ANTINEOPLASTIC COMBINATIONS CONTAINING HKI-272 AND VINORELBINE

BACKGROUND OF THE INVENTION

Breast cancer is the most frequently diagnosed malignancy in women and one of the top two causes of cancer-related deaths in women worldwide. The incidence of breast cancer in the world is increasing, and it is estimated that the disease will affect 5 million women in the next decade. Treatments permit control of symptoms, prolongation of survival, and maintenance of quality of life. However, in about 40% to 50% of all patients treated with curative intent, incurable metastatic disease will develop. Since there is no cure for metastatic breast cancer, current therapeutic goals are palliative.

In several cancer types, deregulation of growth factor signaling is observed, associated with a hyperactivation of the ErbB receptors. The ErbB receptor family includes ErbB-1 (also known as HER-1, epidermal growth factor receptor (EGFR)), ErbB-2 (a.k.a. *neu* or HER-2), HER-3 (a.k.a. ErbB-3), and HER-4 (a.k.a. ErbB-4). Overexpression of ErbB-1 is observed in non-small cell lung cancer (NSCLC) (40%-80%), breast cancer (14%-91%), and pancreatic cancer (30%-89%). In NSCLC, activation by mutation of amplification of ErbB-1 also occurs in 10% to 30% of patients.

Overexpression of ErbB-2, usually resulting from *erbB-2* gene amplification, is observed in tumor tissue in 25% to 30% of patients of patients with metastatic breast cancer (MBC) and is associated with malignant transformation. ErbB-2 overexpression is usually associated with a more aggressive tumor phenotype, worse overall prognosis, and faster relapse times at all stages of cancer development. In women with MBC, this overexpression confers a relative resistance to treatment with either anthracycline/alkylator- or taxane-based chemotherapy. ErbB-2 overexpression in tumorigenesis has been mainly studied in breast cancers but is also observed in other cancers.

Among current therapeutics for cancers, specifically those characterized by overexpression of ErbB-2, are vinorelbine, trastuzumab and HKI-272. Vinorelbine, a semisynthetic vinca alkaloid having broad antitumor activity, acts through microtubule disruption. Vinorelbine presents a lower neurotoxicity profile than vincristine or vinblastine. Vinorelbine has been shown to be less toxic to axonal microtubules than vincristine or

vinblastine at therapeutic concentrations. In studies conducted on subjects with advanced breast cancer, treatment with vinorelbine as a single agent is at least as efficient as other chemotherapies but with a lower risk of toxicity. However, the risk of toxicity increases in parallel with the number of previous anticancer treatments.

Trastuzumab (HERCEPTIN® drug) is a humanized monoclonal antibody specific for the extracellular domain of ErbB-2. It presents significant clinical benefit and significant antitumor activity when used alone or in combination with taxanes in metastatic breast cancer in first-line treatment or in patients who have tumor progression after chemotherapy. Because of the improvement in survival, trastuzumab-based therapies have become standard of care for women with ErbB-2-positive MBC. For women with advanced or metastatic disease, breast cancer eventually recurs despite trastuzumab treatment. Trastuzumab-based therapy is also associated with potential cardiac toxicity. Certain breast cancer cells are resistant to trastuzumab due to the occurrence of secondary ErbB-2 mutations, such as truncation of extracellular domain ErbB-2 receptor. Such mutations can result in cancer cells which are not recognized by the antibody.

In recent studies, trastuzumab in combination with either vinorelbine or taxane (paclitaxel with or without carboplatin, or docetaxel) was utilized to treat subjects with ErbB-2-overexpressing MBC. As expected, the most frequent grade toxicity observed with the combination of trastuzumab and vinorelbine was neutropenia.

HKI-272 is a small molecule, irreversible pan-ErbB receptor inhibitor specific for epidermal growth factor receptor (ErbB-1 or EGFR), ErbB-2 (HER-2), and ErbB-4 (HER-4). HKI-272 blocks kinase activity of the receptor through binding to the intracellular adenosine triphosphate (ATP) binding site of the receptor. HKI-272 blocks ErbB receptor autophosphorylation in cells at doses consistent with inhibition of cell proliferation. *In vitro*, HKI-272 alone inhibits kinase activity of ErbB-1, ErbB-2, and HER-4, inhibits tumor cell growth with breast and lung tumor cell lines, and presents a potent growth inhibition of lung cancer cells resistant to gefitinib or erlotinib. *In vivo*, HKI-272 blocks tumor growth in xenograft animal models. Overall, HKI-272 is less potent against ErbB-1-dependent tumors than ErbB-2-dependent tumors *in vivo*, even though it has equivalent activity against the 2 kinases *in vitro*.

There remains a need in the art for therapeutic methods, regimens, compositions, and kits which are useful in treating metastatic breast cancer and solid tumors.

SUMMARY OF THE INVENTION

This invention addresses the need in the art by providing regimens, compositions and methods using a HKI-272 compound and a vinorelbine compound for the treatment of cancers, such as solid tumors and metastatic breast cancer.

In one aspect, regimens for treating a neoplasm in a subject are provided and include administering a vinorelbine compound and administering a HKI-272 compound. Desirably, the vinorelbine compound is vinorelbine and the HKI-272 compound is HKI-272. In one embodiment, the neoplasm is breast cancer.

In another aspect, a regimen for treating a solid tumor associated with overexpression or amplification of HER-2 in a subject is provided, wherein one cycle of the regimen includes 21 days. The regimen includes orally administering at least one unit dose of HKI-272 starting on day 1 of the cycle and intravenously administering at least one unit dose of vinorelbine on days 1 and 8 of the cycle.

In a further aspect, a regimen for treating a metastatic cancer associated with overexpression or amplification of HER-2 in a subject is provided. One cycle of the regimen includes 21 days and the regimen includes orally administering at least one unit dose of HKI-272 starting on day 2 of the cycle and intravenously administering at least one unit dose of vinorelbine on days 1 and 8 of the cycle.

In still another aspect, a product comprising a vinorelbine compound and HKI-272 compound is provided as a combined preparation for simultaneous, separate or sequential use in treating a neoplasm in a mammal.

In yet a further aspect, a pharmaceutical pack for treating a neoplasm in one individual mammal is provided and includes (a) at least one unit dose of vinorelbine; and (b) at least one unit dose of HKI-272.

In another aspect, a pharmaceutical composition is described and contains vinorelbine, HKI-272, and at least one pharmaceutically acceptable carrier.

In still another aspect, a method of treating a neoplasm associated with overexpression or amplification of HER-2 in a mammal in need thereof is provided and includes administering a unit dose of a vinorelbine compound and administering a unit dose of a HKI-272 compound.

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

DESCRIPTION OF THE INVENTION

This invention provides compositions, methods, and regimens using a combination of a HKI-272 compound and a vinorelbine compound for the treatment of cancers. This invention provides in one embodiment compositions comprising HKI-272 and vinorelbine for the treatment of neoplasms. Also provided are products containing HKI-272 and vinorelbine formulated for simultaneous, separate or sequential use in treating neoplasms in a mammal. The invention is also useful as an adjuvant and/or neoadjuvant therapy of earlier stages of breast cancer. The invention provides, in another embodiment, methods for the combined use or administration of a HKI-272 compound and vinorelbine compound.

The Therapeutic Regimen and Its Components

Without wishing to be bound by theory, the inventors hypothesize that the combination of HKI-272 and vinorelbine for treating a neoplasm is desirable because HKI-272 targets the intracellular ErbB-2 kinase rather than the extracellular domain. Thus, this combination has different mechanisms of sensitivity and resistance, and then presents an advantage over the therapeutic combination of trastuzumab and vinorelbine. Further, the combination of HKI-272 and vinorelbine is anticipated to be more effective than combinations of vinorelbine with other pan-ErbB inhibitors due to the tyrosine kinase inhibition activity of HKI-272 through an irreversible binding at a targeted cysteine residue in the ATP binding pocket of the receptor.

