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(54) **Title:**
TREATMENT REGIMEN UTILIZING NERATINIB FOR BREAST CANCER

(57) **Abstract:**
An extended regimen for treatment of HER-2/neu overexpressed/amplified cancer is described, with involves delivering a course of neratinib therapy to HER-2/neu overexpressed/amplified cancer patients following the completion of surgical and adjuvant therapy. The neratinib regimen may be continued for upwards of twelve months to five years. Also provided are pharmaceutical kits designed to facilitate compliance with the regimen.

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(54) Title: TREATMENT REGIMEN UTILIZING NERATINIB FOR BREAST CANCER

(57) Abstract: An extended regimen for treatment of HER-2/neu overexpressed/amplified cancer is described, with involves delivering a course of neratinib therapy to HER-2/neu overexpressed/amplified cancer patients following the completion of surgical and adjuvant therapy. The neratinib regimen may be continued for upwards of twelve months to five years. Also provided are pharmaceutical kits designed to facilitate compliance with the regimen.

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Treatment Regimen Utilizing Neratinib for Breast Cancer

BACKGROUND OF THE INVENTION

Breast cancer is the most frequently diagnosed malignancy in women and the leading cause of cancer mortality in women worldwide. The global incidence of breast cancer is estimated to reach 5 million women in the next decade [Parkin, DM and Fernandez LM, Use of statistics to assess the global burden of breast cancer. *Breast Journal*. 2006; (12, Suppl 1):S70-80; World Health Statistics. 2008, World Health Organization.] In 2007, breast cancer accounted for approximately 540,000 deaths worldwide [World Health Organization Fact Sheet No. 297. 2008; available from WHO web site.]

The erbB (erythroblastic leukemia viral oncogene homolog) family of TKIs (Tyrosine Kinase Inhibitors) consists of 4 members: erbB-1 (EGFR [epidermal growth factor receptor]), erbB-2 (HER-2, neu), erbB-3 (HER-3) and erbB-4 (HER-4). The erbB family of receptors is involved in cell proliferation, tumorigenesis, and metastasis and is abnormally expressed in multiple tumor types. HER2-positive breast cancers, i.e., those which test positive for the protein called human EGFR, are associated with Erb-2-protein overexpression or erbB-2 gene amplification in breast cancer tumors has been associated with more aggressive clinical disease and poorer prognosis [Slamon D, Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science.* 1987 (235):177-182].

Trastuzumab, a humanized monoclonal antibody that selectively binds to the human erbB-2 receptor, improves the prognosis of women with erbB-2-positive breast cancer. In patients with erbB-2 overexpressing metastatic breast cancer, trastuzumab in combination with chemotherapy improves tumor regression, extends time to tumor progression and prolongs median survival over chemotherapy alone resulting in its approval as first-line treatment in the metastatic setting. [Ligibel JA and Winer EP, Trastuzumab/chemotherapy combinations in metastatic breast cancer. *Seminars in Oncology.* 2002; 29(3 Suppl 11): 38-43]. Herceptin (trastuzumab) [Package insert, Genentech (2008)]. Trastuzumab has also been approved for use in the adjuvant setting in combination with other drugs for treatment of erbB-2 overexpressing node positive or node negative (estrogen receptor/progesterone receptor [ER/PgR] negative) metastatic breast cancer. Thus, trastuzumab has been used as part of a treatment regimen

consisting of (a) doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel, (b) a regimen with docetaxel and carboplatin, and (c) as a single agent following multi-modality anthracycline based therapy.

The current standard of care after diagnosis with HER+ breast cancer is surgery, followed by adjuvant treatment for a year. Standard adjuvant treatment is some combination of chemotherapy, radiation, hormonal therapy for ER/PR positive disease and trastuzumab. Despite completion of adjuvant therapy, patients with early stage breast cancer remain at risk for relapse. Published reports of trastuzumab therapy show disease –free-survival rates ranging from 80.6% [Smith I, *et al.* 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomized controlled trial. *Lancet.* 2007; 369:29-36] at three years to 85.9 % to 82% at four years [Perez EA, *et al.,* Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2-positive breast cancer. *Journal of Clinical Oncology.* ASCO Annual Meeting Proceedings. 2007; 25(18S): 512 and Slamon D, *et al.*, Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: second interim efficacy analysis. Presentation by Slamon D. SABCC 2006].

