level A.

Extent of Disease Assessment

Evaluation can include physical exam via bi-dimensional measurements of breast mass and any auxiliary lymph nodes and/or standard imaging modalities (CT Scans, MRI scans, Ultrasounds) as appropriate. Patients who are being followed via radiologic methods need only to be scanned every other cycle.

Pharmacokinetic Assessments

For patients receiving Antibody A, serum levels of Antibody A and paclitaxel are measured at a central analytical lab using an ELISA based assay. To better understand the PK and safety profile of Compound A and paclitaxel combination, additional analytes may also be measured. Directions for processing and shipping the PK serum samples can be found in the study manual.

Biomarker Assessments

The following assessments are included as part of routine study follow up for all patients participating in the study:

Serum Biomarkers

Blood samples are collected to conduct exploratory studies to further characterize and correlate possible biomarkers that evaluate response, potential resistance, and toxicity to Antibody A. Samples are used to conduct specific biomarker analysis, or, in the event that there is remaining sample available after conducting these analyses, it is stored and

used by the Sponsor for future biomarker analysis related to Antibody A. At the time of informed consent, patients are able to refuse storage of these remaining samples.

Research Core Biopsies

Tumor samples are collected from patients via biopsies performed prior to the first dose administration, after the two-week Antibody A monotherapy run-in (for patients in Arm A), and after week 3 of paclitaxel +/- Antibody A therapy (patients in Arm A may decline this biopsy time point). Tumor samples collected through these biopsies are compared and will also be analyzed to explore the biomarkers that could predict response to the Antibody A. Ki-67 analysis will also be performed centrally on all biopsies.

Statistical Considerations

The primary endpoint of this study is the pCR. The difference in pCR rates in the 2 treatment arms of each group is estimated. The 80% confidence interval for the estimated difference is calculated.

The secondary endpoints include residual cancer burden, change in Ki-67 index in residual disease at surgery, molecular biomarkers associated with Antibody A therapy, PK, immunogenicity, and toxicities. All efficacy evaluation are based on efficacy evaluable population. The residual cancer burden index is measured using the MD Anderson Residual Tumor Burden Calculator and be also reported with 95% CI. Results are provided by treatment arms for each group separately.

All patients receiving at least 1 dose of the study regimen are included in the safety analysis. Toxicities are evaluated according to the CTCAE, version 4.0. Incidence and type of Grade 3 and Grade 4 adverse events (AEs), including serious adverse events (SAEs), are tabulated and summarized using descriptive statistics. Frequency of toxicity are tabulated according to the CTCAE.

Statistical Hypothesis and Determination of Sample Size

The trial is designed as an estimation trial without formal hypothesis testing. The primary analysis will consist of estimating the difference in the pCR rates between treatment arms in each patient group and calculating the 80% confidence interval (CI) for the difference.

For the TN group, 100 patients are enrolled in a 2:1 allocation (67 in Antibody A treated arm and 33 in the control arm). The likelihood that the 80% CI will exclude no effect is about 73% if the assumed pCR rates are 35% in control arm and 55% in Antibody A treated arm. This likelihood will increase to 80% if the pCR rate in Antibody A treated arm is 57% and to 90% if the pCR rate in Antibody A treated arm is 62%, while the pCR rate in the control arm remains to be 35%.

For the ER+/HER2-negative group, 100 patients are enrolled in a 2:1 allocation (67 in Antibody A treated arm and 33 in the control arm). The likelihood that the 80% CI will exclude no effect is about 71% if the assumed pCR rates are 10% in control arm and 25% in Antibody A treated arm. This likelihood will increase to 80% if the pCR rate in Antibody A treated arm is 28% and to 90% if the pCR rate in Antibody A treated arm is 32%, while the pCR rate in the control arm remains to be 10%.

Statistical and Analytical Plans

There are 2 patient populations for this study.

- Efficacy Evaluable: This population includes all patients who receive at least 6 doses of the study drug followed by surgery. This population is the primary population for all efficacy parameters.
- Safety population: The safety population includes all randomized patients who received at least 1 infusion (including a partial dose) of study medication. This population is for safety analyses. All analyses using this population are based on the treatment actually received.