These methods, combinations and products are useful in the treatment of a variety of neoplasms, particularly those associated with overexpression or amplification of HER-2. In one embodiment, the neoplasm is a solid tumor or an advanced solid tumor. In a further embodiment, the neoplasm is metastatic. In another embodiment, neoplasms that may be treated as described herein include, e.g., lung cancers (such as bronchioalveolar carcinoma and non small cell lung cancer), breast cancers (such as metastatic breast cancer and HER-2 -positive breast cancer), prostate cancers, myeloma, head and neck cancer, transitional cell carcinoma, small cell and large cell neuroendocrine carcinoma of the uterine cervix. In still another embodiment, the neoplasm is resistant to trastuzumab.

The regimens, methods, and compositions described herein include the concurrent, simultaneous, sequential or separate administration of the components, *i.e.*, a HKI-272 compound and a vinorelbine compound. The term "composition" as used herein is intended to cover both

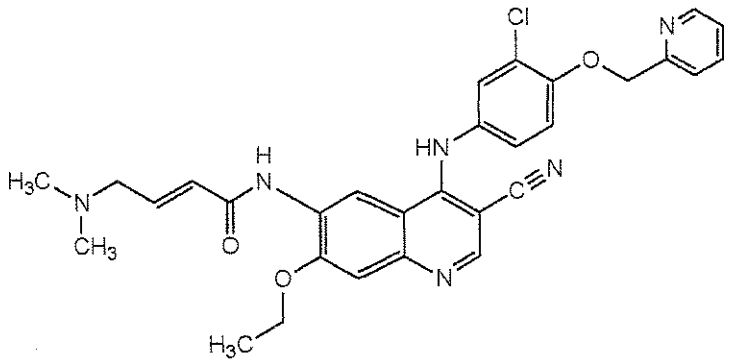
pharmaceutical compositions in which 2 or more components are mixed, compositions of matter such as pharmaceutical kits and packs in which the components are individually packaged for concurrent, simultaneous, sequential, or separate administration. In one aspect of the invention, "a combination" includes simultaneous administration of the HKI-272 and vinorelbine compounds. In a further aspect of the invention, "a combination" includes sequential administration of the HKI-272 and vinorelbine compounds. In one embodiment the HKI-272 is administered before the vinorelbine compound. In another embodiment the vinorelbine compound is administered before the HKI-272 compound. In another aspect, "a combination" includes separate administration of the HKI-272 and vinorelbine compounds in a particular therapeutic regimen in which the two components of the combination are administered at specific times and amounts with respect to each other. In one embodiment, the combination of the HKI-272 and vinorelbine compounds produces a more beneficial therapeutic effect than that achievable by the administration of either a HKI-272 compound alone or a vinorelbine compound alone. Where the administration of those agents is sequential or separate, the delay in administering the second component should not be such as to lose the benefits provided the combination therapy.

In one embodiment, the combination of the HKI-272 and vinorelbine compounds is particularly well suited for treatment of metastatic breast cancer. In another embodiment, the combination of the HKI-272 and vinorelbine compounds are well suited for treatment of breast, kidney, bladder, mouth, larynx, esophagus, stomach, colon, ovary, and lung), and polycystic kidney disease.

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 certain circumstances, these terms refer to experimental animals such as rabbits, rats, and mice, and other animals. 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 HKI-272 and vinorelbine compounds can be administered. In one embodiment, to identify subject patients for treatment according to the methods of the invention, accepted screening methods are employed to determine risk factors associated with a targeted or suspected disease or condition or to determine the status of an existing disease or condition in a

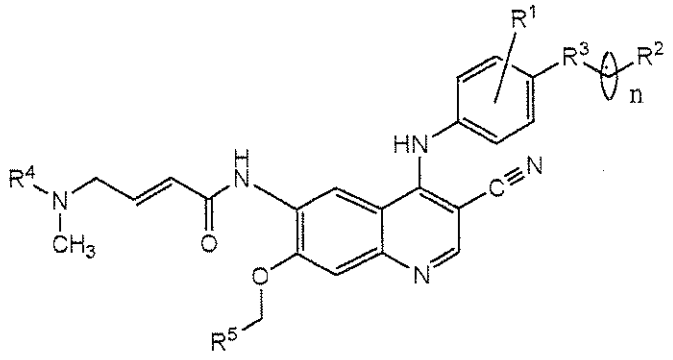
subject. These screening methods include, *e.g.*, conventional work-ups to determine risk factors that are associated with the targeted or suspected disease or condition. These and other routine methods allow the clinician to select patients in need of therapy using the methods and formulations of the present invention. In one embodiment, the "individual", "subject" or "patient" may have had no previously chemotherapeutic treatment. In another embodiment, the "individual", "subject" or "patient" may have previously undergone chemotherapeutic treatment. In another embodiment, the "individual", "subject" or "patient" may have previously been administered an aniloquinazoline class inhibitor. In a further embodiment, the "individual", "subject" or "patient" may have previously been administered lapatinib or geftinib as the aniloquinazoline class inhibitor. Desirably, the blood count of the patient prior to treatment with the described combinations is stable enough to permit administration of the combinations described herein. In one embodiment, the neutrophil count of the patient prior to administration of the vinorelbine and HKI-272 compounds is at least 1500. In another embodiment, the platelet count of the patient prior to administration of the vinorelbine and HKI-272 compounds is at least 100,000/L.

As used herein, "a HKI-272 compound" refers, in one embodiment, to a compound having the following core structure:



or a derivative or pharmaceutically acceptable salt thereof. Suitable derivatives may include, *e.g.*, an ester, ether, or carbamate. The core structure represented above is a particularly HKI-272 compound, called HKI-272, which has the chemical name (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy) anilino] -3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide. In one embodiment, the HKI-272 compound useful in the compositions and methods described herein is HKI-272.

In another embodiment, an HKI-272 compound has 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.

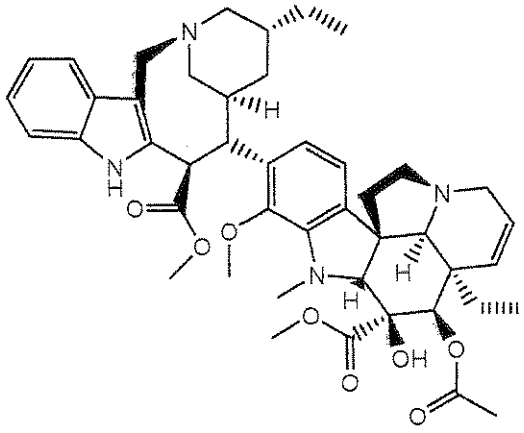
The term "halogen" as used herein refers to Cl, Br, I, and F.

These HKI-272 compounds, of which HKI-272 is a species, are characterized by the ability to act as potent HER-2 inhibitors. *See, e.g.*, US Patent Nos. 6,288,082 and 6,297,258 and US Patent Application Publication No. 2007/0104721, which are hereby incorporated by reference. These compounds and their preparation are described in detail in US Patent Application Publication No. 2005/0059678, which is hereby incorporated by reference. For convenience, "a HKI-272 compound" is used throughout this specification. However, any compound of the structure(s) provided above can be substituted for HKI-272 in the combinations described in detail below.

