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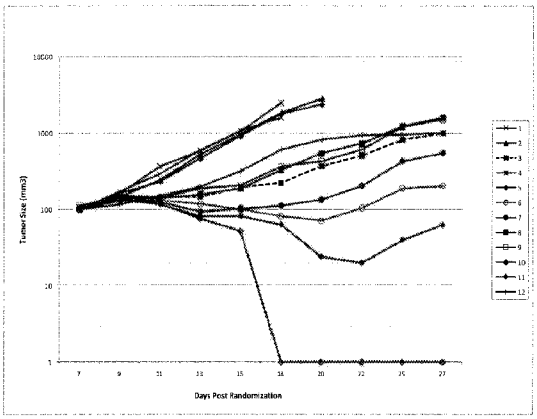
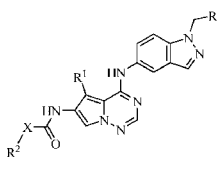
[Continued on next page]

(54) Title: COMBINATION OF AN INDAZOLYLAMINOPYRROLOTRIAZINE AND TAXANE FOR CANCER TREATMENT

(57) Abstract: Provided herein are methods of treating a proliferative disease in a subject, comprising administering to the subject a therapeutically effective amount of an indazolylaminopyrrolotriazine, *e.g.*, a compound of Formula (I), and a taxane. Also provided herein are pharmaceutical compositions which comprise an indazolylaminopyrrolotriazine and taxane, in combination with one or more pharmaceutically acceptable excipients.

FIG. 1





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COMBINATION OF AN INDAZOLYLAMINOPYRROLOTRIAZINE AND TAXANE FOR CANCER TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Application No. 61/159,404, filed March 11, 2009, the disclosure of which is incorporated herein by reference in its entirety.

FIELD

[0002] Provided herein are methods of treating a proliferative disease in a subject, comprising administering to the subject a therapeutically effective amount of an indazolylaminopyrrolotriazine and a taxane. Also provided herein are pharmaceutical compositions which comprise an indazolylaminopyrrolotriazine and taxane, in combination with one or more pharmaceutically acceptable excipients.

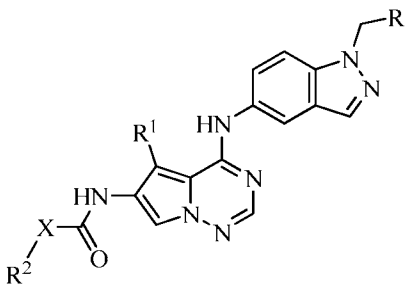
BACKGROUND

[0003] The Her family of receptor tyrosine kinase is comprised of Her 1 (also known as EGFR or ErbB-1), Her2 (ErbB-2), Her3 (ErbB-3), and Her4 (ErbB-4). The activation or overexpression of its members, such as Her1 or Her2, is implicated in human malignancies that include breast cancer, ovarian cancer, endometrial cancer, cervical cancer, esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer, prostate cancer, non-small cell lung cancer (NSCLC), bladder cancer, head and neck cancer, and glioma including glioblastoma. Currently marketed anti-EGFR therapies include the small molecules gefitinib (IRESSA®), which was approved for the treatment of NSCLC, and erlotinib (TARCEVA®), which was approved for the treatment of NSCLC and pancreatic cancer. Currently marketed monoclonal antibody therapies include cetuximab (ERBITUX®), an anti-EGFR antibody that was approved for the treatment of colorectal cancer, and trastuzumab (HERCEPTIN®), an anti-Her2 antibody that was approved for the treatment of Her2-positive breast cancer. Lapatinib (TYKERB®), which is a small molecule inhibitor with dual anti-EGFR/Her2 activity, was most recently approved for the treatment of Her2-positive breast cancer.

[0004] The taxanes are a powerful class of chemotherapeutics that may be isolated from the plant genus *Taxus* or further derivatized as a synthetic analog. The taxanes that comprise this class share the same chemical scaffold and similar mechanism of action and they have been found to have similar preclinical activity and clinical activity. *See*, Eisenhauer *et al.*, *Drugs* **1998**, *55*, 5-30; Huizing *et al.*, *Cancer Investigation* **1995**, *13*, 381-404; and Von Hoff *et al.*, *Seminars in Oncology*, **1997**, *24*, S13-3- S13-10. The first taxane, paclitaxel (TAXOL®), which is 5β,20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine, was isolated in 1971 from the Pacific yew (*Taxus brevifolia*), but may also be prepared using a semi-synthetic process from the European yew (*Taxus baccata*). Another well known taxane, docetaxel (TAXOTERE®), which is (2*R*,3*S*)-*N*-carboxy-3-phenylisoserine, *N*-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate, is also prepared from a semi-synthetic process from *Taxus baccata*. The taxanes belong to the subclass of antimitotics and exert their effect by promoting the polymerization of tubulin to the extent of interfering with the normal dynamic process of tubulin assembly and disassembly during cell cycling. This microtubule dysfunction leads to cell death. Despite these advances in anticancer therapy, there exists a long-felt need for effective therapies for proliferative diseases, in one embodiment, for cancers that are refractory to existing therapies.

SUMMARY OF THE DISCLOSURE

[0005] Provided herein is a method of treating a proliferative disease in a subject, comprising administering to the subject a therapeutically effective amount of (i) a taxane; and (ii) an indazolylaminopyrrolotriazine of Formula I:



(I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof;

wherein:

R is C_{6-14} aryl, heteroaryl, or heterocyclyl;

R^1 is C_{1-6} alkyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

X is a bond, –O–, –S–, $–C(R^3R^4)–$, or $–N(R^3)–$; and

each R^3 and R^4 is independently hydrogen, C_{1-6} alkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

wherein each alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q selected from the group consisting of (a) cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(=NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^aR^d$, $–NR^aC(O)R^b$, $–NR^aC(O)OR^b$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^b$, $–NR^aS(O)_2R^b$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, and $–S(O)_2R^a$; wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl; or (ii) R^b and R^c together with the N atom to which they are attached form heterocyclyl or heteroaryl.

[0006] In one embodiment, the taxane and the indazolylaminopyrrolotriazine described herein, *e.g.,* a compound of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; are administered accordingly to a dosing schedule provided herein.

[0007] Also provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a taxane and an indazolylaminopyrrolotriazine described herein, *e.g.,* a compound of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0008] Further provided herein is a pharmaceutical composition, comprising (i) a taxane; and (ii) an indazolylaminopyrrolotriazine described herein, *e.g.,* a compound of

Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; in combination with one or more pharmaceutically acceptable excipients.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 shows the synergetic effect of AC480 in combination with paclitaxel on MX-1 human breast carcinoma as determined by tumor size. The animals were treated according to the dosing schedules as shown in Table 1.

[0010] FIG. 2 shows the synergetic effect of AC480 in combination with paclitaxel on MX-1 human breast carcinoma as measured by the percentage of complete regression. The animals were treated according to the dosing schedules as shown in Table 1.

[0011] FIG. 3 shows the synergetic effect of AC480 in combination with paclitaxel on MX-1 human breast carcinoma as measured by the percentage of survival after treatment. The animals were treated according to the dosing schedules as shown in Table 1.

[0012] FIG. 4 shows the synergetic effect of AC480 in combination with paclitaxel on MX-1 human breast carcinoma as measured by the percentage of complete regression. The animals were treated according to the dosing schedules as shown in Table 2.

DETAILED DESCRIPTION

[0013] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0014] Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, biochemistry, biology, pharmacology, and others described herein are those well known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

[0015] The term "tumor," "neoplasm," and "neoplastic disorder or disease" are used interchangeably herein and are meant to refer to unwanted cell proliferation of one or more subset of cells in a multicellular organism resulting in harm (*i.e.*, discomfort or decreased life expectancy) to the multicellular organisms. In certain embodiments, a tumor can be benign

(non-invasive) or malignant (invasive).

[0016] The term "cancer" is meant to refer to a malignant neoplasm, which is characterized by uncontrolled cell proliferation where cells have lost their normal regulatory controls that would otherwise govern the rate of cell growth. These unregulated, dividing cells can spread throughout the body and invade normal tissues in a process referred to as "metastasis."

[0017] The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by man. Similarly, "non-naturally occurring" or "non-native" refers to a material that is not found in nature or that has been structurally modified or synthesized by man.

[0018] The terms "HER1," "epidermal growth factor receptor," "EGFR," and "ErbB1" are used interchangeably herein and refer to an EGFR receptor protein or variant thereof, as described, for example, in Carpenter *et al.*, *Ann. Rev. Biochem.* **1987**, *56*, 881-914. HER2 variants include proteins substantially homologous to a native EGFR, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, EGFR derivatives, homologs and fragments), as compared to the amino acid sequence of a native EGFR. The amino acid sequence of an HER2 variant is at least about 80% identical, at least about 90% identical, or at least about 95% identical to a native EGFR. An example of naturally occurring mutant forms of a native EGFR, *i.e.* a deletion mutant EGFR, is described in Humphrey *et al.*, *Proc. Natl. Acad. Sci. USA* **1990**, *87*, 4207-4211.