Efficacy Analyses

The primary endpoint of this study is pathologic complete response (pCR), which is defined as the absence of invasive cancer in the breast and lymph nodes following primary systemic treatment. After completing 12 weeks of treatment with Antibody A + paclitaxel or paclitaxel alone followed by 4 cycles of doxorubicin + cyclophosphamide, patients will undergo surgery for tumor removal. Tumor block/tissue sample is examined locally for pCR and residual disease is quantified for secondary endpoint analyses.

The primary analysis will consist of estimating the difference in the pCR rates between treatment arms in each patient group, including calculation of 80% CI for the difference using normal approximation.

For secondary efficacy endpoints, the residual tumor burden index is measured using the MD Anderson Residual Tumor Burden Calculator at the time of tumor resection. The residual tumor burden index is summarized by treatment arms also reported with 95% CI. The Ki-67 tumor marker in residual disease is obtained at surgery. The change in Ki-67 tumor marker in residual disease at surgery relative to prior research biopsy time points are summarized by treatment arm.

For safety endpoints, treatment-emergent AEs are presented by treatment group, by patient, by NCI CTCAE Grade and by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and preferred term. Separate listings are presented for total AEs, SAEs, AEs related to Antibody A, and Grade 3/4 AEs. Abnormal laboratory values are assessed according to NCI CTCAE Grade, where possible. Evaluation of corrected QT interval (QTc) are based upon Fridericia's correction method (QTcF). The CTCAE criteria are applied to the QTcF. The incidence of anti-Antibody A immunogenicity is summarized by treatment arm.

Pharmacokinetic (PK) Analysis

Serum concentrations are used to determine the PK parameters using standard non-compartmental techniques. The PK parameters are summarized using descriptive statistics, including the median, mean and 95% confidence intervals around parameter estimates by dose level. Pharmacokinetic parameters will include maximum serum concentration of the drug (C_{max}), time to C_{max} (t_{max}), area under the concentration-time curve (AUC), AUC to the last observable concentration at time t (AUC_t), clearance (CL), volume of distribution at steady state (V_{dss}), and the terminal elimination half-life (t_{1/2}), when applicable.

Pharmacodynamic and Biomarker Data Analyses

Tumor blocks or unstained slides containing tumor tissue from time of initial diagnosis is collected from each patient and processed to obtain quantitative measurements of the predictive biomarkers for Antibody A sensitivity. The biomarkers consist of the receptors EGFR (ErbB1), Her-2-neu (Erb-B2), Her-3 (Erb-B3) measured by immunohistochemistry, and the messenger RNA expression of the ligands betacellulin

and heregulin (neuregulin-1) measured by reverse transcription polymerase chain reaction (RT-PCR).

In order to evaluate the pharmacodynamics of the Antibody A combinations, direct sampling of the patient's tumor is completed through core biopsies obtained prior to first dose administration, at the end of the patient's first cycle of treatment and from the surgical specimen obtained after the completion of study therapy. The levels of tErbB3, pErbB3, pAKT, and pERK are analyzed in pre- and post-treatment samples. These tumor samples are analyzed as paired samples (pre- and post-treatment measures from each patient). The data are characterized using means and 95% confidence intervals for pre-treatment concentrations for the population and the mean and 95% confidence intervals for normalized change from baseline in paired samples.

In addition, biomarker measurements are obtained from serum samples collected at baseline and throughout the course of the study to evaluate whether serum markers correlate with findings from the tumor sample analyses and/or overall efficacy findings (serum heregulin, for example).

The primary goal of the biomarker analysis is to assess the potential predictive use of each or any combinations of the candidate biomarkers measured at baseline (pre-treatment). The preliminary approach of the assessment is to examine if the treatment effect is modified by any biomarker(s). For this purpose, a logistic regression model is fitted with pCR as the outcome and with treatment assignment, biomarker of interest and cross-interaction between treatment assignment and biomarker as covariates. If the interaction exists, as determined by an $\alpha=0.10$ test, which implies that the treatment effect is modified by the biomarker, then the biomarker can potentially be predictive and warrant further examinations.