HKI-272, other HKI-272 compounds, and methods of making and formulating same have been described. See, e.g., US Patent Application Publication No. 2005/0059678 and US Patent No. 6,002,008, which are hereby incorporated by reference. The methods described in these documents can also be used to prepare the 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.

As used herein, the term "a vinorelbine compound" means vinorelbine or a pharmaceutically acceptable salt thereof, which has broad antitumor activity and that acts through microtubule disruption. See, Widakowich et al., Anticancer Agents Med. Chem., 8(5):488-496 (June 2008) and Wissner et al., Arch. Pharm. (Weinheim), (May 20, 2008 e-publication). The term includes the neutral vinorelbine compound, *i.e.*, 4-(acetyloxy)-6,7-didehydro-15-((2R,6R,8S)-4-ethyl-1,3,6,7,8,9-hexohydro-8-(methoxycarbonyl)-2,6-methano-2H-azecino(4,3-b)indol-8-yl)-3-hydroxy-16-methoxy-1-methyl, methyl ester, (2β, 3β, 4β, 5α, 12R, 19α)-aspidospermidine-3-carboxylic acid (vinorelbine; tradename: Navelbine). Vinorelbine and its pharmaceutically acceptable salts are available from commercial vendors including Adventrx/SD Pharmaceuticals (SDP-012® drug), Hana (ALOCREST® drug), and Inex Pharmaceuticals Corp. (INX-0125™ drug), and other vinorelbine compounds, including those discussed in US Patent No. 7,235,564, which is hereby incorporated by reference. In one embodiment, a vinorelbine compound includes a compound with a structural similarity to the vinorelbine compound structure below, *e.g.*, compounds with a similar alkaloid structure that have been modified to enhance therapeutic benefit.



The preparation of vinorelbine compounds are described by Langlois et al., in J. Am. Chem. Soc. 98:7017-7024 (1976); and by Mangeney et al., in Tetrahedron, 35:2175-2179 (1979).

The HKI-272 and vinorelbine compounds and corresponding pharmaceutically acceptable salts or esters thereof include isomers either individually or as a mixture, such as enantiomers, diastereomers, and positional isomers.

"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 and potassium, magnesium, calcium, and aluminum. Suitable organic salts include, *e.g.*, those formed with organic bases such as the amine bases, e.g. ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. 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, and the alkane-and arene-sulfonic acids such as methanesulfonic acid and benzenesulfonic acid).

Pharmaceutically acceptable esters include esters formed from carboxy, sulfonyloxy, and phosphonoxy groups present in the compounds of the invention, *e.g.*, C_{1-6} alkyl esters. 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.

Pharmaceutically acceptable salts of the HKI-272 and vinorelbine compounds with an acidic moiety may be formed from organic and inorganic bases including, *e.g.*, salts with alkali metals or alkaline earth metals such as sodium, potassium, lithium, calcium, or magnesium or organic bases and N- tetraalkylammonium salts such as N-tetrabutylammonium salts.

Similarly, when one or more compound utilized herein contains a basic moiety, salts may be formed from organic and inorganic acids. For example, salts may be formed from acids such

as acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic, camphorsulfonic, and similarly known acceptable acids when a compound of this invention contains a basic functional group. 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. In one embodiment, the vinorelbine compound is vinorelbine tartrate.

The compounds can also be used in the form of esters, carbamates and other conventional ester forms, also referred to herein as prodrug forms, which when administered in such form, convert to the active moiety *in-vivo*. Exemplary ester forms of the compounds of this invention include, but are not limited to, 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.

Accordingly, a pharmaceutical composition is provided and contains effective amounts of the HKI-272 and vinorelbine compounds in combination or association with one or more pharmaceutically acceptable carrier. 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 weight of the tablet is at least about 20, 30, 40, 50, 60, or 70 mg.

Optional Components of the Regimens

The regimens described herein may also include the administration of other agents. In one embodiment, the regimen further includes administration of a taxane, *e.g.*, docetaxel and paclitaxel [*e.g.*, a suspension of paclitaxel bound to albumen nanoparticles, which is available as the ABRAXANE® reagent]. Paclitaxel may also be administered on a weekly schedule at doses 60-100 mg/m^2 administered over 1 hour, weekly, or 2-3 weekly doses followed by a one week rest. In one embodiment, paclitaxel is administered intravenously over 3 hours at a dose of 175 mg/m^2, optionally followed by cisplatin at a dose of 75 mg/m^2; or paclitaxel administered intravenously over 24 hours at a dose of 135 mg/m^2, optionally followed by cisplatin at a dose of 75 mg/m^2. In patients previously treated with therapy for carcinoma, paclitaxel can be injected at several doses and schedules. However, the optimal regimen is not yet clear. The recommended regimen is paclitaxel 135 mg/m^2 or 175 mg/m^2 administered intravenously over 3 hours every 3 weeks. These doses may be altered as needed or desired.

In another embodiment, other active agents may be included in a combination with an HKI-272 compound and vinorelbine compound and include, *e.g.*, chemotherapeutic agents, such as alkylating agents or mTOR inhibitors (rapamycin and derivatives thereof); hormonal agents (*i.e.*, estramustine, tamoxifen, toremifene, anastrozole, or letrozole); antibiotics (*i.e.*, plicamycin, bleomycin, mitoxantrone, idarubicin, dactinomycin, mitomycin, or daunorubicin); other antimitotic agents (*i.e.*, vinblastine, vincristine, teniposide); topoisomerase inhibitors (*i.e.*, topotecan, irinotecan, etoposide, or doxorubicin, *e.g.*, CAELYX™ or DOXIL® reagents, pegylated liposomal doxorubicin hydrochloride); and other agents (*i.e.*, hydroxyurea, altretamine, rituximab, paclitaxel, docetaxel, L-asparaginase, or gemtuzumab ozogamicin);

biochemical modulating agents, imatib, EGFR inhibitors such as EKB-569 or other multi-kinase inhibitors, *e.g.*, those that targets serine/threonine and receptor tyrosine kinases in both the tumor cell and tumor vasculature, or immunomodulators (*i.e.*, interferons, IL-2, or BCG). Examples of suitable interferons include interferon α, interferon β, interferon γ, and mixtures thereof.

Desirably, the combination of the HKI-272 compound and vinorelbine compound may be further combined with antineoplastic alkylating agents, *e.g.*, those described in US Patent Application Publication No. 2002-0198137, which is hereby incorporated by reference. Antineoplastic alkylating agents are roughly classified, according to their structure or reactive moiety, into several categories which include nitrogen mustards, such as MUSTARGEN® drug (meclorethamine), cyclophosphamide, ifosfamide, melphalan, and chlorambucil; azidines and epoxides, such as thiotepa, mitomycin C, dianhydrogalactitol, and dibromodulcitol; alkyl sulfinates, such as busulfan; nitrosoureas, such as bischloroethylnitrosourea (BCNU), cyclohexyl-chloroethylnitrosourea (CCNU), and methylcyclohexylchloroethylnitrosourea (MeCCNU); hydrazine and triazine derivatives, such as procarbazine, dacarbazine, and temozolomide; streptazoin, melphalan, chlorambucil, carmustine, methclorethamine, lomustine)and platinum compounds. Platinum compounds are platinum containing agents that react preferentially at the N7 position of guanine and adenine residues to form a variety of monofunctional and bifunctional adducts. (Johnson S W, Stevenson J P, O'Dwyer P J. Cisplatin and Its Analogues. In Cancer Principles & Practice of Oncology 6th Edition. ed. DeVita V T, Hellman S, Rosenberg S A. Lippincott Williams & Wilkins. Philadelphia 2001. p. 378.) These compounds include cisplatin, carboplatin, platinum IV compounds, and multinuclear platinum complexes. Representative examples of alkylating agents including meclorethamine (injectable; MUSTARGEN® drug), cyclophosphamide (injectable; cyclophosphamide, lyophilized CYTOXAN® drug, or NEOSAR® drug; oral tablets cyclophosphamide or CYTOXAN® drug), ifosfamide (injectable; IFEX), melphalan (injectable, ALKERAN® drug; and oral tablets, ALKERAN® drug), chlorambucil (oral tablets, LEUKERAN® drug), thiotepa (injectable, thiotepa or THIOPLEX® drug), mitomycin (injectable, mitomycin or MUTAMYCIN® drug), busulfan (injectable, BUSULFEX® drug; oral tablets, MYLERAN® drug), lomustine (oral capsules; CEENU), carmustine (intracranial implant, GLIADEL); injectable (BICNU), procarbazine (oral capsules, MATULANE® drug), temozolomide (oral capsules, TEMODAR® drug), cisplatin (injectable, cisplatin, PLATINOL® drug, or PLATINOL®-AQ)., carboplatin (injectable, PARAPLATIN® drug), and oxaliplatin (ELOXATIN® drug).