[0019] The terms "HER2" and "ErbB2" are used interchangeably herein and refer to a HER2 receptor protein or variant thereof. For example, a human HER2 protein is described in Semba *et al.*, *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 6497-6501 and Yamamoto *et al. Nature* **1986**, *319*, 230-234 (Genebank accession number X03363). HER2 variants include proteins substantially homologous to a native HER2, *i.e.*, proteins having one or more naturally or non-naturally occurring amino acid deletions, insertions or substitutions (*e.g.*, HER2 derivatives, homologs and fragments), as compared to the amino acid sequence of a native HER2 . The amino acid sequence of a HER2 variant is at least about 80% identical, at least about 90% identical, or at least about 95% identical to a native HER2.

[0020] The term "overexpress" or "overexpression" is meant that a cell associated with a disease, disorder, or condition comprises a detectably higher level of a protein, such as HER1 or HER2, than an otherwise identical cell that is not associated with a disease, disorder or condition.

[0021] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in one embodiment, a human.

[0022] The terms "treat," "treating," and "treatment" are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[0023] The term "contacting" or "contact" is meant to refer to bringing together of a therapeutic agent and cell or tissue such that a physiological and/or chemical effect takes place as a result of such contact. Contacting can take place *in vitro*, *ex vivo*, or *in vivo*. In one embodiment, a therapeutic agent is contacted with a cell in cell culture (*in vitro*) to determine the effect of the therapeutic agent on the cell. In another embodiment, the contacting of a therapeutic agent with a cell or tissue includes the administration of a therapeutic agent to a subject having the cell or tissue to be contacted.

[0024] The term "therapeutically effective amount" are meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (e.g., a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0025] The term "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refers to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In one embodiment, each component

is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, Remington: The Science and Practice of Pharmacy*, 21st Edition, Lippincott Williams & Wilkins: Philadelphia, PA, 2005; *Handbook of Pharmaceutical Excipients*, 5th Edition, Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and *Handbook of Pharmaceutical Additives*, 3rd Edition, Ash and Ash Eds., Gower Publishing Company: 2007; *Pharmaceutical Preformulation and Formulation*, 2nd Edition, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2009.

[0026] The term "about" or "approximately" means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term "about" or "approximately" means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[0027] The terms "active ingredient" and "active substance" refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease. As used herein, "active ingredient" and "active substance" may be an optically active isomer of a compound described herein.

[0028] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease.

[0029] The term "alkyl" refers to a linear or branched saturated monovalent hydrocarbon radical, wherein the alkylene may optionally be substituted as described herein. The term "alkyl" also encompasses both linear and branched alkyl, unless otherwise specified. In certain embodiments, the alkyl is a linear saturated monovalent hydrocarbon radical that has 1 to 20 (C_{1-20}), 1 to 15 (C_{1-15}), 1 to 10 (C_{1-10}), or 1 to 6 (C_{1-6}) carbon atoms, or branched saturated monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10

(C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. As used herein, linear C_{1-6} and branched C_{3-6} alkyl groups are also referred as "lower alkyl." Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl (including all isomeric forms), n-propyl, isopropyl, butyl (including all isomeric forms), n-butyl, isobutyl, *sec*-butyl, t-butyl, pentyl (including all isomeric forms), and hexyl (including all isomeric forms). For example, C_{1-6} alkyl refers to a linear saturated monovalent hydrocarbon radical of 1 to 6 carbon atoms or a branched saturated monovalent hydrocarbon radical of 3 to 6 carbon atoms.

[0030] The term "alkenyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, carbon-carbon double bonds. The alkenyl may be optionally substituted as described herein. The term "alkenyl" also embraces radicals having "*cis*" and "*trans*" configurations, or alternatively, "Z" and "E" configurations, as appreciated by those of ordinary skill in the art. As used herein, the term "alkenyl" encompasses both linear and branched alkenyl, unless otherwise specified. For example, C_{2-6} alkenyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms. In certain embodiments, the alkenyl is a linear monovalent hydrocarbon radical of 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkenyl groups include, but are not limited to, ethenyl, propen-1-yl, propen-2-yl, allyl, butenyl, and 4-methylbutenyl.

[0031] The term "alkynyl" refers to a linear or branched monovalent hydrocarbon radical, which contains one or more, in one embodiment, one to five, carbon-carbon triple bonds. The alkynyl may be optionally substituted as described herein. The term "alkynyl" also encompasses both linear and branched alkynyl, unless otherwise specified. In certain embodiments, the alkynyl is a linear monovalent hydrocarbon radical of 2 to 20 (C_{2-20}), 2 to 15 (C_{2-15}), 2 to 10 (C_{2-10}), or 2 to 6 (C_{2-6}) carbon atoms, or a branched monovalent hydrocarbon radical of 3 to 20 (C_{3-20}), 3 to 15 (C_{3-15}), 3 to 10 (C_{3-10}), or 3 to 6 (C_{3-6}) carbon atoms. Examples of alkynyl groups include, but are not limited to, ethynyl (–C≡CH) and propargyl ($–CH_2C≡CH$). For example, C_{2-6} alkynyl refers to a linear unsaturated monovalent hydrocarbon radical of 2 to 6 carbon atoms or a branched unsaturated monovalent hydrocarbon radical of 3 to 6 carbon atoms.

[0032] The term "cycloalkyl" refers to a cyclic saturated bridged and/or non-bridged monovalent hydrocarbon radical, which may be optionally substituted as described herein. In certain embodiments, the cycloalkyl has from 3 to 20 (C_{3-20}), from 3 to 15 (C_{3-15}), from 3 to 10 (C_{3-10}), or from 3 to 7 (C_{3-7}) carbon atoms. Examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, decalinyl, and adamantyl.

[0033] The term "aryl" refers to a monocyclic aromatic group and/or multicyclic monovalent aromatic group that contain at least one aromatic hydrocarbon ring. In certain embodiments, the aryl has from 6 to 20 (C_{6-20}), from 6 to 15 (C_{6-15}), or from 6 to 10 (C_{6-10}) ring atoms. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, fluorenyl, azulenyl, anthryl, phenanthryl, pyrenyl, biphenyl, and terphenyl. Aryl also refers to bicyclic or tricyclic carbon rings, where one of the rings is aromatic and the others of which may be saturated, partially unsaturated, or aromatic, for example, dihydronaphthyl, indenyl, indanyl, or tetrahydronaphthyl (tetralinyl). In certain embodiments, aryl may be optionally substituted as described herein.

[0034] The term "aralkyl" or "arylalkyl" refers to a monovalent alkyl group substituted with one or more aryl groups. In certain embodiments, the aralkyl has from 7 to 30 (C_{7-30}), from 7 to 20 (C_{7-20}), or from 7 to 16 (C_{7-16}) carbon atoms. Examples of aralkyl groups include, but are not limited to, benzyl, 2-phenylethyl, and 3-phenylpropyl. In certain embodiments, aralkyl may also be optionally substituted as described herein.

[0035] The term "heteroaryl" refers to a monocyclic aromatic group and/or multicyclic aromatic group that contain at least one aromatic ring, wherein at least one aromatic ring contains one or more heteroatoms independently selected from O, S, and N. Each ring of a heteroaryl group can contain one or two O atoms, one or two S atoms, and/or one to four N atoms, provided that the total number of heteroatoms in each ring is four or less and each ring contains at least one carbon atom. In certain embodiments, the heteroaryl has from 5 to 20, from 5 to 15, or from 5 to 10 ring atoms. Examples of monocyclic heteroaryl groups include, but are not limited to, furanyl, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, oxadiazolyl, oxazolyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridyl, pyrimidinyl, pyrrolyl, thiadiazolyl, thiazolyl, thienyl, tetrazolyl, triazinyl, and triazolyl. Examples of bicyclic heteroaryl groups include, but are not limited to, benzofuranyl, benzimidazolyl,

benzoisoxazolyl, benzopyranyl, benzothiadiazolyl, benzothiazolyl, benzothienyl, benzothiophenyl, benzotriazolyl, benzoxazolyl, furopyridyl, imidazopyridinyl, imidazothiazolyl, indolizinyl, indolyl, indazolyl, isobenzofuranyl, isobenzothienyl, isoindolyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxazolopyridinyl, phthalazinyl, pteridinyl, purinyl, pyridopyridyl, pyrrolopyridyl, quinolinyl, quinoxalinyl, quinazolinyl, thiadiazolopyrimidyl, and thienopyridyl. Examples of tricyclic heteroaryl groups include, but are not limited to, acridinyl, benzindolyl, carbazolyl, dibenzofuranyl, perimidinyl, phenanthrolinyl, phenanthridinyl, phenarsazinyl, phenazinyl, phenothiazinyl, phenoxazinyl, and xanthenyl. In certain embodiments, heteroaryl may also be optionally substituted as described herein.