The power to detect treatment and biomarker interaction was assessed by simulations. It is assumed that the biomarker values (or transforms) are normally distributed with common variance and the biomarker is predictive with the biomarker values differing between the responders and non-responders only in the Antibody A treated arm. It is further assumed that effectively all patients will have a pre-treatment measurement for the biomarker of interest, and the pCR rates are 55% and 35% in the

Antibody A treated arm and chemo-alone arm, respectively, in the TN patient cohort, and 25% and 10% in the Antibody A treated arm and chemo-alone arm, respectively, in the ER+ patient cohort. If the mean biomarker values differ between responders and non-responders in the Antibody A treated arm by 1.5 standard deviations, then the power to detect an interaction between the biomarker and treatment based on an $\alpha=0.10$ test is about 88% in the TN cohort and 63% in the ER+ cohort. If the means differ by 2 standard deviations, the power will increase to 97% in the TN cohort and 77% in the ER+ cohort. However, if the difference in the means is as small as 1 standard deviation, then the power will drop to 67% in the TN cohort and 40% in the ER+ cohort.

Other metrics including positive predictive value, negative predictive, sensitivity and specificity is evaluated by treatment arms if appropriate biomarker thresholds can be established.

Intra- and inter-arm pharmacodynamic (PD) changes in biomarkers (e.g., tErbB3, pErbB3, pAKT, and pERK) are evaluated utilizing paired pre-/post-treatment patient tumor biopsies. All patients are expected to have a pre-treatment tumor biopsy. Within the Antibody A arm a second biopsy is specified as mandatory after 2 weeks of monotherapy and a third is optional after 3 weeks of Antibody A and paclitaxel combined therapy. A mandatory second biopsy is also specified after 3 weeks of treatment in the paclitaxel arm.

A 1-sample t-test is used to assess intra-arm PD effects after 2 weeks of monotherapy in the Antibody A treated arm and after 3 weeks of monotherapy in the paclitaxel arm, respectively. The analyses is done within each cohort separately and in the combined cohorts assuming consistent inter-cohort intra-arm biomarker changes.

A 2-sample t-test is used to assess whether there is an inter-arm difference in intra-arm biomarker PD effects after 2 weeks of monotherapy with Antibody A alone versus 3 weeks of monotherapy with paclitaxel alone). The same type of analysis is used to compare the difference in intra-arm biomarker PD effects in the Antibody A arm after 3 weeks of combination therapy to that in the paclitaxel arm after 3 weeks of monotherapy with paclitaxel alone.

Those skilled in the art will recognize, and is 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.

All patents, patent applications and publications cited herein are incorporated herein by reference in their entireties.

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 tcttgccgccg ccagcggctt caccttcagc cactacgtga tggcctgggt gcggcaggcc ccaggcaagg gcctggaatg ggtgtccagc atcagcagca gcggcggctg gacctgtac gccgacagcg tgaagggcag gttcaccatc agcagggaca acagcaagaa caccctgtac ctgcagatga acagcctgag ggccgaggac accgccgtgt actactgcac caggggcctg aagatggcca ccatcttcga ctactggggc cagggcaccc tgggtaccgt 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 tgaccagcc cggcagcgtg agcggcagcc caggccagag catcaccatc agctgcaccg gcaccagcag cgacgtgggc agctacaacg tgggtgctctg gtatcagcag caccgccgca agggcccaaa gctgatcatc tacgaggtgt cccagaggcc 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	Human	PROTEIN	His Tyr Val Met Ala

	CDR1 (CDRH1) of Antibody A	CDRH1		
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 EVQLLES GGG LVQP GGS LRL SCAAS GFTFS HYVMAWVRQA PGKGLEWVSS 51 ISSSGGWITLY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCTRGL 101 KMATIFDYWG QGTLVTSSA STKGPSVFPL APCSRSTSES TAALGCLVKD 151 YFPEPVTWSV NSGALTSGVH TFP AVLQSSG LYSLSSVTV PSSNFGTQTY 201 TCNVDHKPSN TKVDKTV ERK CCVECPPCPA PPVAGPSVFL FPPKPKDILM 251 ISRTPEVTCV VVDVSHEDPE VQFNWYVDGV EVHNAKTKPR EEQFNSTFRV 301 VSVLTIVHQD WLNGKEYKCK VSNKGLPAPI EKTIISKTKGQ PREPQVYILP 351 PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQFENNYK TTPPMLDS DG 401 SFFLYSKLTV DKSRWQOGNV 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 KVGVEITKPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCRV 201 THEGSTVEKT VAPAECS
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CLAIMS