In another embodiment, a combination described herein may further include an antineoplastic antimetabolite, as described in US Patent Application Publication Nos. 2005/0187184 or 2002/0183239, which are hereby incorporated by reference. As used herein accordance, the term "antimetabolite" means a substance which is structurally similar to a critical natural intermediate (metabolite) in a biochemical pathway leading to DNA or RNA synthesis which is used by the host in that pathway, but acts to inhibit the completion of that pathway (*i.e.*, synthesis of DNA or RNA). More specifically, antimetabolites typically function by (1) competing with metabolites for the catalytic or regulatory site of a key enzyme in DNA or RNA synthesis, or (2) substitute for a metabolite that is normally incorporated into DNA or RNA, and thereby producing a DNA or RNA that cannot support replication. Major categories of antimetabolites include (1) folic acid analogs, which are inhibitors of dihydrofolate reductase (DHFR); (2) purine analogs, which mimic the natural purines (adenine or guanine) but are structurally different so they competitively or irreversibly inhibit nuclear processing of DNA or RNA; and (3) pyrimidine analogs, which mimic the natural pyrimidines (cytosine, thymidine, and uracil), but are structurally different so thy competitively or irreversibly inhibit nuclear processing of DNA or RNA. Representative examples of antimetabolites include, without limitation, 5-Fluorouracil (5-FU; 5-fluoro-2,4(1H,3H)-pyrimidinedione; topical cream, FLUOROPLEX® or EFUDEX® drugs; topical solution, FLUOROPLEX® or EFUDEX® drugs; injectable, ADRUCIL® drug or flurouracil), floxuradine (2'-deoxy-5-fluorouridine; injectable, FUDR or floxuradine), thioguanine (2-amino-1,7-dihydro-6-H-purine-6-thione (oral tablets, thioguanine), cytarabine (4-amino-1-(β)-D-arabinofuranosyl-2(1H)-pyrimidinone; liposomal injectable, DEPOCYT® reagent; liquid injectable, cytarabine or CYTOSAR-U® drug), fludarabine (9-H-Purin-6-amine,2-fluoro-9-(5-O-phosphono-(β)-D-a-rabinofuranosyl; liquid injectable, FLUDARA), 6-Mercaptopurine (1,7-dihydro-6H-purine-6-thione; oral tablets, PURINETHOL)., methotrexate (MTX; N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid; liquid injectable, methotrexate sodium or FOLEX; oral tablets, methotrexate sodium), gemcitabine (2'-deoxy-2',2'-difluorocytidine monohydrochloride ((β)-isomer); liquid injectable, GEMZAR), capecitabine (5'-deoxy-5-fluoro-N-[(pentyloxy)carbonyl]-cytidine; oral tablet, XELODA), pentostatin ((R)-3-(2-deoxy-(beta)-D-erythro-pentofuranosyl)-3,6,7,8-tetrahydroimidazo[4,5-d][1,3]diazepin-8-ol; liquid injectable, NIPENT), trimetrexate (2,4-diamino-5-methyl-6-[(3,4,5-

trimethoxyanilino)methyl]quinazoline mono-D-glucuronate; liquid injectable, NEUTREXIN), cladribine (2-chloro-6-amino-9-(2-deoxy-(β)-D-erythropento-furanosyl) purine; liquid injectable, LEUSTATIN).

The term "biochemical modulating agent" is well known and understood to those skilled in the art as an agent given as an adjunct to anti-cancer therapy, which serves to potentate its antineoplastic activity, as well as counteract the side effects of the active agent, *e.g.*, an antimetabolite. Leucovorin and levofolinate are typically used as biochemical modulating agents for methotrexate and 5-FU therapy. Leucovorin (5-formyl-5,6,7,8-tetrahydrofolic acid) is commercially available as an injectable liquid (leucovorin calcium or WELLCOVORIN) and as oral tablets (leucovorin calcium). Levofolinate (pharmacologically active isomer of 5-formyltetrahydrofolic acid) is commercially available as an injectable containing (ISOVORIN) or as oral tablets (ISOVORIN).

In still another embodiment, the combination further includes a kinase inhibitor. Particularly desirable kinase inhibitors include multi-kinase inhibitors target serine/threonine and receptor tyrosine kinases in both the tumor cell and tumor vasculature. Examples of suitable kinase inhibitors include, without limitation, sorafenib (BAY 43-9006, commercially available as NEXAVAR), which has been granted Fast Track status by the FDA for metastatic renal cell cancer, zarnestra (R115777, tipifarnib), suntinib (SUTENT), and other compounds that target Ras/Raf/MEK and/or MAP kinases including, *e.g.*, avastin, ISIS 5132, and MEK inhibitors such as CI-1040 or PD 0325901. Alternatively, the kinase inhibitor may be administered to the patient prior to or subsequent to treatment with the vinorelbine compound and/or HKI-272 compound.

In still further embodiment, the combination may include an anti diarrheal. One of skill in the art would readily be able to select a suitable antidiarrheal for use herein including, without limitation, loperamide or diphenoxylate hydrochloride and atropine sulfate. Alternatively, the anti-diarrheal may be administered to the patient prior to or subsequent to treatment with the vinorelbine compound and/or HKI-272 compound.

In a further embodiment, the combination further contains an antiemetic agent. Examples of antiemetic agents include, without limitation, metoclopramide, Dolasetron, Granisetron, Ondansetron, Tropisetron, and Palonosetron, among others. Alternatively, the antiemetic may be

administered to the patient prior to or subsequent to treatment with the vinorelbine compound and/or HKI-272 compound.

In yet a further embodiment, the combination also contains an antihistamine. Examples of antihistamines include, without limitation, Cyclizine, Diphenhydramine, Dimenhydrinate (Gravol), Meclizine, Promethazine (Pentazine, Phenergan, Promacot), or Hydroxyzine, among others. Alternatively, the antihistamine may be administered to the patient prior to or subsequent to treatment with the vinorelbine compound and/or HKI-272 compound.

In yet another embodiment, the combination may include a growth factor to prevent and/or treat neutropenia. Such growth factors may readily be selected by those skill in the art according to practice guidelines from the American Society of Clinical Oncology (ASCO; 2006). Alternatively, the growth factor may be administered to the patient prior to or subsequent to treatment with the vinorelbine compound and/or HKI-272 compound.

Administration of the Compositions/Combinations

As used herein, the term "effective amount" or "pharmaceutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following: (1) preventing the disease; *e.g.*, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease; (2) inhibiting the disease; *e.g.*, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, arresting or slowing further development of the pathology and/or symptomatology); and (3) ameliorating the disease; *e.g.*, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology). For example, an effective amount," when administered to a subject to treat cancer, is sufficient to inhibit, slow, reduce, or eliminate tumor growth in a subject having cancer.