[0036] The term "heterocyclyl" or "heterocyclic" refers to a monocyclic non-aromatic ring system and/or multicyclic ring system that contains at least one non-aromatic ring, wherein one or more of the non-aromatic ring atoms are heteroatoms independently selected from O, S, or N; and the remaining ring atoms are carbon atoms. In certain embodiments, the heterocyclyl or heterocyclic group has from 3 to 20, from 3 to 15, from 3 to 10, from 3 to 8, from 4 to 7, or from 5 to 6 ring atoms. In certain embodiments, the heterocyclyl is a monocyclic, bicyclic, tricyclic, or tetracyclic ring system, which may include a fused or bridged ring system, and in which the nitrogen or sulfur atoms may be optionally oxidized, the nitrogen atoms may be optionally quaternized, and some rings may be partially or fully saturated, or aromatic. The heterocyclyl may be attached to the main structure at any heteroatom or carbon atom which results in the creation of a stable compound. Examples of such heterocyclic radicals include, but are not limited to, azepinyl, benzodioxanyl, benzodioxolyl, benzofuranonyl, benzopyranonyl, benzopyranyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, benzothiopyranyl, benzoxazinyl, β-carbolinyl, chromanyl, chromonyl, cinnolinyl, coumarinyl, decahydroisoquinolinyl, dihydrobenzisothiazinyl, dihydrobenzisoxazinyl, dihydrofuryl, dihydroisoindolyl, dihydropyranyl, dihydropyrazolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dioxolanyl, 1,4-dithianyl, furanonyl, imidazolidinyl, imidazolinyl, indolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isochromanyl, isocoumarinyl, isoindolinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, oxazolidinonyl, oxazolidinyl, oxiranyl, piperazinyl, piperidinyl, 4-piperidonyl, pyrazolidinyl, pyrazolinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuryl, tetrahydroisoquinolinyl,

tetrahydropyranyl, tetrahydrothienyl, thiamorpholinyl, thiazolidinyl, tetrahydroquinolinyl, and 1,3,5-trithianyl. In certain embodiments, heterocyclic may also be optionally substituted as described herein.

[0037] The term "halogen", "halide" or "halo" refers to fluorine, chlorine, bromine, and/or iodine.

[0038] The term "optionally substituted" is intended to mean that a group, such as an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or alkoxy group, may be substituted with one or more substituents independently selected from, e.g., (a) alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; and (b) halo, cyano (–CN), nitro ($–NO_2$), $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^bR^c$, $–NR^aC(O)R^d$, $–NR^aC(O)OR^d$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^d$, $–NR^aS(O)_2R^d$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, $–S(O)_2R^a$, $–S(O)NR^bR^c$, and $–S(O)_2NR^bR^c$, wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q; or (iii) R^b and R^c together with the N atom to which they are attached form heteroaryl or heterocyclyl, optionally substituted with one or more, in one embodiment, one, two, three, or four, substituents Q. As used herein, all groups that can be substituted are "optionally substituted," unless otherwise specified.

[0039] In one embodiment, each Q is independently selected from the group consisting of (a) cyano, halo, and nitro; and (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^e$, $–C(O)OR^e$, $–C(O)NR^fR^g$, $–C(NR^e)NR^fR^g$, $–OR^e$, $–OC(O)R^e$, $–OC(O)OR^e$, $–OC(O)NR^fR^g$, $–OC(=NR^e)NR^fR^g$, $–OS(O)R^e$, $–OS(O)_2R^e$, $–OS(O)NR^fR^g$, $–OS(O)_2NR^fR^g$, $–NR^fR^g$, $–NR^eC(O)R^h$, $–NR^eC(O)OR^h$, $–NR^eC(O)NR^fR^g$, $–NR^eC(=NR^h)NR^fR^g$, $–NR^eS(O)R^h$, $–NR^eS(O)_2R^h$, $–NR^eS(O)NR^fR^g$, $–NR^eS(O)_2NR^fR^g$, $–SR^e$, $–S(O)R^e$, $–S(O)_2R^e$, $–S(O)NR^fR^g$, and $–S(O)_2NR^fR^g$; wherein each R^e, R^f, R^g, and R^h is independently (i) hydrogen; (ii) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{6-14} aryl, C_{7-15} aralkyl, heteroaryl, or

heterocyclyl; or (iii) R^f and R^g together with the N atom to which they are attached form heteroaryl or heterocyclyl.

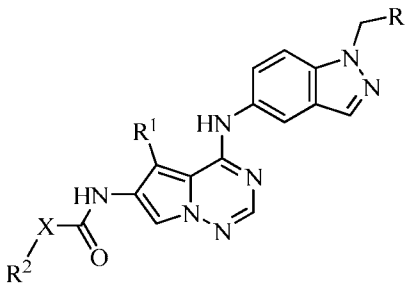
[0040] In certain embodiments, "optically active" and "enantiomerically active" refer to a collection of molecules, which has an enantiomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of the desired enantiomer and about 5% or less of the less preferred enantiomer based on the total weight of the racemate in question.

[0041] In describing an optically active compound, the prefixes R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (-) are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (-) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the molecule, R and S.

[0042] The term "solvate" refers to a compound provided herein or a salt thereof, which further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

Indazolylaminopyrrolotriazines

[0043] In one embodiment, the indazolylaminopyrrolotriazine described herein has the structure of Formula I:



(I)

and enantiomers, mixtures of enantiomers, and mixtures of two or more diastereomers thereof; and pharmaceutically acceptable salts, solvates, hydrates, and prodrugs thereof; wherein:

R is C_{6-14} aryl, heteroaryl, or heterocyclyl;

R^1 is C_{1-6} alkyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

X is a bond, –O–, –S–, $–C(R^3R^4)–$, or $–N(R^3)–$; and

each R^3 and R^4 is independently hydrogen, C_{1-6} alkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

wherein each alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q selected from the group consisting of (a) cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(=NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^aR^d$, $–NR^aC(O)R^b$, $–NR^aC(O)OR^b$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^b$, $–NR^aS(O)_2R^b$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, and $–S(O)_2R^a$; wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl; or (ii) R^b and R^c together with the N atom to which they are attached form heterocyclyl or heteroaryl.

[0044] In one embodiment, in the indazolylaminopyrrolotriazine of Formula I, R is C_{6-14} aryl, R^1 is C_{1-4} alkyl, each optionally substituted with one or more substituents Q, in one embodiment, one, two, or three substituents Q.

[0045] In another embodiment, in the indazolylaminopyrrolotriazine of Formula I, X

is O, and R^2 is C_{3-10} cycloalkyl, heteroaryl, or heterocyclyl, each optionally substituted with one or more substituents Q, in one embodiment, one, two, or three substituents Q.

[0046] In another embodiment, the indazolylaminopyrrolotriazine is selected from the group consisting of:

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*)-2-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-[(3*S*)-3-hydroxy-1-pyrrolidinyl]propyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-[(3*S*)-3-hydroxy-1-piperidinyl]propyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-[(3*R*)-3-hydroxy-1-pyrrolidinyl]propyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, [(2*S*)-1-methyl-2-pyrrolidinyl]methyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*)-2-morpholinylmethyl ester;

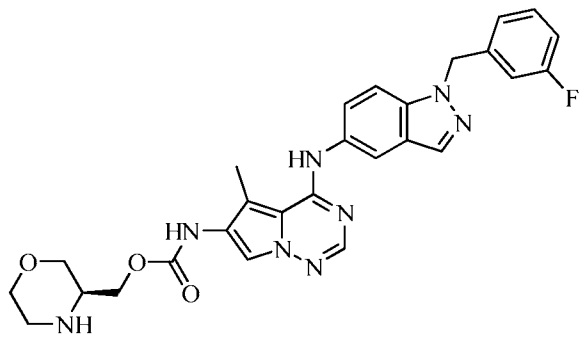
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, [(3*R*)-1-methyl-3-pyrrolidinyl]methyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *trans*-4-aminocyclohexyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-piperidinyl ester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-piperidinyl ester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-aminocyclohexyl;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*,4*R*)-2-(hydroxymethyl)-4-piperidinyl ester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-(hydroxymethyl)-4-piperidinyl ester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-(aminomethyl)cyclohexyl ester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-amino-4-methylcyclohexyl ester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, [(2*R*,4*R*)-4-(hydroxy-2-piperidinyl]methylester;
[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *trans*-4-(aminomethyl)cyclohexyl ester;
[5-ethyl-4-[[1-(2-oxazolylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2, 4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(2-thienylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(4-thiazolylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(3-thienylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(2-pyridinylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(2-thiazolylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(3-pyridinylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-

carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[5-ethyl-4-[[1-(pyrazinylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *trans*-4-aminocyclohexyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*,4*R*)-2-(hydroxymethyl)-4-piperidinyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*,4*S*)-2-(hydroxymethyl)-4-piperidinyl ester;
[4-[[-1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]-triazin-6-yl]-carbamic acid, *cis*-4-aminocyclohexyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-amino-4-methyl-cyclohexyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*)-2-aminopropyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-aminopropyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-morpholinylmethyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-piperidinyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-piperidinyl ester;
3-[[[[[4-[[1[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]-triazin-6-yl]amino]carbonyl]oxy]methyl]-4-morpholinecarboxylic acid, (3*S*)-1,1-dimethylethyl ester;
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-morpholinylmethyl ester; and
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-morpholinylmethyl ester;
and pharmaceutically acceptable salts, solvates, hydrates, or prodrugs thereof.