WE CLAIM:

1. A method of treating breast cancer 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) paclitaxel, wherein the method comprises at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the anti-ErbB3 antibody is administered at a weekly dose of 20 mg/kg and the paclitaxel is administered at a weekly dose of 80 mg/m².
2. The method of claim 1, wherein the anti-ErbB3 antibody is Antibody A.
3. The method of claims 1 or 2, wherein said effective amount comprises administering the anti-ErbB3 antibody as a monotherapy prior to said at least one cycle.
4. The method of any one of claims 1-3, wherein said anti-ErbB3 antibody monotherapy is administered for two weeks, wherein the anti-ErbB3 antibody is administered at 40 mg/kg the first week and at 20 mg/kg the second week.
5. The method of any one of claims 1-4, wherein said breast cancer tests positive for estrogen receptor and is a HER2 non-overexpressing invasive breast cancer.
6. The method of any one of claims 1-5, wherein said breast cancer is triple negative breast cancer.
7. The method of any one of claims 1-6, wherein paclitaxel is administered immediately following the anti-ErbB3 antibody.
8. The method of any one of claims 1-7, wherein the patient is pretreated with an agent that prevents hypersensitivity prior to paclitaxel administration.

9. The method of claim 8, wherein the agent that prevents hypersensitivity is selected from the group consisting of: 20 mg of dexamethasone; 50 mg of diphenhydramine; 300 mg of cimetidine; and 50 mg of ranitidine.
10. The method according to any one of claims 1-9, wherein the patient does not have metastatic disease.
11. The method according to any one of claims 1-10, wherein the method further comprises at least one additional cycle, wherein the additional cycle is a period of two weeks, and wherein for each additional cycle doxorubicin is administered at a dose of 60 mg/m² and cyclophosphamide is administered at a dose of 600 mg/m².
12. The method of claim 11, wherein said breast cancer tests positive for estrogen receptor and is a HER2 non-overexpressing invasive breast cancer.
13. The method of claim 11, wherein said breast cancer is triple negative breast cancer.
14. The method of any of claims 11-13, wherein said method comprises four additional cycles.
15. The method of claim 11, wherein the patient is further treated with peg-filgrastim on day 2 of each additional cycle, following said administration of doxorubicin and cyclophosphamide.
16. The method according to claim 11, wherein the patient subsequently undergoes surgery to remove cancerous tissue.
17. The method of any one of claims 1-16, wherein the treatment produces at least one therapeutic effect selected from the group consisting of reduction in size of a tumor, reduction in number of metastatic lesions over time, complete response, partial response, stable disease, increase in overall response rate, or a pathologic complete response.
18. A combination for use in treating breast cancer in a human patient, the combination 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), (b) paclitaxel, (c) doxorubicin and (d) cyclophosphamide.

19. The combination of claim 18, wherein the anti-ErbB3 antibody is Antibody A.

20. The combination of claims 18 or 19, wherein the antibody is formulated for intravenous administration at a dose of 20 mg/kg.

21. A kit comprising a dose of an anti-ErbB3 antibody comprising CDRH1, CDRH2, and CDRH3 sequences comprising the amino acid sequences set forth, respectively, 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, respectively, in SEQ ID NO: 8 (CDRL1) SEQ ID NO: 9 (CDRL2) and SEQ ID NO: 10 (CDRL3), and instructions for using the anti-ErbB3 antibody in the method of claim 1.