Use of a combination of the HKI-272 compound and vinorelbine compound also provides for the use of combinations of each of the agents in which one or both agent is used at subtherapeutically effective dosages. Subtherapeutically effective dosages may be readily

determined by one of skill in the art, in view of the teachings herein. In one embodiment, the subtherapeutically effective dosage is a dosage which is effective at a lower dosage when used in the combination regimen described herein, as compared to the dosage that is effective when used alone. Also provided are one or more of the active agents in the combinations herein to be used in a supratherapeutic amount, *i.e.*, at a higher dosage in the combination than when used alone. In this embodiment, the other active agent(s) may be used in a therapeutic or subtherapeutic amount.

The term "treating" or "treatment" refers to any indicia of success in amelioration of an injury, pathology, or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology, or condition more tolerable to the patient; slowing the rate of degeneration or decline; making the final point of degeneration less debilitating; or improving a subject's physical or mental well-being. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neurological examination, and/or psychiatric evaluation. Accordingly, the term "treating" includes the administration of the HKI-272 and vinorelbine compounds to a subject to prevent or delay, to alleviate, or to arrest or inhibit development of the symptoms or conditions associated with cancers, including tumor growth associated with cancer. A skilled medical practitioner will know how to use standard methods to determine whether a patient is suffering from a disease associated with cancer by examining the patient and determining whether the patient is suffering from cancer.

As used herein, the term "providing" with respect to providing a HKI-272 compound and a vinorelbine compound, means either directly administering the HKI-272 compound and vinorelbine compound, or administering a prodrug, derivative, or analog which will form an effective amount of the HKI-272 compound and/or vinorelbine compound within the body.

The invention therefore includes administering an HKI-272 compound and vinorelbine compound to a patient for the treatment of a neoplasm in a patient. In one embodiment, the HKI-272 compound is administered separately from the vinorelbine compound. In a further embodiment, the HKI-272 compound is administered prior to the vinorelbine compound. In another embodiment, the HKI-272 compound is administered subsequent to the vinorelbine compound. In still another embodiment, the HKI-272 compound and the vinorelbine compound are administered simultaneously, but separately. In one embodiment, the HKI-272 compound and the vinorelbine compound are administered together as a combined preparation.

In one embodiment, a product contains an HKI-272 compound and vinorelbine compound as a combined preparation for simultaneous, separate or sequential use in treating a neoplasm in a mammal in need thereof. In one embodiment, the HKI-272 compound is separately formulated from the vinorelbine compound. In another embodiment, a product contains the HKI-272 compound and the vinorelbine compound as a combined preparation for simultaneous, separate or sequential use in a neoplasm in a mammal in need thereof.

In one embodiment, a pharmaceutical pack contains a course of treatment of a neoplasm for one individual mammal, wherein the pack contains units of an HKI-272 compound in unit dosage form and units of a vinorelbine compound in unit dosage form. In another embodiment, a pharmaceutical pack contains a course of treatment of a neoplasm for one individual mammal, wherein the pack contains units of an HKI-272 compound in unit dosage form and units of a vinorelbine compound in unit dosage form. In yet another embodiment, a pharmaceutical pack as described herein contains a course of treatment of metastatic breast cancer for one individual mammal.

Administration of the individual components or a composition containing two or more of the individual components may employ any suitable route. Such routes may be selected from, *e.g.*, oral, intravenous (i.v.), respiratory (*e.g.*, nasal or intrabronchial), infusion, parenteral (aside from i.v., such as intralesional, intraperitoneal and subcutaneous injections), intraperitoneal, transdermal (including all administration across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues), and vaginal (including intrauterine administration). Other routes of administration are also feasible and include, without limitation, liposome-mediated delivery, topical, nasal, sublingual, uretheral, intrathecal, ocular or otic delivery, implant, rectal, or intranasal.

While the components may be delivered via the same route, a product or pack described herein may contain a vinorelbine compound for delivery by a different route than that of an HKI-272 compound, *e.g.*, one or more of the components may be delivered orally, while one or more of the others are administered intravenously. In one embodiment, the HKI-272 compound is prepared for oral delivery and the vinorelbine compound is prepared for intravenous delivery. In another embodiment, both the HKI-272 and vinorelbine compounds are prepared for intravenous delivery. In still another embodiment, both the HKI-272 and vinorelbine compounds are prepared for oral delivery. Optionally, other active components may be delivered by the same or

different routes as the HKI-272 and/or vinorelbine compounds. Other variations would be apparent to one skilled in the art.

In still another embodiment, the compounds or components of the therapeutic regimen are administered once a week. In certain situations, dosing with the HKI-272 compound 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 is known to one of skill in the art; it will also be dependent upon the form of the HKI-272 compound. One of skill in the art could routinely perform empirical activity tests to determine the bioactivity of the HKI-272 compound in bioassays and thus determine a suitable dosage to administer.

The HKI-272 and vinorelbine compounds or other optional compounds used in the combination and products described herein may be formulated in any suitable manner. However, the amounts of each compound in the unit dose can vary widely depending on the type of composition, regimen, size of a unit dosage, kind of excipients, and other factors well known to those of ordinary skill in the art. In one embodiment, the unit dose can contain, *e.g.*, 0.000001 percent by weight (% w) to 10% w of either compound. In another embodiment the unit dose can contain about 0.00001% w to 1% w, with the remainder being the excipient or excipients.

The compositions described herein may be in a form suitable for oral administration, *e.g.*, tablet, caplet, capsule, buccal forms, troches, lozenges and oral liquids, suspensions or solutions; parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), *e.g.*, as a sterile solution, suspension or emulsion; topical administration, *e.g.*, an ointment or cream; rectal administration, *e.g.*, a suppository; or the route of administration may be by direct injection into the tumor or by regional delivery or by local delivery. In other embodiments, one or both components of the combination treatment may be delivered endoscopically, intratracheally, intralesionally, percutaneously, intravenously, subcutaneously, intraperitoneally or intratumorally. In general the compositions described herein may be prepared in a conventional manner using conventional excipients or carriers that are well known in the art. Pharmaceutical compositions for oral use may also be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid excipient, *e.g.*, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil, such as peanut oil, liquid paraffin or olive oil. In one embodiment, one or

both of said vinorelbine compound and said HKI-272 compound are delivered orally to said subject.

Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (*e.g.* corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc.

Useful tablet or caplet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine.

Oral formulations herein, *e.g.*, tablets, caplets, or capsules described above, may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, *e.g.*, water, ethanol, polyol (*e.g.*, glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and

vegetable oils. Preferred injectable formulations containing vinorelbine are described in the art. In one embodiment, the compounds may be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. In one embodiment, one or both of the vinorelbine and HKI-272 compounds are delivered intravenously.

For use herein, transdermal administrations include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be performed using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal). Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

In another embodiment, one or both of the HKI-272 and vinorelbine compounds can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, *i.e.*, by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are

otherwise preferentially directed to a specific organ, one can focus the delivery of one or more compound into the target cells *in vivo*. (See, e.g., Al-Muhammed, J. Microencapsul. 13:293-306, 1996; Chonn, Curr. Opin. Biotechnol. 6:698-708, 1995; Ostro, Am. J. Hosp. Pharm. 46:1576-1587, 1989). In other cases, the preferred preparation of one or more of the components can be a lyophilized powder.