HKI-272 (neratinib) has been described for the treatment of neoplasms [US Patent 6,288,082]. Neratinib is a potent irreversible pan erbB inhibitor. Neratinib is an orally available small molecule that inhibits erbB-1, erbB-2 and erbB-4 at the intracellular tyrosine kinase domains, a mechanism of action that is different from trastuzumab. Neratinib reduces erbB-1 and erbB-2 autophosphorylation, downstream signaling, and the growth of erbB-1 and erbB-2 dependent cell lines. Preclinical data suggest that neratinib will have antitumor activity in erbB-1 - and/or erbB 2-expressing carcinoma cell lines, with cellular IC50 <100 nM [Rabindran SK, *et al.* Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer Research*. 2004;64(11):3958-65].

What are needed are drugs and regimens which improve patient survival rates and/or drugs and regimens which decrease recurrence of breast cancer following completion of primary and adjuvant treatment.

SUMMARY OF THE INVENTION

In one aspect, the invention provides a regimen for treatment of a HER-2/neu overexpressed/amplified neoplasm comprising delivering a course of neratinib therapy as an extension of trastuzumab adjuvant therapy, to HER-2/neu overexpressed/amplified cancer patients, *e.g.,* neratinib is delivered following the completion of surgery and standard adjuvant therapy.

In another aspect, the invention provides a method or regimen for decreasing rate of recurrence of HER-2/neu overexpressed/amplified breast cancer in patients as compared to patients receiving only primary and trastuzumab adjuvant therapy. The method involves delivering neratinib to said patients following primary therapy and standard adjuvant therapy with trastuzumab. In one embodiment, the method also follows completion of one or more conventional neoadjuvant or standard adjuvant therapies.

In still another aspect, the invention provides a regimen for improving invasive disease free survival comprising treating cancer patients with neratinib following completion of primary and standard adjuvant therapy with trastuzumab. In one embodiment, the treatment with neratinib commences within two weeks to forty-eight months following post-surgical and standard adjuvant therapy with trastuzumab.

Still other aspects and advantages of the invention will be readily apparent from the following detailed description of the invention.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention provides an extended adjuvant regimen for treatment of HER-2/neu overexpressed/amplified cancer comprising delivering a course of neratinib therapy to HER-2/neu overexpressed/amplified cancer patients. Such extended adjuvant therapy involves beginning the neratinib therapy at the completion of adjuvant therapy with trastuzumab. This extended adjuvant therapy is used to provide improved invasive disease-free survival (IDFS) or disease-free survival (DFS) - ductal carcinoma *in situ* (DCIS) and/or improvements in overall survival, time to distant recurrence, and/ distant disease-free survival.

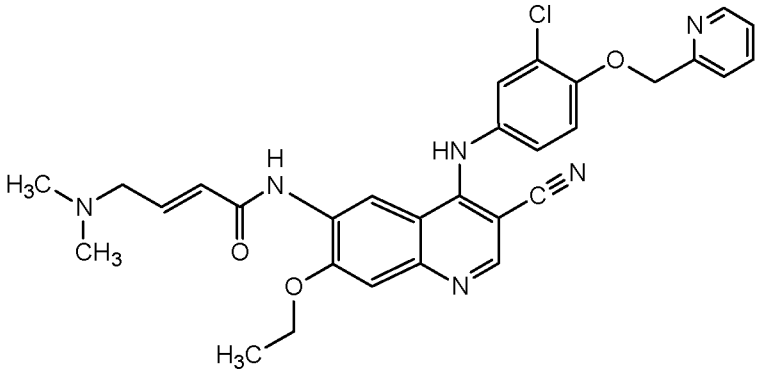
As used herein, invasive disease-free survival (IDFS) is defined as time from date of randomization to date of an IDFS event, including: invasive ipsilateral breast tumor recurrence, local/regional invasive recurrence, distant recurrence, death from any

cause, invasive contralateral breast cancer, and second primary invasive cancer (nonbreast). DFS-DCIS is defined as the time from randomization to the first occurrence of any IDFS event or ductal carcinoma *in situ*. Distant Disease Free Survival (DDFS) is the time from randomization to the first distant recurrence, or death from any cause. Time to distant recurrence (TTDR) is defined as the time between randomization and the date of the first distant tumor recurrence, ignoring locoregional recurrences and second breast or nonbreast cancers and taking into account deaths before recurrence of distant breast cancer as censoring events.