[0047] In yet another embodiment, the indazolylaminopyrrolotriazine has the structure of Formula II:



(II)

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[0048] The compound of Formula II is also known as AC480 or BMS-599626.

[0049] Further examples of indazolylaminopyrrolotriazines that are suitable for use in the pharmaceutical compositions and methods provided herein are illustrated in U.S. Pat. Nos. 6,916,815; 7,102,001; and 7,148,220; and U.S. Pat. Pub. Nos. 2005/0209454 and 2006/0014741, each of which is incorporated herein by reference in its entirety.

[0050] The compound of Formula I can be prepared according to the methods as described in U.S. Pat. Nos. 6,916,815; 7,102,001; and 7,148,220; and U.S. Pat. Pub. No. 2005/0209454 and 2006/0014741. The compound can be also synthesized according to other methods apparent to those of skill in the art based upon the teaching herein.

[0051] In one embodiment, the indazolylaminopyrrolotriazine is a compound of Formula I, or a pharmaceutically acceptable solvate or hydrate thereof. In one embodiment, the compound of Formula I is a solid. In another embodiment, the compound of Formula I is a solid in an amorphous form. In yet another embodiment, the compound of Formula I is a solid in a crystalline form. In yet another embodiment, the compound of Formula I is a solvate. In yet another embodiment, the compound of Formula I is a hydrate. In yet another embodiment, the compound of Formula I is a monohydrate. In still another embodiment, the compound of Formula I is a monohydrate in a crystalline form.

[0052] In another embodiment, the indazolylaminopyrrolotriazine used in the methods provided herein is a free base of the compound of Formula II, or a pharmaceutically

acceptable solvate or hydrate thereof. In one embodiment, the free base is a solid. In another embodiment, the free base is a solid in an amorphous form. In yet another embodiment, the free base is a solid in a crystalline form, including, but not limited to, the N-2 form. In yet another embodiment, the free base is a solid in the N-2 form. In yet another embodiment, the compound is a solvate. In yet another embodiment, the compound is a hydrate. In yet another embodiment, the compound is a monohydrate. In still another embodiment, the compound is a monohydrate in the H-1 form. The compound of Formula II in solid forms can be prepared according to the method described in U.S. Pat. Pub. No. 2006/0014741, which is incorporated herein by reference in its entirety; or using other suitable methods known in the art.

[0053] The compounds provided herein are intended to encompass all possible stereoisomers, unless a particular stereochemistry is specified. Where the indazolylaminopyrrolotriazine provided herein contains an alkenyl or alkenylene group, the compound may exist as one or a mixture of geometric *cis/trans* (or Z/E) isomers. Where structural isomers are interconvertible *via* a low energy barrier, the indazolylaminopyrrolotriazine may exist as a single tautomer or a mixture of tautomers. This can take the form of proton tautomerism in the indazolylaminopyrrolotriazine that contains, for example, an imino, keto, or oxime group; or so-called valence tautomerism in the compound that contain an aromatic moiety. It follows that a single indazolylaminopyrrolotriazine may exhibit more than one type of isomerism.

[0054] The indazolylaminopyrrolotriazines provided herein may be enantiomerically pure, such as a single enantiomer or a single diastereomer, or be stereoisomeric mixtures, such as a mixture of enantiomers, *e.g.*, a racemic mixture of two enantiomers; or a mixture of two or more diastereomers. As such, one of skill in the art will recognize that administration of a compound in its (*R*) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (*S*) form. Conventional techniques for the preparation/isolation of individual enantiomers include synthesis from a suitable optically pure precursor, asymmetric synthesis from achiral starting materials, or resolution of an enantiomeric mixture, for example, chiral chromatography, recrystallization, resolution, diastereomeric salt formation, or derivatization into diastereomeric adducts followed by separation.

[0055] When the indazolylaminopyrrolotriazines provided herein contains an acidic or basic moiety, it may also be provided as a pharmaceutically acceptable salt (*See*, Berge *et al.*, *J. Pharm. Sci.* **1977**, *66*, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stahl and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002).

[0056] Suitable acids for use in the preparation of pharmaceutically acceptable salts include, but are not limited to, acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, boric acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1*S*)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, cyclohexanesulfamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxoglutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, lauric acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, perchloric acid, phosphoric acid, L-pyroglutamic acid, saccharic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid, undecylenic acid, and valeric acid.

[0057] Suitable bases for use in the preparation of pharmaceutically acceptable salts, including, but not limited to, inorganic bases, such as magnesium hydroxide, calcium hydroxide, potassium hydroxide, zinc hydroxide, and sodium hydroxide; and organic bases, such as primary, secondary, tertiary, and quaternary, aliphatic, aromatic, heteroaryl, and heterocyclic amines, including L-arginine, benethamine, benzathine, choline, deanol, diethanolamine, diethylamine, dimethylamine, dipropylamine, diisopropylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylamine, ethylenediamine, isopropylamine, *N*-methyl-glucamine, hydrabamine, 1*H*-imidazole, L-lysine, morpholine, 4-(2-hydroxyethyl)-morpholine, methylamine, piperidine, piperazine, propylamine, pyrrolidine, 1-(2-hydroxyethyl)-pyrrolidine, pyridine, quinuclidine, quinoline, isoquinoline, secondary amines, triethanolamine, trimethylamine, triethylamine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, and tromethamine.

[0058] In one embodiment, the compound suitable for use in the methods provided herein is a pharmaceutically acceptable salt of the compound of Formula II. In one embodiment, the salt is a solid. In another embodiment, the salt is a solid in an amorphous form. In yet another embodiment, the salt is a solid in a crystalline form, including, but not limited to, the N-1 form. In yet another embodiment, the salt is a solid in the N-1 form. In yet another embodiment, the salt is a hydrochloride salt. In yet another embodiment, the hydrochloride salt is in a crystalline form, including, but not limited to, the N-1 form. In still another embodiment, the hydrochloride salt is in the N-1 form. The pharmaceutically acceptable salt compound of Formula II in solid forms can be prepared according to the method described in U.S. Pat. Pub. No. 2006/0014741, which is incorporated herein by reference in its entirety; or using other suitable methods known in the art.

[0059] In certain embodiments, the salt is a sulfonic acid salt. *See, e.g.,* U.S. Provisional Application No. _____, filed on March 11, 2010, the disclosure of which is incorporated herein by reference in its entirety. In certain embodiments, the sulfonic salt is in an amorphous form. In certain embodiments, the sulfonic salt is in a crystalline form.

[0060] In certain embodiments, the compound suitable for use in the methods provided herein is an ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof. As used herein, the term "ethanesulfonic acid salt" is used interchangeably with the term "esylate salt."

[0061] In certain embodiments, the molar ratio of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate versus ethanesulfonic acid in the salt provided herein, including hydrates and pharmaceutically acceptable solvates thereof, is ranging from about 0.5 to about 3, from about 0.5 to about 2, or from about 0.8 to about 1.2. In certain embodiments, the molar ratio of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate versus ethanesulfonic acid in the salt provided herein, including hydrates and pharmaceutically acceptable solvates thereof, is about 0.5, about 0.6, about 0.7, about 0.8, about 0.9, about 1, about 1.1, about 1.2, about 1.4, about 1.5, about 1.6, about 1.8, about 2, about 2.2, about 2.4, about 2.6, about 2.8, or about 3.

[0062] In one embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl

4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, comprises about one molar equivalent of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate and about one molar equivalent of ethanesulfonic acid. In certain embodiments, the molar ratio of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate versus ethanesulfonic acid is determined based on its ^{1}H NMR spectrum.