Encapsulating materials can also be employed with one or more of the compounds and the term "composition" can include the active ingredient in combination with an encapsulating material as a formulation, with or without other carriers. For example, the compounds can also be delivered as microspheres for slow release in the body. In one embodiment, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, J. Biomater Sci. Polym. Ed. 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao, Pharm. Res. 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, J. Pharm. Pharmacol. 49:669-674, 1997). Both transdermal and intradermal routes afford constant delivery for weeks or months. Cachets can also be used in the delivery of the compounds of the present invention, e.g., anti-atherosclerotic medicaments.

Dosages of the HKI-272 Compound and Vinorelbine Compound

As is typical with oncology treatments, dosage regimens are closely monitored by the treating physician, based on numerous factors including the severity of the disease, response to the disease, any treatment related toxicities, age, and health of the patient. Dosage regimens are expected to vary according to the route of administration.

The dosages and schedules described hereinbefore may be varied according to the particular disease state and the overall condition of the patient. For example, it may be necessary or desirable to reduce the above-mentioned doses of the components of the combination treatment in order to reduce toxicity. Dosages and schedules may also vary if, in addition to a combination of an HKI-272 compound and a vinorelbine, one or more additional chemotherapeutic agents are used. Scheduling can be determined by the practitioner who is treating any particular patient using his professional skill and knowledge.

For the HKI-272 compound and/or vinorelbine compound, it is desired each compound of the combination of compounds is in the form of a unit dose. The term "unit dose" or "unit dose

form" as used herein describes a single dose form including, without limitation, tablets, caplets, capsules, powders in sachets or vials, saline infusion bags, as described above.

Unit dose forms contain from about 0.1 to about 300 mg of a HKI-272 compound. In another embodiment, the unit dose form contains about 5 to about 300 mg of the HKI-272 compound. In another embodiment, the unit dose form contains about 50 to about 300 mg of the HKI-272 compound. In a further embodiment, the unit dose form contains about 75 to about 300 mg of the HKI-272 compound. In still a further embodiment, the unit dose form contains about 100 to about 300 mg of the HKI-272 compound. In yet another embodiment, the unit dose form contains about 120 to about 300 mg of the HKI-272 compound. In yet a further embodiment, the unit dose form contains about 160 to about 300 mg of the HKI-272 compound. In another embodiment, the unit dose form contains about 200 to about 300 mg of the HKI-272 compound. In yet another embodiment, the unit dose form contains about 240 to about 300 mg of the HKI-272 compound. In a further embodiment, the unit dose form contains about at least about 120 mg. In still a further embodiment, the unit dose form contains at least about 160 mg. In another embodiment, the unit dose form contains at least about 240 mg.

The HKI-272 compound can be administered, *e.g.*, orally, at a dose range of about 0.01 to 100 mg/kg. In one embodiment, the HKI-272 compound is administered at a dose range of about 0.1 to about 90 mg/kg. In another embodiment, the HKI-272 compound is administered at a dose range of about 1 to about 80 mg/kg. In a further embodiment, the HKI-272 compound is administered at a dose range of about 10 to about 70 mg/kg. In yet another embodiment, the HKI-272 compound is administered at a dose range of about 15 to about 60 mg/kg. In still a further embodiment, the HKI-272 compound is administered at a dose range of about 20 to about 50 mg/kg. In another embodiment, the HKI-272 compound is administered at a dose range of about 30 to about 50 mg/kg. 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, the oral dosage of the HKI-272 compound is at least about 700 mg/week. In another embodiment, the oral dosage of the HKI-272 compound is about 800 mg/week to at least to about 1700 mg/week. In another embodiment, the oral dosage of the HKI-272 compound is about 840 mg/week to about 1680 mg/week. In another embodiment, the oral dosage of the HKI-272 compound is about 900 mg/week to about 1600 mg/week. In a further embodiment, the oral dosage of the HKI-272 compound is about 1000 mg/week to about 1500

mg/week. In yet another embodiment, the oral dosage of the HKI-272 compound is about 1100 mg/week to about 1400 mg/week. In still a further embodiment, the oral dosage of the HKI-272 compound 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.

Desirably, the patient is administered about 0.1 to about 50 mg/kg of the vinorelbine compound. In one embodiment, the patient is administered about 1 to about 30 mg/kg of the vinorelbine compound. In another embodiment, the patient is administered about 5 to about 25 mg/kg of the vinorelbine compound. In a further embodiment, the patient is administered about 10 to about 20 mg/kg of the vinorelbine compound. In still a further embodiment, the patient is administered about 20 mg/kg of the vinorelbine compound.

Unit dose forms contain about 0.1 to about 100 mg of a vinorelbine compound. In another embodiment, the unit dose form contains about 1 to about 70 mg of the vinorelbine compound. In another embodiment, the unit dose form contains about 5 to about 500 mg of the vinorelbine compound. In a further embodiment, the unit dose form contains about 10 to about 250 mg of the vinorelbine compound. In still a further embodiment, the unit dose form contains about 15 to about 100 mg of the vinorelbine compound. In yet another embodiment, the unit dose form contains about 20 to about 75 mg of the vinorelbine compound. In yet a further embodiment, the unit dose form contains about 25 to about 50 mg of the vinorelbine compound. In another embodiment, the unit dose form contains about 30 to about 40 mg of the vinorelbine compound. In yet another embodiment, the unit dose form contains about 240 to about 300 mg of the vinorelbine compound. In a further embodiment, the unit dose form contains about at least about 120 mg. In still a further embodiment, the unit dose form contains at least about 160 mg. In another embodiment, the unit dose form contains at least about 240 mg.

In one embodiment, i.v. infusion dosages of the vinorelbine compound are from about 5 to about 25 mg/L. The initial infusion dosage of the vinorelbine compound may be more or less, as determined by the treating physician. In one embodiment, the i.v. infusion dosage of the vinorelbine compound is about 10 to about 20 mg/L. In a further embodiment, the i.v. infusion dosage of the vinorelbine compound is about 20 to about 25 mg/L. In yet another embodiment, the i.v. infusion dosage of the vinorelbine compound is at least about 10 mg/L. In another embodiment, the i.v. infusion dosage of the vinorelbine compound is at least about 15 mg/L. In yet another embodiment, the i.v. infusion dosage of the vinorelbine compound is at least about 20

mg/L. In yet another embodiment, the i.v. infusion dosage of the vinorelbine compound is at least about 25 mg/L. 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. In one embodiment, the vinorelbine compound is administered by i.v. infusion or orally, preferably in the form of tablets or capsules.

As described herein, subtherapeutically effective amounts of the HKI-272 compound and vinorelbine compound may be used to achieve a therapeutic effect when administered in combination. In one embodiment, the HKI-272 compound is provided at dosages of 5 to 50% lower when provided along with the vinorelbine compound. In another embodiment, the HKI-272 compound is provided at dosages of 10 to 25% lower when provided along with the vinorelbine compound. In a further embodiment, the HKI-272 compound is provided at dosages of 15 to 20% lower when provided along with the vinorelbine compound. In one embodiment, a resulting HKI-272 compound dosage is about 8 to 40 mg. In another embodiment, a resulting HKI-272 compound dosage is about 8 to 30 mg. In a further embodiment, a resulting HKI-272 compound dosage is about 8 to 25 mg. Subtherapeutically effective amounts of the HKI-272 compound and vinorelbine compound are expected to reduce the side-effects of treatment.

Alternatively, one or more of the active agents in the combination described herein is to be used in a supratherapeutic amount, *i.e.*, at a higher dosage in the combination than when used alone. In this embodiment, the other active agent(s) are used in a therapeutic or subtherapeutic amount.