Thus, the extended adjuvant therapy of the invention using neratinib increases the disease-free survival by reducing the risk of recurrence or death. In one embodiment, the extended neratinib adjuvant therapy reduces the risk, *i.e.,* hazard rate, of cancer recurrence or death by 30% or 20% compared to conventional observation after trastuzumab therapy.

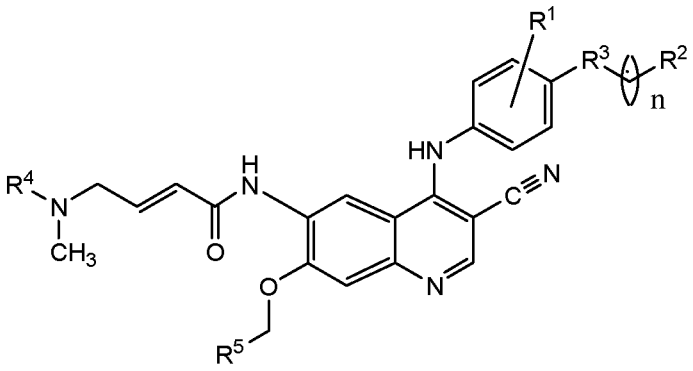
In another embodiment, using the extended neratinib regimen described herein, less than 15%, less than 10% and/or less than 5% of patients who have received primary and adjuvant therapy have cancer at three years post-inception of therapy. In still another embodiment, using the extended neratinib regimen described herein, less than 20%, less than 15% and/or less than 5% of patients who have received primary and adjuvant therapy have cancer at five years post inception of therapy.

As used herein, neratinib refers to HKI-272, which has the following core structure:



in its free base form. Optionally, a pharmaceutically acceptable salt or hydrate thereof may be used. The core structure represented above is a particular HKI-272 compound, called HKI-272 or neratinib, which has the chemical name [(2E)-N-[4-[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide].

Although currently less preferred, another HKI-272 compound may be used in the place of neratinib. "A HKI-272 compound" refers, in one embodiment, to a compound derived from the core structure of neratinib shown above. Suitable derivatives may include, *e.g.*, an ester, ether, or carbamate. Such an HKI-272 compound may have the structure:



wherein:

R^1 is halogen;

R^2 is pyridinyl, thiophenyl, pyrimidinyl, thiazolyl, or phenyl, wherein R^2 is optionally substituted with up to three substituents;

R^3 is O or S;

R^4 is CH_3 or $CH_2CH_2OCH_3$;

R^5 is CH_3 or CH_2CH_3; and

n is 0 or 1.

The term "halogen" as used herein refers to Cl, Br, I, and F.

Also encompassed are pharmaceutically acceptable salts, hydrates, and prodrugs of neratinib and/or the other HKI compounds described herein. "Pharmaceutically acceptable salts and esters" refers to salts and esters that are pharmaceutically acceptable and have the desired pharmacological properties. Such salts include, *e.g.*, salts that can be formed where acidic protons present in the compounds are capable of reacting with inorganic or organic bases. Suitable inorganic salts include, *e.g.*, those formed with the alkali metals or alkaline earth metals, *e.g.* sodium, potassium, magnesium, calcium, aluminum. Suitable organic salts also include, *e.g.*, those formed with organic bases such as the amine bases, *e.g.,* ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like, and those which can form N- tetraalkylammonium salts such as N-tetrabutylammonium salts. Pharmaceutically acceptable salts can also include acid addition salts formed from the reaction of basic moieties, such as amines, in the parent compound with inorganic acids

(*e.g.,* hydrochloric and hydrobromic acids) and organic acids (*e.g.,* acetic acid, citric acid, maleic acid, propionic, lactic, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, and the alkane- and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid naphthalenesulfonic, toluenesulfonic, camphorsulfonic). Other suitable examples of pharmaceutically acceptable salts include, but are not limited, to sulfate; citrate, acetate; oxalate; chloride; bromide; iodide; nitrate; bisulfate; phosphate; acid phosphate; isonicotinate; lactate; salicylate; acid citrate; tartrate; oleate; tannate; pantothenate; bitartrate; ascorbate; succinate; maleate; gentisinate; fumarate; gluconate; glucaronate; saccharate; formate; benzoate; glutamate; methanesulfonate; ethanesulfonate; benzenesulfonate; p-toluenesulfonate; pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)); and salts of fatty acids such as caproate, laurate, myristate, palmitate, stearate, oleate, linoleate, and linolenate salts.