[0063] In certain embodiments, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, has a purity of at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 98.5%, at least about 99%, at least about 99.2%, at least about 99.4%, at least about 99.5%, at least about 99.6%, at least about 99.7%, at least about 99.8%, or at least about 99.9%. In certain embodiments, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, contains the nitrosamine at a level of no greater than about 5 ppm, no greater than about 4 ppm, no greater than about 3 ppm, no greater than about 2 ppm, no greater than about 1.5 ppm, no greater than about 1 ppm, no greater than about 0.8 ppm, no greater than about 0.6 ppm, no greater than about 0.4 ppm, no greater than about 0.2 ppm, or no greater than about 0.1 ppm.

[0064] In one embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is in an amorphous form. In another embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is crystalline. In certain embodiments, the ethanesulfonic acid salt has an endotherm with a peak temperature of about 202 ºC and an onset temperature of 197 ºC in a DSC thermogram. In certain embodiments, the ethanesulfonic acid salt shows no greater than about 1%, no greater than about 0.8%, no greater than about 0.6%, no greater than about 0.4%, no greater than about 0.2%, no greater than about 0.1%, no greater than about 0.09%, no greater than about 0.08%, no greater than about 0.07%, no greater than about 0.06%, or no greater than about 0.05% weight loss

between 25 °C to 150 °C in a thermogravimetric thermogram. In certain embodiments, the ethanesulfonic acid salt shows about 0.1% weight loss between 25 °C to 150 °C in a thermogravimetric thermogram.

[0065] In one embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is in crystalline Form II-A.

[0066] In another embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is in crystalline Form II-B.

[0067] In yet another embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is in crystalline Form II-C.

[0068] In yet another embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is in crystalline Form II-D.

[0069] In still another embodiment, the ethanesulfonic acid salt of (*S*)-morpholin-3-ylmethyl 4-(1-(3-fluorobenzyl)-1*H*-indazol-5-ylamino)-5-methylpyrrolo[1,2-*f*][1,2,4]triazin-6-ylcarbamate, or a hydrate or pharmaceutically acceptable solvate thereof, is in crystalline Form II-E.

[0070] The compound provided herein may also be provided as a prodrug, which is a functional derivative of the compound, for example, of Formula I or II and is readily convertible into the parent compound in vivo. Prodrugs are often useful because, in some situations, they may be easier to administer than the parent compound. They may, for instance, be bioavailable by oral administration whereas the parent compound is not. The prodrug may also have enhanced solubility in pharmaceutical compositions over the parent compound. A prodrug may be converted into the parent drug by various mechanisms,

including enzymatic processes and metabolic hydrolysis. See Harper, *Progress in Drug Research* **1962**, *4*, 221-294; Morozowich *et al.* in "Design of Biopharmaceutical Properties through Prodrugs and Analogs," Roche Ed., APHA Acad. Pharm. Sci. 1977; "Bioreversible Carriers in Drug in Drug Design, Theory and Application," Roche Ed., APHA Acad. Pharm. Sci. 1987; "Design of Prodrugs," Bundgaard, Elsevier, 1985; Wang *et al.*, *Curr. Pharm. Design* **1999**, *5*, 265-287; Pauletti *et al.*, *Adv. Drug. Delivery Rev.* **1997**, *27*, 235-256; Mizen *et al.*, *Pharm. Biotech.* **1998**, *11*, 345-365; Gaignault *et al.*, *Pract. Med. Chem.* **1996**, 671-696; Asgharnejad in "Transport Processes in Pharmaceutical Systems," Amidon *et al.*, Ed., Marcell Dekker, 185-218, 2000; Balant *et al.*, *Eur. J. Drug Metab. Pharmacokinet.* **1990**, *15*, 143-53; Balimane and Sinko, *Adv. Drug Delivery Rev.* **1999**, *39*, 183-209; Browne, *Clin. Neuropharmacol.* **1997**, *20*, 1-12; Bundgaard, *Arch. Pharm. Chem.* **1979**, *86*, 1-39; Bundgaard, *Controlled Drug Delivery* **1987**, *17*, 179-96; Bundgaard, *Adv. Drug Delivery Rev.* **1992**, *8*, 1-38; Fleisher *et al.*, *Adv. Drug Delivery Rev.* **1996**, *19*, 115-130; Fleisher *et al.*, *Methods Enzymol.* **1985**, *112*, 360-381; Farquhar *et al.*, *J. Pharm. Sci.* **1983**, *72*, 324-325; Freeman *et al.*, *J. Chem. Soc., Chem. Commun.* **1991**, 875-877; Friis and Bundgaard, *Eur. J. Pharm. Sci.* **1996**, *4*, 49-59; Gangwar *et al.*, *Des. Biopharm. Prop. Prodrugs Analogs*, **1977**, 409-421; Nathwani and Wood, *Drugs* **1993**, *45*, 866-94; Sinhababu and Thakker, *Adv. Drug Delivery Rev.* **1996**, *19*, 241-273; Stella *et al.*, *Drugs* **1985**, *29*, 455-73; Tan *et al.*, *Adv. Drug Delivery Rev.* **1999**, *39*, 117-151; Taylor, *Adv. Drug Delivery Rev.* **1996**, *19*, 131-148; Valentino and Borchardt, *Drug Discovery Today* **1997**, *2*, 148-155; Wiebe and Knaus, *Adv. Drug Delivery Rev.* **1999**, *39*, 63-80; and Waller *et al.*, *Br. J. Clin. Pharmac.* **1989**, *28*, 497-507.

Taxanes

[0071] As used herein, the term "taxane" includes both naturally derived and chemically synthesized terpenes or derivatives thereof, including, but not limited to, paclitaxel (TAXOL®) and docetaxel (TAXOTERE®). Paclitaxel and its derivatives are described in U.S. Pat. Nos. 4,942,184; 5,440,056; 5,496,804; 5,641,803; 5,670,537; and 6,380,405; each of which is incorporated herein by reference in its entirety. Docetaxel is described in U.S. Pat. Nos. 4,814,470; 5,438,072; 5,698,582; and 5,714,512; each of which is incorporated herein by reference in its entirety.

[0072] In certain embodiments, the taxane is paclitaxel. In certain embodiments, the

taxane is albumin-bound paclitaxel (ABRAXANE®). In certain embodiments, the taxane is docetaxel.

Pharmaceutical Compositions

[0073] In one embodiment, provided herein are pharmaceutical compositions comprising a taxane and an indazolylaminopyrrolotriazine provided herein, *e.g.*, a compound of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[0074] In another embodiment, provided herein are pharmaceutical compositions comprising an indazolylaminopyrrolotriazine provided herein, *e.g.*, a compound of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[0075] In yet another embodiment, provided herein are pharmaceutical compositions comprising an indazolylaminopyrrolotriazine provided herein, *e.g.*, a compound of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with hydroxypropyl-b-cyclodextrin, mannitol, water, or a mixture thereof.

[0076] In yet another embodiment, provided herein are pharmaceutical compositions comprising [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, in combination with hydroxypropyl-β-cyclodextrin, mannitol, water, or a mixture thereof.

[0077] In yet another embodiment, provided herein is a pharmaceutical composition comprising [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, ethanesulfonate, or a pharmaceutically acceptable solvate or hydrate, thereof, in combination with hydroxypropyl-β-cyclodextrin, mannitol, water, or a mixture thereof.

[0078] In yet another embodiment, provided herein is a pharmaceutical composition comprising about 15% by weight of [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, ethanesulfonate, about 75% by weight of hydroxypropyl-β-cyclodextrin, and 10% by weight of mannitol.

[0079] In yet another embodiment, provided herein is a pharmaceutical composition in a unit-dosage, comprising about 363 mg of [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, ethanesulfonate, about 1,800 mg of hydroxypropyl-β-cyclodextrin, and 1,240 mg by weight of mannitol.

[0080] In certain embodiments, a pharmaceutical composition in a unit-dosage, comprising about 363 mg of [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, ethanesulfonate in a crystalline form. In certain embodiments, a pharmaceutical composition in a unit-dosage, comprising about 363 mg of [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, ethanesulfonate in crystalline Form II-B.

[0081] In yet another embodiment, provided herein are pharmaceutical compositions comprising a taxane and a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[0082] The taxane-containing compositions provided herein can also be formulated as known to those skilled in the art. Some examples of taxane-containing pharmaceutical compositions are described in U.S. Pat. Nos. 4,814,470; 4,942,184; 5,438,072; 5,440,056; 5,496,804; 5,641,803; 5,670,537; 5,698,582; 5,714,512; and 6,380,405; each of which is incorporated herein by reference in its entirety.