Regimen Using the HKI-272 Compound and Vinorelbine Compound

As used herein, the components of the therapeutic "combined" regimen, *i.e.*, the HKI-272 compound and the vinorelbine compound, can be administered simultaneously. Alternatively, the two components can be administered in a staggered regimen, *i.e.*, with the HKI-272 compound being given at a different time during the course of chemotherapy than the vinorelbine compound. This time differential may range from several minutes, hours, days, weeks, or longer between administration of the at least two agents. Therefore, the term combination (or combined) does not necessarily mean administered at the same time or as a unitary dose or single composition, but that each of the components are administered during a desired treatment period. The agents may also be administered by different routes. As used herein in one embodiment, 1 "cycle" includes 3 weeks.

These regimens or cycles may be repeated, or alternated, as desired. Other dosage regimens and variations are foreseeable, and are determined through physician guidance. The regimen may include "non-treatment" steps/visits including screening periods and post-treatment periods. In one embodiment, the regimen continues at least about 2 weeks, at least about 6 weeks, at least about 12 weeks, at least about 24 weeks, at least about 33 weeks, at least about 40 weeks, and at least about 46 weeks. Additional screening weeks and final monitoring weeks may also be included. For example, the regimen may include 4 weeks of screening and 6 weeks for final visit.

Single doses and multiple doses are contemplated. In one embodiment, the vinorelbine and/or HKI-272 compound is administered only once in the treatment. In another embodiment, the vinorelbine and/or HKI-272 compound is administered at least once over a period of 21 days. In a further embodiment, the vinorelbine and/or HKI-272 compound is administered at least twice over a period of 21 days. In still another embodiment, the vinorelbine and/or HKI-272 compound is administered on days 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and/or 21 of the cycle. In a further embodiment, the vinorelbine and/or HKI-272 compound is administered on days 1 and 8 of the cycle. In still a further embodiment, the vinorelbine and/or HKI-272 compound is administered at least once daily. In yet another embodiment, the vinorelbine and/or HKI-272 compound HKI-272 compound is administered on day 1. Desirably, the HKI-272 compound is administered on day 1 if the neoplasm is non-metastatic. In a further embodiment, the vinorelbine and/or HKI-272 compound is administered on day 2 of said regimen. Desirably, the HKI-272 compound is administered on day 2 if the neoplasm is metastatic. In still a further embodiment, the HKI-272 compound is administered orally at least once a day. In another embodiment, the HKI-272 compound is administered at least 1, 2, 3, 4, 5, or 6 times a day. In a further embodiment the HKI-272 compound is administered 1 to 4 times a day.

In one embodiment, a single loading dose of the vinorelbine compound and/or HKI-272 compound is administered. The single loading dose of the vinorelbine compound and/or the HKI-272 compound may be the same dose as the subsequent doses or the single loading dose may be greater than the dose administered to the patient throughout the remaining treatment. In a further embodiment, the vinorelbine compound /or the HKI-272 compound may be administered at a larger dose only once per cycle, *i.e.*, one day per cycle.

If certain subjects do not tolerate one or more of the components of the composition, *i.e.*, the HKI-272 compound or vinorelbine compound, or if the subject does not recover from treatment-related toxicity after more than 3 consecutive weeks, or if any grade 4 nonhematologic

toxicity occurs that is treatment related, a dose reduction may be performed. In one embodiment, administration of one or both of the HKI-272 compound and the vinorelbine compound is discontinued if patent acquires one or more of a symptom including, without limitation, selected from the group consisting of neuropathy, neutropenia, thrombocytopenia, nausea, vomiting, decreased platelet count, and increased bilirubin count. In another embodiment, administration of one or both of the HKI-272 compound and the vinorelbine compound is discontinued or interrupted if the patient's neutrophil count of is less than about 1000/L. In a further embodiment, administration of one or both of the HKI-272 compound and the vinorelbine compound is discontinued or interrupted if the patient's platelet count is less than 75,000/L.

Alternatively, for those subjects do not tolerate one or more of the components of the composition, *i.e.*, the HKI-272 compound or vinorelbine compound, dose reductions may be performed. In one embodiment, 1 or 2 dose reductions are performed. More desirably, only 1 dose reduction is performed.

For subjects who not recover from vinorelbine or HKI-272-related toxicity after more than 3 consecutive weeks, treatment with vinorelbine or HKI-272, respectively, may be discontinued. However, administration of the other agent, *i.e.*, HKI-272 or vinorelbine, respectively, may be continued.

The regimen is typically continued for at least about 2 weeks. In one embodiment, the regimen is continued for no more than 46 weeks. In another embodiment, the regiment is continued for about 6 weeks. The length of participation is dependent on a subject's tolerance of the treatment and status of his or her disease. However, the treating physician may determine that shorter or longer treatment can be pursued. For example, subjects may receive more than 12 cycles of treatment if it is well tolerated, if the neoplasm has not progressed, if the subject is clinically stable, and if the subject has received an overall benefit.

In addition, the vinorelbine compound /or the HKI-272 compound may also be administered after completion of chemotherapy as maintenance therapy.

Pharmaceutical Packs and Kits

Also included is 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 the HKI-272 compound in unit dosage form and, optionally,

one, one to four, or more unit(s) of the HKI-272 and vinorelbine compounds, and optionally, another active agent. The combinations may be in the form of a kit of parts.

In one embodiment a kit includes a first container with a suitable composition containing a HKI-272 compound and a second container with a suitable composition containing a vinorelbine compound. Accordingly, there is provided a kit for use in the treatment or prophylaxis of cancer. This kit includes comprising: a) HKI-272 compound together with a pharmaceutically-acceptable excipient or carrier, in a first unit dosage form; b) a vinorelbine compound together with a pharmaceutically-acceptable excipient or carrier, in a second unit dosage form; and c) a container for containing said first and second dosage forms.

In another embodiment, pharmaceutical packs contain a course of anti-neoplastic treatment for one individual mammal comprising a container having a unit of a HKI-272 compound in unit dosage form, a containing having a unit of a vinorelbine compound, and optionally, a container with another active agent.

In some embodiments, the compositions are in packs in a form ready for administration. In other embodiments, the compositions 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 described herein in solid form and, optionally, a separate container with a suitable solvent or carrier.

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 are readily apparent to one of skill in the art.

Concurrent Treatments

In addition to the optional chemotherapeutic agents and optional compounds noted above, the regimens and methods described herein can be performed prior to, concurrently with, or subsequent to other non-medication procedures. In one embodiment, radiation may be performed prior to, concurrently with, or subsequent to treatment with the HKI-272 and vinorelbine compounds.

Preferred Embodiments

In one embodiment, a regimen for treating a solid tumor associated with overexpression or amplification of HER-2 in a subject is provided. One cycle of the regimen includes 21 days and

the regimen includes orally administering at least one unit dose of HKI-272 starting on day 1 of the cycle and intravenously administering at least one a unit dose of vinorelbine on days 1 and 8 of the cycle.

In another embodiment, a regimen for treating a metastatic cancer associated with overexpression or amplification of HER-2 in a subject is provided. One cycle of the regimen includes 21 days and the regimen includes orally administering at least one unit dose of HKI-272 starting on day 2 of the cycle and intravenously administering at least one unit dose of vinorelbine on days 1 and 8 of the cycle.

In a further embodiment, a product containing vinorelbine and HKI-272 is provided. The product is useful as a combined preparation for simultaneous, separate or sequential use in treating a neoplasm in a mammal.

In still a further embodiment, a pharmaceutical pack for treating a neoplasm in one individual mammal is provided. The pharmaceutical pack contains at least one unit of vinorelbine and at least one unit of HKI-272.