Pharmaceutically acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the compounds of the invention, *e.g.*, straight chain alkyl esters having from 1 to 6 carbon atoms or branched chain alkyl groups containing 1 to 6 carbon atoms, including methyl, ethyl, propyl, butyl, 2-methylpropyl and 1,1-dimethylethyl esters, cycloalkyl esters, alkylaryl esters, benzyl esters, and the like. When there are two acidic groups present, a pharmaceutically acceptable salt or ester can be a mono-acid-mono-salt or ester or a di-salt or ester; and similarly where there are more than two acidic groups present, some or all of such groups can be salified or esterified. Compounds utilized herein may be present in unsalified or unesterified form, or in salified and/or esterified form, and the naming of such compounds is intended to include both the original (unsalified and unesterified) compound and its pharmaceutically acceptable salts and esters. Also, one or more compounds utilized herein may be present in more than one stereoisomeric form, and the naming of such compounds is intended to include all single stereoisomers and all mixtures (whether racemic or otherwise) of such stereoisomers.

The preparation of HKI-272 compounds, of which neratinib is a species, are described in detail in US Patent Application Publication No. 2005/0059678, which is hereby incorporated by reference. *See, also*, US Patent Nos. 6,288,082, US Patent No. 6,002,008, US Patent No. 6,297,258 and US Patent Application Publication No. 2007/0104721, which are hereby incorporated by reference. The methods described in these documents can also be used to prepare neratinib and/or the other HKI-272 and

substituted 3-quinoline compounds used herein and are hereby incorporated by reference. In addition to the methods described in these documents, International Patent Publication Nos. WO-96/33978 and WO-96/33980, which are hereby incorporated by reference, describe methods that are useful for the preparation of these HKI-272 compounds. Although these methods describe the preparation of certain quinazolines, they are also applicable to the preparation of correspondingly substituted 3-cyanoquinolines and are hereby incorporated by reference.

The term "treating" or "treatment" refers to the administration of the neratinib to a subject to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with neoplasms.

Trastuzumab, and methods of making and formulating same have been described. *See, e.g.,* US Patent 6,821,515; US Patent No. 6,399,063 and US Patent No. 6,387,371. Trastuzumab is available commercially from Genentech under the name “Herceptin”. As used herein, the term “a trastuzumab” includes includes trastuzumab and altered forms of, and derivatives of, trastuzumab. The term “a trastuzumab” includes agents that target the same epitope on the Her-2 receptor as targeted by trastuzumab. The epitope is known from H.S. Cho *et al.*, Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab, *Nature* 421 (2003), pp. 756–760.

As used herein, neoplasms which amplify/overexpress erB-2 (used interchangeably with Her-2 and neu) include certain breast cancers and other neoplasms, which may include, ovarian, bladder, gastric, pancreatic, colorectal, prostate, and lung cancers, including non-small cell lung cancers. Other neoplasms in which ErbB1 is expressed or overexpressed include a variety of solid human tumors, including non–small cell lung (NSCL), prostate, breast, colorectal, and ovarian cancers. Methods for screening samples to determine if the neoplasm overexpresses erb-1 and/or erB-2/Her-2 are known to those of skill in the art.

Primary and Adjuvant Anti-Neoplastic Therapy

As defined herein, primary therapy is the initial therapy provided to a patient following diagnosis with a neoplasm, such as a HER-2/neu overexpressed/amplified neoplasm. Primary therapy is also called definitive local therapy. Primary therapy for a HER-2/neu overexpressed/amplified neoplasm includes surgery (in the case of breast cancer this may include lumpectomy, modified radical mastectomy, mastectomy) and/or

radiation, alone or in combination. Adjuvant therapy refers to therapy conventionally provided following initial or primary therapy to increase the likelihood of a cure. Currently, standard adjuvant therapy for a HER-2/neu overexpressed/amplified neoplasm includes, *e.g.,* chemotherapy and/or antibody therapy. Typically, if one or more of these adjuvant therapies is delivered prior to primary therapy (*e.g.,* surgery), it is termed neoadjvant therapy. Throughout the following portions of the specification, the term "neo/adjuvant" is used as shorthand to refer to both neoadjuvant and standard adjuvant therapy. One or more types of adjuvant therapy may be delivered concomitantly.