[0083] The pharmaceutical compositions provided herein can further comprise an additional active agent provided herein. In one embodiment, the additional active agent is cisplatin, capecitabine, carboplatin, cetuximab, vinorelbine, gefitinib, gemcitabine, etoposide, irinotecan, lapatinib, trastuzumab, vinblastine, mitomycin, ifosfamide, pemetrexed, erlotinib, bevacizumab, or cetuximab.

[0084] The pharmaceutical compositions provided herein may be formulated in various dosage forms for oral, parenteral, and topical administration. The pharmaceutical compositions may also be formulated as modified release dosage forms, including delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. These dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*See, Remington: The Science and Practice of Pharmacy*, supra; *Modified-Release Drug Deliver Technology*, Rathbone *et al.*, Eds., Drugs and the Pharmaceutical Science, Marcel Dekker, Inc.: New York, NY, 2003; Vol. 126).

[0085] In one embodiment, the pharmaceutical compositions provided herein are formulated in a dosage form for oral administration. In another embodiment, the pharmaceutical compositions provided herein are formulated in a dosage form for parenteral administration. In yet another embodiment, the pharmaceutical compositions provided herein are formulated in a dosage form for topical administration.

[0086] The pharmaceutical compositions provided herein may be provided in a unit-dosage or multiple-dosage form. A unit-dosage form, as used herein, refers to physically discrete a unit suitable for administration to a subject, *e.g.*, a human and animal subject, and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of an active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. A unit-dosage form may be administered in fractions or multiples thereof. A multiple-dosage form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dosage form. Examples of a multiple-dosage form include a vial, bottle of tablets or capsules, or bottle of pints or gallons.

[0087] The pharmaceutical compositions provided herein may be administered at once, or multiple times at intervals of time. It is understood that the precise dosage and duration of treatment may vary with the age, weight, and condition of the patient being treated, and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test or diagnostic data. It is further understood that for any particular individual, specific dosage regimens should be adjusted over time according to the individual

need and the professional judgment of the person administering or supervising the administration of the formulations.

A. Oral Administration

[0088] The pharmaceutical compositions provided herein for oral administration can be provided in solid, semisolid, or liquid dosage forms for oral administration. As used herein, oral administration also includes buccal, lingual, and sublingual administration. Suitable oral dosage forms include, but are not limited to, tablets, fastmelts, chewable tablets, capsules, pills, strips, troches, lozenges, pastilles, cachets, pellets, medicated chewing gum, bulk powders, effervescent or non-effervescent powders or granules, oral mists, solutions, emulsions, suspensions, wafers, sprinkles, elixirs, and syrups. In addition to the active ingredient(s), the pharmaceutical compositions can contain one or more pharmaceutically acceptable carriers or excipients, including, but not limited to, binders, fillers, diluents, disintegrants, wetting agents, lubricants, glidants, coloring agents, dye-migration inhibitors, sweetening agents, flavoring agents, emulsifying agents, suspending and dispersing agents, preservatives, solvents, non-aqueous liquids, organic acids, and sources of carbon dioxide.

[0089] Binders or granulators impart cohesiveness to a tablet to ensure the tablet remaining intact after compression. Suitable binders or granulators include, but are not limited to, starches, such as corn starch, potato starch, and pre-gelatinized starch (e.g., STARCH 1500); gelatin; sugars, such as sucrose, glucose, dextrose, molasses, and lactose; natural and synthetic gums, such as acacia, alginic acid, alginates, extract of Irish moss, panwar gum, ghatti gum, mucilage of isabgol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone (PVP), Veegum, larch arabogalactan, powdered tragacanth, and guar gum; celluloses, such as ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose, methyl cellulose, hydroxyethylcellulose (HEC), hydroxypropylcellulose (HPC), hydroxypropyl methyl cellulose (HPMC); microcrystalline celluloses, such as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, AVICEL-PH-105 (FMC Corp., Marcus Hook, PA); and mixtures thereof. Suitable fillers include, but are not limited to, talc, calcium carbonate, microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The amount of a binder or filler in the pharmaceutical compositions provided herein varies upon the type of formulation, and is

readily discernible to those of ordinary skill in the art. The binder or filler may be present from about 50 to about 99% by weight in the pharmaceutical compositions provided herein.

[0090] Suitable diluents include, but are not limited to, dicalcium phosphate, calcium sulfate, lactose, sorbitol, sucrose, inositol, cellulose, kaolin, mannitol, sodium chloride, dry starch, and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose, and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such compressed tablets can be used as chewable tablets. The amount of a diluent in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[0091] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The amount of a disintegrant in the pharmaceutical compositions provided herein varies upon the type of formulation, and is readily discernible to those of ordinary skill in the art. The pharmaceutical compositions provided herein may contain from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[0092] Suitable lubricants include, but are not limited to, calcium stearate; magnesium stearate; mineral oil; light mineral oil; glycerin; sorbitol; mannitol; glycols, such as glycerol behenate and polyethylene glycol (PEG); stearic acid; sodium lauryl sulfate; talc; hydrogenated vegetable oil, including peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil; zinc stearate; ethyl oleate; ethyl laureate; agar; starch; lycopodium; silica or silica gels, such as AEROSIL® 200 (W.R. Grace Co., Baltimore, MD) and CAB-O-SIL® (Cabot Co. of Boston, MA); and mixtures thereof. The pharmaceutical compositions provided herein may contain about 0.1 to about 5% by weight of a lubricant.

[0093] Suitable glidants include, but are not limited to, colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Suitable coloring agents include, but are not limited to, any of the approved, certified, water soluble FD&C dyes, and water insoluble FD&C dyes suspended on alumina hydrate, and color lakes and mixtures thereof. A color lake is the combination by adsorption of a water-soluble dye to a hydrous oxide of a heavy metal, resulting in an insoluble form of the dye. Suitable flavoring agents include, but are not limited to, natural flavors extracted from plants, such as fruits, and synthetic blends of compounds which produce a pleasant taste sensation, such as peppermint and methyl salicylate. Suitable sweetening agents include, but are not limited to, sucrose, lactose, mannitol, syrups, glycerin, and artificial sweeteners, such as saccharin and aspartame. Suitable emulsifying agents include, but are not limited to, gelatin, acacia, tragacanth, bentonite, and surfactants, such as polyoxyethylene sorbitan monooleate (TWEEN® 20), polyoxyethylene sorbitan monooleate 80 (TWEEN® 80), and triethanolamine oleate. Suitable suspending and dispersing agents include, but are not limited to, sodium carboxymethylcellulose, pectin, tragacanth, Veegum, acacia, sodium carbomethylcellulose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Suitable wetting agents include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether. Suitable solvents include, but are not limited to, glycerin, sorbitol, ethyl alcohol, and syrup. Suitable non-aqueous liquids utilized in emulsions include, but are not limited to, mineral oil and cottonseed oil. Suitable organic acids include, but are not limited to, citric and tartaric acid. Suitable sources of carbon dioxide include, but are not limited to, sodium bicarbonate and sodium carbonate.

[0094] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[0095] The pharmaceutical compositions provided herein for oral administration can be provided as compressed tablets, tablet triturates, chewable lozenges, rapidly dissolving tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets. Enteric-coated tablets are compressed tablets coated with substances that resist the action of stomach acid but dissolve or disintegrate in the intestine, thus protecting the active ingredients from the acidic environment of the stomach. Enteric-coatings include, but are not

limited to, fatty acids, fats, phenyl salicylate, waxes, shellac, ammoniated shellac, and cellulose acetate phthalates. Sugar-coated tablets are compressed tablets surrounded by a sugar coating, which may be beneficial in covering up objectionable tastes or odors and in protecting the tablets from oxidation. Film-coated tablets are compressed tablets that are covered with a thin layer or film of a water-soluble material. Film coatings include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000, and cellulose acetate phthalate. Film coating imparts the same general characteristics as sugar coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle, including layered tablets, and press-coated or dry-coated tablets.

[0096] The tablet dosage forms can be prepared from the active ingredient in powdered, crystalline, or granular forms, alone or in combination with one or more carriers or excipients described herein, including binders, disintegrants, controlled-release polymers, lubricants, diluents, and/or colorants. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

[0097] The pharmaceutical compositions provided herein for oral administration can be provided as soft or hard capsules, which can be made from gelatin, methylcellulose, starch, or calcium alginate. The hard gelatin capsule, also known as the dry-filled capsule (DFC), consists of two sections, one slipping over the other, thus completely enclosing the active ingredient. The soft elastic capsule (SEC) is a soft, globular shell, such as a gelatin shell, which is plasticized by the addition of glycerin, sorbitol, or a similar polyol. The soft gelatin shells may contain a preservative to prevent the growth of microorganisms. Suitable preservatives are those as described herein, including methyl- and propyl-parabens, and sorbic acid. The liquid, semisolid, and solid dosage forms provided herein may be encapsulated in a capsule. Suitable liquid and semisolid dosage forms include solutions and suspensions in propylene carbonate, vegetable oils, or triglycerides. Capsules containing such solutions can be prepared as described in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. The capsules may also be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient.