22. The kit of claim 21, said kit comprising at least 500 mg of the antibody.

23. The kit of claim 21, said kit comprising at least 1 mg of paclitaxel.

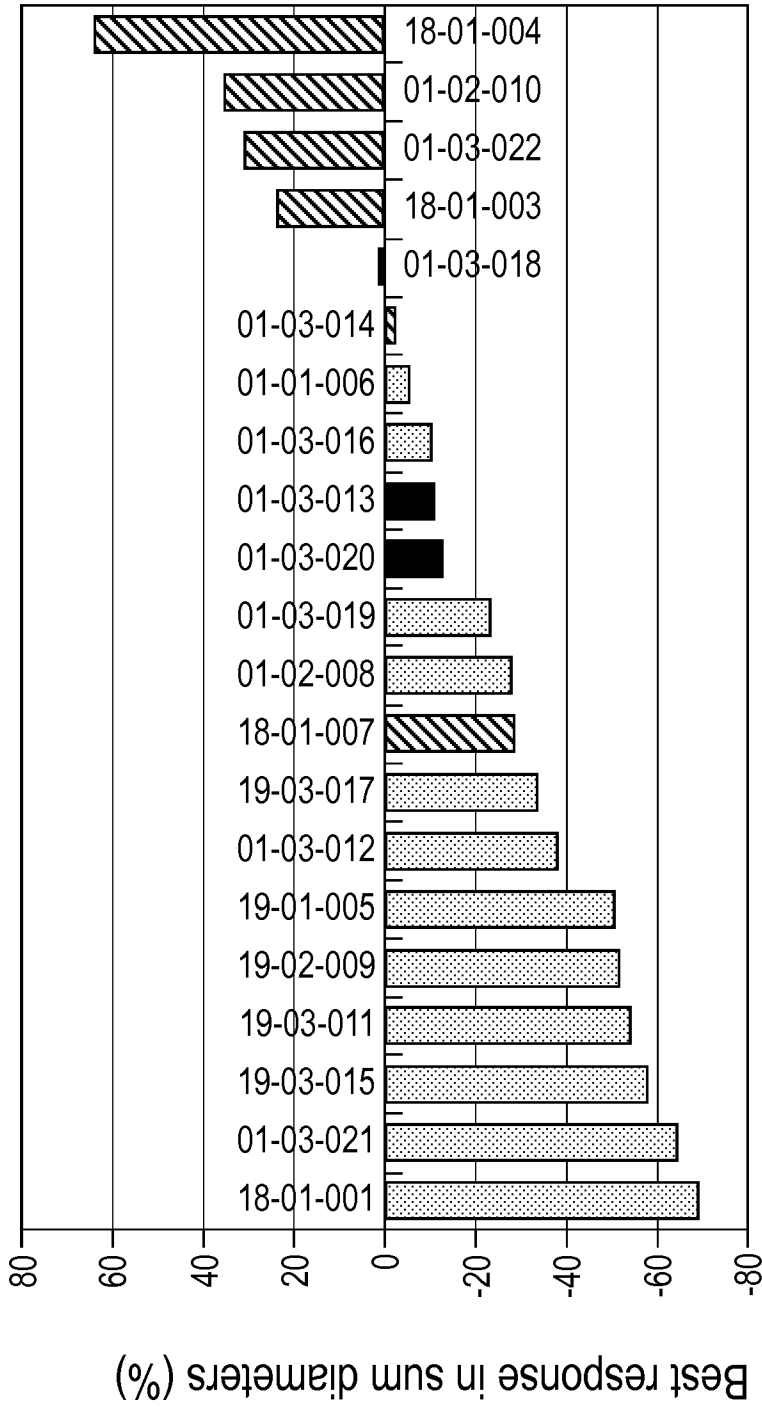
24. An antiErbB3 antibody comprising SEQ ID NO: 5 (CDRH1), SEQ ID NO: 6 (CDRH2), SEQ ID NO: 7 (CDRH3), SEQ ID NO: 8 (CDRL1), SEQ ID NO: 9 (CDRL2), and SEQ ID NO: 10 (CDRL3), for co-administration with paclitaxel in at least one cycle, wherein the cycle is a period of 3 weeks, and wherein for each cycle the anti-ErbB3 antibody is administered at a weekly dose of 20 mg/kg and the paclitaxel is administered at a weekly dose of 80 mg/m²