In one embodiment, the patient may have been subject to chemotherapy involving delivery of either an anthracycline or a taxane or any cyclophosphamide, methotrexate and 5-fluorouracil regimen. Such chemotherapies may include one or more of an anthracycline, such as doxorubicin, cyclophosphamide, paclitaxel, docetaxel, and carboplatin. Another suitably neo/adjuvant therapy is a multi-modality anthracycline based therapy. Still other neo/adjuvant therapies include lapatinib [Lapatinib ditoxylate, TYKERB®], pertuzumab [Roche, Genentech], bevacizumab [Avastin®, Genentech], trastuzumab-DM-1 [Genentech], amongst others. The selection of the neoadjuvant or adjuvant therapy is not a limitation of the present invention. The extended adjuvant therapy of the invention begins following completion of therapy with trastuzumab. Trastuzumab is typically delivered after completion of or concurrent with chemotherapy as maintenance therapy. For trastuzumab, single doses and multiple doses are contemplated. In one embodiment, a single loading dose of trastuzumab is administered as a 90-minute intravenous infusion in a range of about 4- 5 mg/kg on day 1, followed by about 2 mg/kg per week starting on day 8. Typically, 3 weeks is 1 cycle. From 1, to 2 to 3, weeks may be provided between cycles. In another embodiment, trastuzumab is delivered with an every-3-weeks dosing schedule, using 8 mg/kg as a loading dose and 6 mg/kg as the maintenance dose. Trastuzumab may also be given at a dose of 6 mg/kg once every 3 – 4 weeks. Still other trastuzumab dosing regimens may be designed and utilized.

In one embodiment, the patient may have received primary as well as, in addition to trastuzumab neo/adjuvant therapy, other neo/adjuvant therapy. In one embodiment, one or more of the adjuvant therapies may continue following completion of the trastuzumab therapy during the extended adjuvant therapy. Suitably, neither the

primary therapy nor the neo/adjuvant therapy involves neratinib therapy prior to the onset of the extended neratinib regimen of the invention.

Extended Neratinib Regimen of Invention

In one embodiment, the extended neratinib regimen described herein is initiated at about one year, about two years or about three years following the start of primary therapy. The extended neratinib adjuvant regimen is started following the completion of neo/adjuvant therapy with trastuzumab. Completion of adjuvant therapy with

The extended regimen described herein may start following completion of at least one dose, at least 3 week cycle, at least three 3 week cycles, at least four months, at least six months, at least eight months, or at least one year of trastuzumab neo/adjuvant therapy. In one embodiment, the extended neratinib regimen is initiated at least about two weeks, at least about one month, at least about six months, at least about nine months, or at about one year to four years following completion of the trastuzumab therapy.

As described herein, the extended neratinib regimen is used to decrease the rate of recurrence of HER-2/neu overexpressed/amplified breast cancer in patients. These rates may be measured at a time point six months, one year, three years, or five years following inception of treatment. The regimen involves providing neratinib to these patients following primary and neo/adjuvant therapy. In another embodiment, the extended neratinib is used to improve invasive disease free survival, DFS-DCIS, distant disease free survival, and/or time to distant recurrence in cancer patients.

This extended adjuvant therapy of the invention may involve only a single dose of neratinib post-completion of trastuzumab therapy. However, in another embodiment, the extended neratinib regimen is administered over a period of one month, two months, at least six months, at least one year, at least 18 months, or for longer periods as needed or desired. In another embodiment, the patients are treated with neratinib for about 8 months to about 5 years, about 12 months (one year) to about three years, or for longer or shorter periods as determined by a medical professional.

As used herein, the term "providing" with respect to providing a neratinib, means either directly administering the compound or composition, or administering a prodrug, derivative, or analog which will form an effective amount of the neratinib compound within the body.

As used herein and except where noted, the terms "individual", "subject" and "patient" are used interchangeably, and refer to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, non-human primates, and humans. Desirably, the term "individual", "subject" or "patient" refers to a human. In most embodiments, the subjects or patients are in need of the therapeutic treatment. Accordingly, the term "subject" or "patient" as used herein means any mammalian patient or subject to which the claimed regimen can be administered.

As used herein, the term "effective amount" or "pharmaceutically effective amount" when administered to a subject to treat a neoplasm, is sufficient to inhibit, slow, reduce, or eliminate lesions or tumor growth in a subject, or to inhibit, slow, or reduce progression of disease and/or to increase progression-free survival rate of the subject.