[0098] The pharmaceutical compositions provided herein for oral administration can be provided in liquid and semisolid dosage forms, including emulsions, solutions, suspensions, elixirs, and syrups. An emulsion is a two-phase system, in which one liquid is

dispersed in the form of small globules throughout another liquid, which can be oil-in-water or water-in-oil. Emulsions may include a pharmaceutically acceptable non-aqueous liquid or solvent, emulsifying agent, and preservative. Suspensions may include a pharmaceutically acceptable suspending agent and preservative. Aqueous alcoholic solutions may include a pharmaceutically acceptable acetal, such as a di(lower alkyl) acetal of a lower alkyl aldehyde, e.g., acetaldehyde diethyl acetal; and a water-miscible solvent having one or more hydroxyl groups, such as propylene glycol and ethanol. Elixirs are clear, sweetened, and hydroalcoholic solutions. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may also contain a preservative. For a liquid dosage form, for example, a solution in a polyethylene glycol may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be measured conveniently for administration.

[0099] Other useful liquid and semisolid dosage forms include, but are not limited to, those containing the active ingredient(s) provided herein, and a dialkylated mono- or poly-alkylene glycol, including, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether, wherein 350, 550, and 750 refer to the approximate average molecular weight of the polyethylene glycol. These formulations can further comprise one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, bisulfite, sodium metabisulfite, thiodipropionic acid and its esters, and dithiocarbamates.

[00100] The pharmaceutical compositions provided herein for oral administration can be also provided in the forms of liposomes, micelles, microspheres, or nanosystems. Micellar dosage forms can be prepared as described in U.S. Pat. No. 6,350,458.

[00101] The pharmaceutical compositions provided herein for oral administration can be provided as non-effervescent or effervescent, granules and powders, to be reconstituted into a liquid dosage form. Pharmaceutically acceptable carriers and excipients used in the non-effervescent granules or powders may include diluents, sweeteners, and wetting agents. Pharmaceutically acceptable carriers and excipients used in the effervescent granules or powders may include organic acids and a source of carbon dioxide.

[00102] Coloring and flavoring agents can be used in all of the above dosage forms.

[00103] The pharmaceutical compositions provided herein for oral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

B. Parenteral Administration

[00104] The pharmaceutical compositions provided herein can be administered parenterally by injection, infusion, or implantation, for local or systemic administration. Parenteral administration, as used herein, include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, intrasynovial, intravesical, and subcutaneous administration.

[00105] The pharmaceutical compositions provided herein for parenteral administration can be formulated in any dosage forms that are suitable for parenteral administration, including solutions, suspensions, emulsions, micelles, liposomes, microspheres, nanosystems, and solid forms suitable for solutions or suspensions in liquid prior to injection. Such dosage forms can be prepared according to conventional methods known to those skilled in the art of pharmaceutical science (*see, Remington: The Science and Practice of Pharmacy*, supra).

[00106] The pharmaceutical compositions intended for parenteral administration can include one or more pharmaceutically acceptable carriers and excipients, including, but not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, cryoprotectants, lyoprotectants, thickening agents, pH adjusting agents, and inert gases.

[00107] Suitable aqueous vehicles include, but are not limited to, water, saline, physiological saline or phosphate buffered saline (PBS), sodium chloride injection, Ringers injection, isotonic dextrose injection, sterile water injection, dextrose and lactated Ringers injection. Suitable non-aqueous vehicles include, but are not limited to, fixed oils of vegetable origin, castor oil, corn oil, cottonseed oil, olive oil, peanut oil, peppermint oil,

safflower oil, sesame oil, soybean oil, hydrogenated vegetable oils, hydrogenated soybean oil, and medium-chain triglycerides of coconut oil, and palm seed oil. Suitable water-miscible vehicles include, but are not limited to, ethanol, 1,3-butanediol, liquid polyethylene glycol (e.g., polyethylene glycol 300 and polyethylene glycol 400), propylene glycol, glycerin, *N*-methyl-2-pyrrolidone, *N,N*-dimethylacetamide, and dimethyl sulfoxide.

[00108] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoates, thimerosal, benzalkonium chloride (e.g., benzethonium chloride), methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents are those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00109] When the pharmaceutical compositions provided herein are formulated for multiple dosage administration, the multiple dosage parenteral formulations must contain an antimicrobial agent at bacteriostatic or fungistatic concentrations. All parenteral formulations must be sterile, as known and practiced in the art.

[00110] In one embodiment, the pharmaceutical compositions for parenteral administration are provided as ready-to-use sterile solutions. In another embodiment, the pharmaceutical compositions are provided as sterile dry soluble products, including lyophilized powders and hypodermic tablets, to be reconstituted with a vehicle prior to use. In yet another embodiment, the pharmaceutical compositions are provided as ready-to-use

sterile suspensions. In yet another embodiment, the pharmaceutical compositions are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, the pharmaceutical compositions are provided as ready-to-use sterile emulsions.

[00111] The pharmaceutical compositions provided herein for parenteral administration can be formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00112] The pharmaceutical compositions provided herein for parenteral administration can be formulated as a suspension, solid, semi-solid, or thixotropic liquid, for administration as an implanted depot. In one embodiment, the pharmaceutical compositions provided herein are dispersed in a solid inner matrix, which is surrounded by an outer polymeric membrane that is insoluble in body fluids but allows the active ingredient in the pharmaceutical compositions diffuse through.

[00113] Suitable inner matrixes include, but are not limited to, polymethylmethacrylate, polybutyl-methacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinyl acetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers, such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinyl alcohol, and cross-linked partially hydrolyzed polyvinyl acetate.

[00114] Suitable outer polymeric membranes include but are not limited to, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinyl acetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer.

C. Topical Administration

[00115] The pharmaceutical compositions provided herein can be administered topically to the skin, orifices, or mucosa. The topical administration, as used herein, includes

(intra)dermal, conjunctival, intracorneal, intraocular, ophthalmic, auricular, transdermal, nasal, vaginal, urethral, respiratory, and rectal administration.

[00116] The pharmaceutical compositions provided herein can be formulated in any dosage forms that are suitable for topical administration for local or systemic effect, including emulsions, solutions, suspensions, creams, gels, hydrogels, ointments, dusting powders, dressings, elixirs, lotions, suspensions, tinctures, pastes, foams, films, aerosols, irrigations, sprays, suppositories, bandages, and dermal patches. The topical formulation of the pharmaceutical compositions provided herein can also comprise liposomes, micelles, microspheres, nanosystems, and mixtures thereof.

[00117] Pharmaceutically acceptable carriers and excipients suitable for use in the topical formulations provided herein include, but are not limited to, aqueous vehicles, water-miscible vehicles, non-aqueous vehicles, antimicrobial agents or preservatives against the growth of microorganisms, stabilizers, solubility enhancers, isotonic agents, buffering agents, antioxidants, local anesthetics, suspending and dispersing agents, wetting or emulsifying agents, complexing agents, sequestering or chelating agents, penetration enhancers, cryoprotectants, lyoprotectants, thickening agents, and inert gases.

[00118] The pharmaceutical compositions can also be administered topically by electroporation, iontophoresis, phonophoresis, sonophoresis, or microneedle or needle-free injection, such as POWDERJECT™ (Chiron Corp., Emeryville, CA), and BIOJECT™ (Bioject Medical Technologies Inc., Tualatin, OR).

[00119] The pharmaceutical compositions provided herein can be provided in the forms of ointments, creams, and gels. Suitable ointment vehicles include oleaginous or hydrocarbon vehicles, including lard, benzoinated lard, olive oil, cottonseed oil, and other oils, white petrolatum; emulsifiable or absorption vehicles, such as hydrophilic petrolatum, hydroxystearin sulfate, and anhydrous lanolin; water-removable vehicles, such as hydrophilic ointment; water-soluble ointment vehicles, including polyethylene glycols of varying molecular weight; emulsion vehicles, either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, including cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid (*see*, *Remington: The Science and Practice of Pharmacy*, supra). These vehicles are emollient but generally require addition of antioxidants and preservatives.

[00120] Suitable cream base can be oil-in-water or water-in-oil. Suitable cream vehicles may be water-washable, and contain an oil phase, an emulsifier, and an aqueous phase. The oil phase is also called the "internal" phase, which is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation may be a nonionic, anionic, cationic, or amphoteric surfactant.