Phase 1 Antibody A plus paclitaxel in Breast and Ovarian Cancer

Patient	Cancer	Treatment Duration												Best Response	Reason for Study Discontinuation	Comments
Cohort 1																
18-01-001	Ovarian													PR (-69%)	PD	unrelated to disease / treatment
19-01-002	Breast													UNK	Death	
18-01-003	ER+, HER2- Breast													PD (24%)	PD	tumor growth slowed? clinical deterioration
18-01-004	ER+, HER2- Breast													PD (64%)	PD	
19-01-005	Ovarian													PR (-51%)	PD	
01-01-006	Ovarian													SD (-6%)	PD (27%)	
18-01-007	Ovarian													SD (-29%)	PD (n/a)	
01-02-008	Ovarian													SD (-28%)	**	
19-02-009	Ovarian													PR (-52%)	**	tumor growth slowed? clinical deterioration
01-02-010	Ovarian													PD (35%)	PD (35%)	
Expansion Cohort 1																
19-03-011	ER+/PR+, HER2- Breast													PR (-55%)	**	Symptomatic deterioration Pneumonitis no shrinkage
01-03-012	Ovarian													PR (-38)	AE	
01-03-013	Ovarian													SD (-10%)	SAE	
01-03-014	Ovarian													SD (-3%)	PD (n/a)	
19-03-015	ER+, HER2-Breast													PR (-58%)	PD (n/a)	PD liver mets only
01-03-016	Ovarian													SD (-10%)	PD (n/a)	
Expansion Cohort 2																
19-03-017	ER+, HER2- Breast													PR (-34%)	**	G3 Fatigue G3 Fatigue
01-03-018	Ovarian													SD (1%)	AE	
01-03-019	Ovarian													SD (-23%)	**	
01-03-020	Ovarian													SD (-13%)	AE	
01-03-021	TNBC													PR (-64%)	**	on study off study
01-03-022	Ovarian													PD (32%)	PD	
01-03-023	ER+, HER2- Breast															
Expansion Cohort 3																