Neratinib (or the selected HKI-272 compound) can be administered, *e.g.*, orally, at a dose range of about 0.01 to 100 mg/kg. In one embodiment, neratinib is administered at a dose range of about 0.1 to about 90 mg/kg. In another embodiment, neratinib is administered at a dose range of about 1 to about 80 mg/kg. In a further embodiment, neratinib is administered at a dose range of about 10 to about 70 mg/kg. In yet another embodiment, neratinib is administered at a dose range of about 15 to about 60 mg/kg. In still a further embodiment, neratinib is administered at a dose range of about 20 to about 240 mg per day, at least about 40 mg, at least about 120 mg, or at least about 160 mg, on the days in the cycle on which it is administered. One of skill in the art could routinely perform empirical activity tests to determine the bioactivity of the compound in bioassays and thus determine what dosage to administer when the compound is delivered by another route.

In one embodiment, the oral dosage of neratinib is at least about 700 mg/week. In another embodiment, the oral dosage of neratinib is about 800 mg/week to at least to about 1700 mg/week. In another embodiment, the oral dosage of neratinib is about 840 mg/week to about 1680 mg/week. In another embodiment, the oral dosage of neratinib is about 900 mg/week to about 1600 mg/week. In a further embodiment, the oral dosage of neratinib is about 1000 mg/week to about 1500 mg/week. In yet another embodiment, the oral dosage of neratinib is about 1100 mg/week to about 1400 mg/week. In still a further embodiment, the oral dosage of neratinib is about 1200 mg/week to about 1300 mg/week. Precise dosages are determined by the administering physician based on experience with the individual subject to be treated.

Other dosage regimens and variations are foreseeable, and are determined through physician guidance.

For neratinib, it is desired that the compound be in the form of a unit dose. Neratinib can be administered at a dose range of about 0.01 to 100 mg/kg or at a dose range of 0.1 to 10 mg/kg. In one embodiment, neratinib is administered orally from 1 to 6 times a day, more usually from 1 to 4 times a day. Suitable unit dose forms include tablets, capsules and powders in sachets or vials. Such unit dose forms may contain from 0.1 to 300 mg of neratinib, from 2 to 100 mg, at a dose of 120 mg to 300 mg daily, or 240 mg daily. Alternatively, neratinib may be administered through another suitable route, *e.g.,* intravenous. In still another embodiment, neratinib is administered once a week. In certain situations, dosing with neratinib may be delayed or discontinued for a brief period (*e.g.,* 1, 2 or three weeks) during the course of treatment. Such a delay or discontinuation may occur once, or more, during the course of treatment. The effective amount will be known to one of skill in the art; it will also be dependent upon the form of the compound. One of skill in the art could routinely perform empirical activity tests to determine the bioactivity of the compound in bioassays and thus determine what dosage to administer.

In one embodiment, suitable examples of pharmaceutical carriers used herein include, but are not limited to, excipients, diluents, fillers, disintegrants, lubricants and other agents that can function as a carrier. The term "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic, and desirable, and includes excipients that are acceptable for veterinary use as well as for human pharmaceutical use. Such excipients can be solid, liquid, semisolid, or, in the case of an aerosol composition, gaseous. Pharmaceutical compositions are prepared in accordance with acceptable pharmaceutical procedures, such as described in Remingtons Pharmaceutical Sciences, 17th edition, ed. Alfonoso R. Gennaro, Mack Publishing Company, Easton, Pa. (1985). Pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the formulation and biologically acceptable. Suitable pharmaceutically-acceptable excipients or carriers for a tablet or caplet formulation include, *e.g.*, inert excipients such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or alginic acid; binding agents such as gelatin or starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl 4-

hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet or caplet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance using conventional coating agents and procedures well known in the art.

In one embodiment, the invention provides an extended regimen for treatment of HER-2/neu overexpressed/amplified cancer comprising delivering a course of extended neratinib therapy to HER-2/neu overexpressed/amplified cancer patients. Such extended therapy involves beginning the neratinib therapy at the completion of surgical/or and adjuvant therapy. This extended therapy is used to provide improved invasive disease-free survival and/or improvements in overall survival, time to distant recurrence, and distant disease-free survival.