In another embodiment, a pharmaceutical composition is provided and contains vinorelbine, HKI-272, and at least one pharmaceutically acceptable carrier. Desirably, the pharmaceutical composition is useful for treating a neoplasm in a mammal.

In still another embodiment, a method of treating a neoplasm associated with overexpression or amplification of HER-2 in a mammal in need thereof is provided. The method includes administering a unit dose of a vinorelbine compound and administering a unit dose of a HKI-272 compound.

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.

EXAMPLE 1: COMBINATION REGIMEN OF HKI-272 AND VINORELBINE IN LUNG CANCER CELL PROLIFERATION ASSAYS

A standard cell proliferation assay was utilized to independently analyze the response of lung cell lines NCI-H1666, NCI-H1650, and NCI-H1975 to various dilutions of HKI-272 and vinorelbine in combination. Briefly, fetal bovine serum (FBS) RPMI-1640 (Media) was added

to each well of 96 well plates containing one of the cell lines. Each column of wells contained a different dilution of HKI-272 and solutions of vinorelbine were added to each well at a variety of dilutions with respect to the HKI-272 dilutions (the highest final concentration of HKI-272 was 1 μM for the H1650 and H1666 cell lines; the highest final concentration of HKI-272 was 9 μM for the H1975 cell line; and the highest final concentration of vinorelbine was 0.1 μM for all of the cell lines). Following incubation of the cell plates at 37 °C, 5% CO_2 for 72 hours, cell proliferation was assessed.

Cell proliferation was reduced after incubation with HKI-272 and vinorelbine.

EXAMPLE 2: COMBINATION REGIMEN OF HKI-272 AND VINORELBINE IN TREATMENT OF NON-METASTATIC BREAST CANCERS

Patients having diagnosed non-metastatic breast cancers are treated using a regimen of HKI-272 and vinorelbine. Patients are administered HKI-272 at either dose level 1 or 2. Dosing of HKI-272 begins at cycle 1, day 1 with daily oral administration of HKI-272 at the dosages in Table 3. HKI-272 is taken orally on the remaining days of the each cycle. On those days that HKI-272 and vinorelbine are administered on the same day, *i.e.*, days 1 and 8 of the cycle, HKI-272 is administered prior to the vinorelbine infusion.

Table 3

Dose Level	HKI-272 Dose (mg)	Vinorelbine Dose (mg/m^2)
1	160	25
2	240	

Vinorelbine is administered on days 1 and 8 of each 21-day cycle, provided that the combination of HKI-272 and vinorelbine is well tolerated and there is no evidence of disease progression. Vinorelbine is administered intravenously using preferentially a central venous route, through a free-flowing IV line over approximately 10 minutes, followed by 125 mL of saline solution infused over approximately 30 minutes.

If the patient has any serious side-effects during the treatment, dose adjustments of HKI-272 and/or vinorelbine are permitted. See, Tables 4 and 5.

Table 4

Dose Adjustment	HKI-272 (mg)
-1[a]	120
1[b]	160
2	240

a. The -1 dose level is used only if dose reduction is required.

b. The dose 1 level is to be used as first level of dose reduction in case the defined maximum tolerated dose is 240 mg.

Table 5

Dose Adjustment	Vinorelbine (mg/m^2)
-1[a]	20
1	25

a. The -1 dose level is to be used only if dose reduction is needed.

It is predicted that a decrease in tumor growth will be observed.

EXAMPLE 3: COMBINATION REGIMEN OF HKI-272 AND VONORELBINE IN TREATMENT OF METASTATIC BREAST CANCERS

Patients having diagnosed metastatic breast cancers are treated using a regimen of HKI-272 and vinorelbine.

Vinorelbine is administered on day 1 and day 8 of the cycle using the dosages described in Example 2, Table 3 or 5. The vinorelbine is administered over a 30-minute period using an in-line filter and an automatic dispensing pump. Optionally, antihistamine (diphenhydramine, 25 to 50 mg IV or the equivalent) is administered about 30 minutes prior to vinorelbine infusion.

Dosing of HKI-272 begins at cycle 1, day 2 with daily oral administration of HKI-272 at the dosages provided in Example 2, Table 3 or 4. HKI-272 is taken orally on the remaining days of the each cycle. On those days that HKI-272 and vinorelbine are administered on the same day, *i.e.*, day 8 of the cycle, HKI-272 is administered prior to the vinorelbine infusion. If the patient has any serious side-effects during the treatment, the dose adjustments of HKI-272 and/or vinorelbine are permitted.

It is predicted that a decrease in tumor growth will be observed.

All patents, patent publications, articles, and other documents referenced herein are incorporated by reference. It will be clear to one of skill in the art that modifications can be made to the specific embodiments described herein without departing from the scope of the invention.

WHAT IS CLAIMED IS:

1. A regimen for treating a neoplasm in a subject, said regimen comprising:
administering a vinorelbine compound; and
administering a HKI-272 compound.

2. The regimen according to claim 1, wherein the administering steps occur concurrently, sequentially, simultaneously, in a specified order, or according to a specific temporal relationship.

3. The regimen according to claim 1, wherein said vinorelbine compound is administered in a unit dose.

4. The regimen according to claim 1, wherein said HKI-272 compound is administered in a unit dose.

5. The regimen according to claim 1, wherein said vinorelbine compound is vinorelbine.

6. The regimen according to claim 1, wherein said HKI-272 compound is HKI-272.

7. The regimen according to claim 1, wherein one or both of said vinorelbine compound and said HKI-272 compound are delivered intravenously to said subject.

8. The regimen according to claim 1, wherein one or both of said vinorelbine compound and said HKI-272 compound are delivered orally to said subject.

9. The regimen according to claim 1, wherein said neoplasm is associated with overexpression or amplification of HER-2.

10. The regimen according to claim 1, wherein said neoplasm is metastatic.

11. The regimen according to claim 1, wherein said neoplasm is selected from the group consisting of a lung cancer, breast cancer, myeloma, prostate cancer, head and neck cancer, transitional cell carcinoma, small cell neuroendocrine carcinoma of the uterine cervix, and large cell neuroendocrine carcinoma of the uterine cervix.

12. The regimen according to claim 11, wherein said neoplasm is a breast cancer.

13. The regimen according to claim 12, wherein said breast cancer is a metastatic, HER-2 -positive breast cancer.

14. The regimen according to claim 1, wherein said neoplasm is an advanced solid tumor.

15. The regimen according to claim 1, wherein said vinorelbine compound is administered in an amount of at least about 20 mg/L.

16. The regimen according to claim 15, wherein said vinorelbine compound is administered in an amount of about 20 to about 25 mg/L.

17. The regimen according to claim 16, wherein said vinorelbine compound is administered in an amount of about 25 mg/L.

18. The regimen according to claim 1, wherein said HKI-272 compound is administered in an amount of at least about 120 mg.

19. The regimen according to claim 18, wherein said HKI-272 compound is administered in an amount of at least about 160 mg.

20. The regimen according to claim 19, wherein said HKI-272 compound is administered in an amount of at least about 240 mg.

21. The regimen according to claim 4, wherein said unit dose is a tablet.

22. The regimen according to claim 1, wherein said HKI- 272 compound is administered daily.

23. The regimen according to claim 1, wherein said HKI-272 compound is administered at least once daily.

24. The regimen according to claim 1, wherein said HKI-272 compound is administered on day 1 of said regimen.

25. The regimen according to claim 10, wherein said HKI-272 compound is administered on day 2 of said regimen.

26. The regimen according to claim 1, wherein said HKI-272 compound is administered for at least 2 continuous weeks.

27. A pharmaceutical composition according to claim 1, further comprising at least one pharmaceutically acceptable carrier.

28. The regimen according to claim 1, further comprising radiation.