Fig. 1

Preliminary Phase 1 Antibody A plus paclitaxel in Breast and Ovarian Cancer

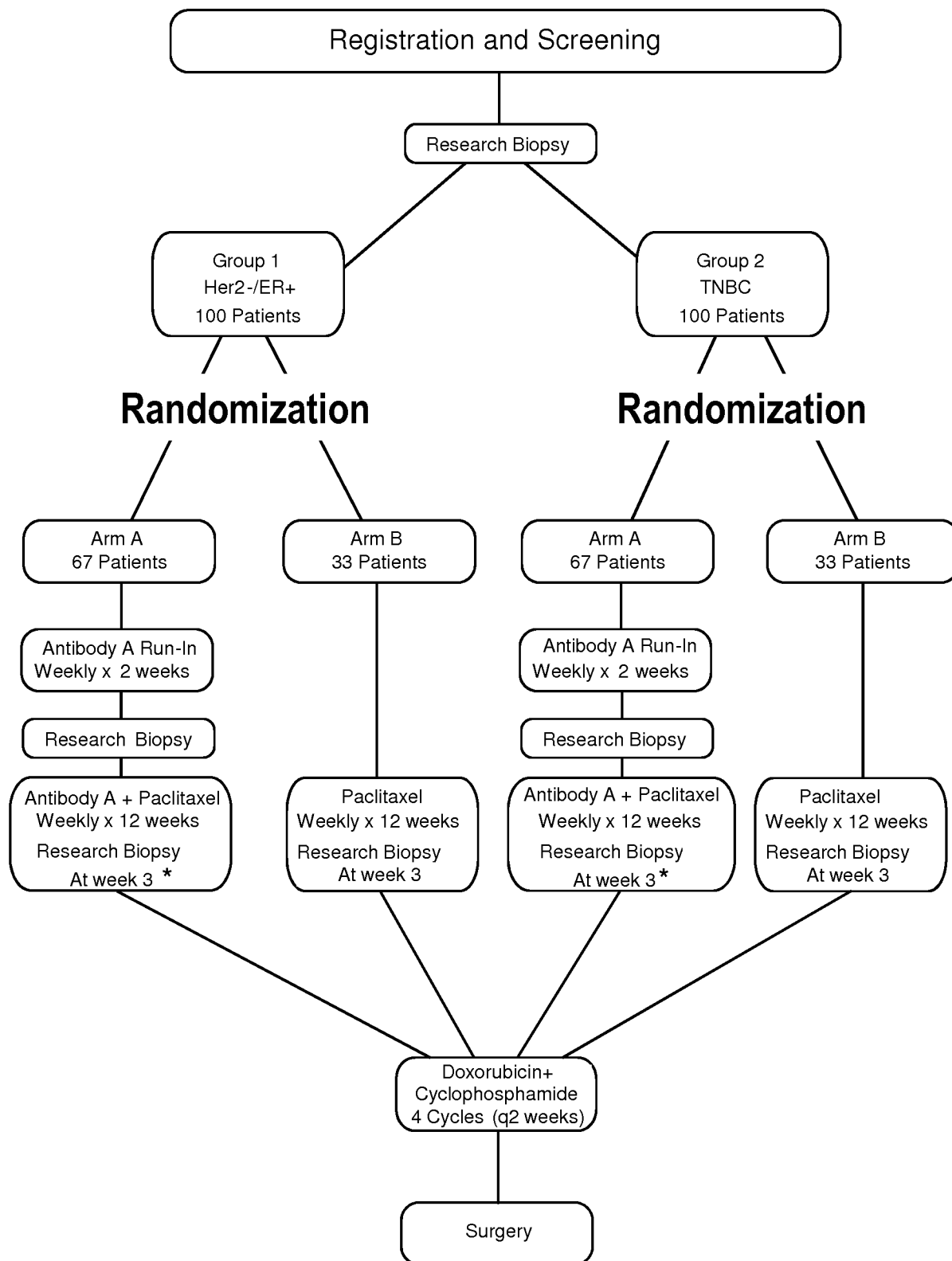


Patients had:

- Clinical Benefit (PR or SD > 4 months)
- No Clinical Benefit (PD or SD < 4 mo.)
- Not evaluable (withdrew for AEs with SDs)

Fig. 2

3/3

**Fig. 3**

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/42039

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 35/00; A61K 39/395 (2012.01)

USPC - 514/19.4; 424/130.1; 424/138.1

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): A61P 35/00; A61K 39/395 (2012.01)

USPC: 514/19.4; 424/130.1; 424/138.1

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

USPC: 514/19.2, 514/19.3; 424/133.1, 424/139.1, 424/141.1, 424/143.1; 435/326; 530/387.1

(Text Search)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PubWEST (PGPB,USPT, EPAB,JPAB); Google Web; Google Scholar and esp@cenet.

Search Terms: ERBB, ERBB3, paclitaxel, taxol, antibody, dose, dosage, cycle, weeks, day, week, monotherapy, combination, mab, doxorubicin, cyclophosphamide, weekly, 80 mg/m2, 80 mg.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US 2010/0056761 A1 (SCHOEBERL et al.) 04 March 2010 (04.03.2010) SEQ ID NOs: 7-12, 26-26; abstract; para [0001], [0002], [0004], [0008], [0021], [0025], [0126]-[0128], [0130], [0174], [0182]-[0183], [0189], [0201], [0202], [0204], Table 1; fig 22A.	24 ----- 1-3 and 18-23
Y	US 2010/0178651 A1 (HATZIS et al.) 15 July 2010 (15.07.2010) abstract; para [0123]	1-3 and 21-23
Y	HUDIS, C. A. Trastuzumab - Mechanism of Action and Use in Clinical Practice. The New England J of Medicine. 05 July 2007, Vol 357(1), Pages 39-51; Table 4; abstract; pg 45, col 1, para 3 to col 2, para 1	18-20
Y	US 7,846,440 B2 (SCHOEBERL et al.) 07 December 2010 (07.12.2010) entire document	1-3 and 18-24
A	MORANDI, P. Biological agents and gemcitabine in the treatment of breast cancer. Annals of Oncology. 2006. Vol 17, Supplement 5, Pages v177-v180, especially abstract; pg v177, col 2, para 1; pg v178, col 2, para 2.	1-3 and 18-24
A	Merrimack Pharmaceuticals Initiates Enrollment in Phase 1 Combination Study of MM-121 and paclitaxel in Gynecologic and Breast Cancers [online]. 01 December 2010 [retrieved on 21 August 2012]. Retrieved from the Internet URL <http://www.prweb.com/releases/2010/11/prweb8011292.htm>.	18-20



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

21 September 2012 (21.09.2012)

Date of mailing of the international search report

05 OCT 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

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

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/42039

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: SEQ ID NOs: 5-10.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 12/42039

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.: 4-17
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:

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.:

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.