As described herein, the extended neratinib regimen is initiated at least one, at least two, or at least three years following inception of initial therapy. In one embodiment, neratinib therapy is initiated at least about 2 weeks after and up to about four years following the completion of primary and standard neo/adjuvant therapy.

In one embodiment, selected concominant therapies may be used in conjunction with the extended neratinib regimen. For example, patients may be further undergoing concomitant therapy with bisphosphonates for osteopenia or osteoporosis. In another example, patients may be further undergoing concomitant endocrine therapy. Optionally, such concomitant therapies may be non-adjuvant therapies, but rather are for treatment of other conditions or symptoms which the patient may have.

Pharmaceutical Packs/Kits

The invention includes a product or pharmaceutical pack containing a course of an anti-neoplastic treatment for one individual mammal comprising one or more container(s) having one, one to four, or more unit(s) of neratinib and, optionally, one, one to four, or more unit(s) of another active agent.

In another embodiment, pharmaceutical packs contain a course of anti-neoplastic treatment for one individual mammal comprising a container having a unit of a rapamycin in unit dosage form, a containing having a unit of neratinib and optionally, a container with another active agent.

In some embodiments, the compositions of the invention are in packs in a form ready for administration. In other embodiments, the compositions of the invention are in

concentrated form in packs, optionally with the diluent required to make a final solution for administration. In still other embodiments, the product contains a compound useful in the invention in solid form and, optionally, a separate container with a suitable solvent or carrier for the compound useful in the invention.

In still other embodiments, the above packs/kits include other components, *e.g.,* instructions for dilution, mixing and/or administration of the product, other containers, syringes, needles, etc. Other such pack/kit components will be readily apparent to one of skill in the art.

The following examples illustrate of the uses of the combinations of the invention. It will be readily understood that alterations or modifications, e.g., in the formulation of the components, the routes of delivery, and the dosing, can be made for reasons known to those of skill in the art.

EXAMPLES

Neratinib as a single agent has been studied in a phase 2 trial in subjects with metastatic erbB-2 positive breast cancer. Sixty-six subjects with prior trastuzumab based therapy were enrolled into Arm A; 70 subjects without any prior trastuzumab exposure were enrolled into Arm B. Objective response rate and median progression free survival were used as estimates of antitumor activity.

According to preliminary data based on independent radiology assessment, among subjects with prior trastuzumab treatment, the overall response rate (ORR) was 26% (95% confidence index (CI)) and median progression-free survival (PFS) was 23 weeks (95% CI). For subjects without prior exposure to trastuzumab, the ORR was 57% (95% CI) and median PFS was 40 weeks (95% CI). The antitumor activity in arm A provides the basis for the testing neratinib as a single agent in trastuzumab refractory subjects.

In Arm A, the median duration of trastuzumab exposure was 60 weeks. Twenty-eight (28%) of subjects received trastuzumab as adjuvant or neoadjuvant therapy. The majority (48%) of subjects received one trastuzumab based regimen in the metastatic setting and approximately 43% received a second or third trastuzumab based regimen for metastatic disease. Arm A subjects also had extensive prior cytotoxic treatment with 53% of subjects receiving 2-3 prior regimens and another 27% receiving > 3 prior cytotoxic regimens. Taken together, these treatment characteristics described a heavily

pretreated, and likely refractory, study population in Arm A. As such, an ORR of 26% in a refractory population suggests that neratinib is likely to be a highly active agent for erbB-2 positive breast cancer.

Main adverse event associated with neratinib is diarrhea, which has been generally well manageable with medication, treatment interruption, or dose modification. Other common adverse events are nausea, vomiting, fatigue, and anorexia.

Example 1

In a randomized, double-blind, placebo-controlled phase 3 trial, neratinib is compared against placebo following trastuzumab in women with early-stage HER-2/neu overexpressed/amplified breast cancer. Subjects must have completed a course of prior adjuvant trastuzumab. If less than 12 months of trastuzumab have been given, at least 8 prior doses must have been given and it must be specified that the subject is either not eligible or unable to receive further adjuvant therapy with trastuzumab. Following completion of a course of prior adjuvant therapy involving at least 8, and preferably 12 months of trastuzumab, subjects are eligible for treatment with the regimen described herein. The last dose of trastuzumab must have been given > 2 weeks and < 4 years from inception of randomization. Randomization will be stratified by the following factors: ER and/or PgR positive vs. ER and PgR negative; nodal status (0, 1-3, 4 or more); < or > 3 years from diagnosis; trastuzumab given sequentially vs. concurrently with chemotherapy.

Eligible subjects are randomly assigned in a 1:1 ratio to one of the following two arms: Neratinib 240 mg daily for 1 year or Placebo daily for 1 year. After discontinuing study treatment, subjects will continue to be followed for disease recurrence and survival until the planned number of invasive disease free survival (IDFS) events has been reached, and for survival thereafter until the end of the study. The primary efficacy endpoint of IDFS and time-to-event secondary endpoints will be analyzed using a stratified log-rank test. The hazard ratio and the corresponding 95% confidence interval will be derived from a stratified Cox proportional hazards regression model [DR Cox, 1972, “Regression Models and Life Tables (with Discussion)”,Journal of the Royal Statistical Society, Series B 34:187—220]. The median times to event and the associated 95% confidence intervals will be estimated using the Kaplan-Meier method [Kaplan, E.L. and Meier, Paul. "Nonparametric estimation from incomplete observations." J. Am. Stat. Assoc. 53, 457-481 (1958)]. The primary efficacy analysis

will be conducted on the intent to treat population, defined as all subjects randomized. Adverse events and serious adverse events will be summarized by treatment arm for the safety population, defined as all subjects dosed with neratinib or placebo. The incidence of grade 3 or higher diarrhea will also be summarized and differences across treatment arms will be tested using the Mantel-Haenszel test. [Mantel N & Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J. Nat. Cancer Inst.* **22**:719-48, 1959].

All publications cited in this specification are incorporated herein by reference. While the invention has been described with reference to particular embodiments, it will be appreciated that modifications can be made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

Claims:

1. A regimen for treatment of HER-2/neu overexpressed/amplified cancer comprising delivering neratinib therapy to HER-2/neu overexpressed/amplified cancer patients at the completion of trastuzumab therapy.

2. The regimen according to claim 1, wherein the course of neratinib therapy comprises treating cancer patients with neratinib for at least one month.

3. The regimen according to claim 1, wherein the course of neratinib therapy is in the range of 8 months to 5 years.

4. The regimen according to claim 2, wherein the cancer patients are treated with neratinib for at least about 12 months.

5. The regimen according to claim 1, wherein the neratinib therapy is started about 2 weeks to about one year from the completion of surgical and standard adjuvant therapy.

6. The regimen according to claim 1, wherein neratinib is delivered orally.

7. The regimen according to claim 6, wherein neratinib is delivered in tablet form.

8. The regimen according to claim 1, wherein neratinib is administered daily.

9. The regimen according to claim 1, wherein neratinib is delivered at a dose of 120 mg to 300 mg daily.

10. The regimen according to claim 9, wherein neratinib is delivered at a dose of 240 mg.

11. A method for improving invasive disease-free survival (IDFS) or disease-free survival (DFS) -ductal carcinoma in situ (DCIS) and/or improvements in overall

survival, time to distant recurrence, and/ distant disease-free survival in a patient, said method comprising delivering neratinib to said patient following trastuzumab therapy.

12. The method according to 11, wherein the patient has received at least three cycles of trastuzumab.

13. The method according to 12, wherein the patient has received twelve cycles of trastuzumab.

14. The method according to 11, wherein the patient received standard adjuvant therapy consisting of trastuzumab and one or more chemotherapy.

15. The method according to 14, wherein the chemotherapy involved one or more of doxorubicin, cyclophosphamide, paclitaxel, docetaxel, carboplatin, lapatinib, pertuzimab, bevacizumab, trastuzumab-DM-1, or anthracycline based therapy.

16. A regimen for improving invasive disease free survival, disease-free survival-ductal carcinoma *in situ*, overall survival, time to distant recurrence, and/or distant disease-free survival comprising treating cancer patients with neratinib for at least one month to six months, wherein said treatment with neratinib following adjuvant therapy with trastuzumab.

17. The regimen according to claim 16, wherein the patients are treated with neratinib for at least twelve months.

18. The regimen according to claim 16, wherein the neratinib therapy commences about two weeks to about four years following completion of trastuzumab therapy.

19. The regimen according to claim 16, wherein the neratinib therapy commences about six months to about twelve months following completion of trastuzumab therapy.

20. The regimen according to claim 16, wherein the patients are further undergoing concomitant therapy selected from one or more of bisphosphonates for osteopenia or osteoporosis and endocrine therapy.