[00121] Gels are semisolid, suspension-type systems. Single-phase gels contain organic macromolecules distributed substantially uniformly throughout the liquid carrier. Suitable gelling agents include, but are not limited to, crosslinked acrylic acid polymers, such as carbomers, carboxypolyalkylenes, and CARBOPOL®; hydrophilic polymers, such as polyethylene oxides, polyoxyethylene-polyoxypropylene copolymers, and polyvinylalcohol; cellulosic polymers, such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose; gums, such as tragacanth and xanthan gum; sodium alginate; and gelatin. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by trituration, mechanical mixing, and/or stirring.

[00122] The pharmaceutical compositions provided herein can be administered rectally, urethrally, vaginally, or perivaginally in the forms of suppositories, pessaries, bougies, poultices or cataplasm, pastes, powders, dressings, creams, plasters, contraceptives, ointments, solutions, emulsions, suspensions, tampons, gels, foams, sprays, or enemas. These dosage forms can be manufactured using conventional processes as described in *Remington: The Science and Practice of Pharmacy*, supra.

[00123] Rectal, urethral, and vaginal suppositories are solid bodies for insertion into body orifices, which are solid at ordinary temperatures but melt or soften at body temperature to release the active ingredient(s) inside the orifices. Pharmaceutically acceptable carriers utilized in rectal and vaginal suppositories include bases or vehicles, such as stiffening agents, which produce a melting point in the proximity of body temperature, when formulated with the pharmaceutical compositions provided herein; and antioxidants as described herein, including bisulfite and sodium metabisulfite. Suitable vehicles include, but are not limited to, cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene

glycol), spermaceti, paraffin, white and yellow wax, appropriate mixtures of mono-, di- and triglycerides of fatty acids, hydrogels, such as polyvinyl alcohol, hydroxyethyl methacrylate, and polyacrylic acid. Combinations of the various vehicles can also be used. Rectal and vaginal suppositories may be prepared by compressing or molding. The typical weight of a rectal and vaginal suppository is about 2 to about 3 g.

[00124] The pharmaceutical compositions provided herein can be administered ophthalmically in the forms of solutions, suspensions, ointments, emulsions, gel-forming solutions, powders for solutions, gels, ocular inserts, and implants.

[00125] The pharmaceutical compositions provided herein can be administered intranasally or by inhalation to the respiratory tract. The pharmaceutical compositions can be provided in the form of an aerosol or solution for delivery using a pressurized container, pump, spray, atomizer, such as an atomizer using electrohydrodynamics to produce a fine mist, or nebulizer, alone or in combination with a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. The pharmaceutical compositions can also be provided as a dry powder for insufflation, alone or in combination with an inert carrier such as lactose or phospholipids; and nasal drops. For intranasal use, the powder can comprise a bioadhesive agent, including chitosan or cyclodextrin.

[00126] Solutions or suspensions for use in a pressurized container, pump, spray, atomizer, or nebulizer can be formulated to contain ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the active ingredient provided herein; a propellant as solvent; and/or a surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

[00127] The pharmaceutical compositions provided herein can be micronized to a size suitable for delivery by inhalation, such as about 50 micrometers or less, or about 10 micrometers or less. Particles of such sizes can be prepared using a comminuting method known to those skilled in the art, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying.

[00128] Capsules, blisters, and cartridges for use in an inhaler or insufflator can be formulated to contain a powder mix of the pharmaceutical compositions provided herein; a suitable powder base, such as lactose or starch; and a performance modifier, such as *l*-

leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate. Other suitable excipients or carriers include, but are not limited to, dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose, and trehalose. The pharmaceutical compositions provided herein for inhaled/intranasal administration can further comprise a suitable flavor, such as menthol and levomenthol; and/or sweeteners, such as saccharin and saccharin sodium.

[00129] The pharmaceutical compositions provided herein for topical administration can be formulated to be immediate release or modified release, including delayed-, sustained-, pulsed-, controlled-, targeted, and programmed release.

D. Modified Release

[00130] The pharmaceutical compositions provided herein can be formulated as a modified release dosage form. As used herein, the term "modified release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when administered by the same route. Modified release dosage forms include, but are not limited to, delayed-, extended-, prolonged-, sustained-, pulsatile-, controlled-, accelerated- and fast-, targeted-, programmed-release, and gastric retention dosage forms. The pharmaceutical compositions in modified release dosage forms can be prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, microspheres, liposomes, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes and polymorphorism of the active ingredient(s).

[00131] Examples of modified release include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,639,480; 5,733,566; 5,739,108; 5,891,474; 5,922,356; 5,972,891; 5,980,945; 5,993,855; 6,045,830; 6,087,324; 6,113,943; 6,197,350; 6,248,363; 6,264,970; 6,267,981; 6,376,461; 6,419,961; 6,589,548; 6,613,358; and 6,699,500.

1. Matrix Controlled Release Devices

[00132] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada et al. in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz Ed., Wiley, 1999).

[00133] In certain embodiments, the pharmaceutical compositions provided herein in a modified release dosage form is formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including, but not limited to, synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00134] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethyl hydroxyethyl cellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methyl methacrylate, ethyl methacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00135] In certain embodiments, the pharmaceutical compositions provided herein are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device include, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene,

polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinyl acetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinyl chloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubbers, epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, ethylene/vinyloxyethanol copolymer, polyvinyl chloride, plasticized nylon, plasticized polyethylene terephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, and silicone carbonate copolymers; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00136] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00137] The pharmaceutical compositions provided herein in a modified release dosage form can be prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, and melt-granulation followed by compression.

2. Osmotic Controlled Release Devices

[00138] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated using an osmotic controlled release device, including, but not limited to, one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) a core which contains an active ingredient; and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00139] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water

from the environment of use into the core of the device. One class of osmotic agents is water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels." Suitable water-swellable hydrophilic polymers as osmotic agents include, but are not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00140] The other class of osmotic agents is osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-toluenesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00141] Osmotic agents of different dissolution rates can be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example, amorphous sugars, such as MANNOGEM™ EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00142] The core can also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00143] Materials useful in forming the semipermeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00144] Semipermeable membrane can also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00145] The delivery port(s) on the semipermeable membrane can be formed post-coating by mechanical or laser drilling. Delivery port(s) can also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in the core. In addition, delivery ports can be formed during coating process, as

in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00146] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semipermeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00147] The pharmaceutical compositions in an osmotic controlled-release dosage form can further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00148] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* **1995**, *35*, 1-21; Verma et al., *Drug Development and Industrial Pharmacy* **2000**, *26*, 695-708; Verma et al., *J. Controlled Release* **2002**, *79*, 7-27).

[00149] In certain embodiments, the pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See*, U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00150] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

3. Multiparticulate Controlled Release Devices

[00151] The pharmaceutical compositions provided herein in a modified release dosage form can be fabricated as a multiparticulate controlled release device, which comprises a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such

multiparticulates can be made by the processes known to those skilled in the art, including wet-and dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, and by spray-coating seed cores. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00152] Other excipients or carriers as described herein can be blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles can themselves constitute the multiparticulate device or can be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

4. Targeted Delivery

[00153] The pharmaceutical compositions provided herein can also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated, including liposome-, resealed erythrocyte-, and antibody-based delivery systems. Examples include, but are not limited to, those disclosed in U.S. Pat. Nos. 6,316,652; 6,274,552; 6,271,359; 6,253,872; 6,139,865; 6,131,570; 6,120,751; 6,071,495; 6,060,082; 6,048,736; 6,039,975; 6,004,534; 5,985,307; 5,972,366; 5,900,252; 5,840,674; 5,759,542; and 5,709,874.

Methods of Use

[00154] In one embodiment, provided herein is a method of treating a proliferative disease in a subject, comprising administering to the subject a therapeutically effective amount of (i) a taxane; and (ii) an indazolylaminopyrrolotriazine provided herein, *e.g.*, a compound of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof. In certain embodiments, the combination of the taxane and indazolylaminopyrrolotriazine has a synergetic effect when compared to the administration of the taxane or indazolylaminopyrrolotriazine alone.

[00155] In another embodiment, the method further comprises administering to the subject a therapeutically effective amount of a platinum agent. In certain embodiments, the platinum agent is cisplatin, carboplatin, oxaliplatin, satraplatin (JM-216), or CI-973. In certain embodiments, the platinum agent is carboplatin. In certain embodiments, the

combination of the taxane, platinum agent, and indazolylaminopyrrolotriazine has a synergetic effect when compared to the administration of the combination of taxane and platinum agent, or indazolylaminopyrrolotriazine alone.

[00156] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered once a day. In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered once a day with food. In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered twice a day. In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered twice a day with food.

[00157] In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject in the amount ranging from about 0.01 to about 1,000 mg/kg, from about 0.1 to about 500 mg/kg, from about 0.1 to about 250 mg/kg, or from about 0.1 to about 100 mg/kg.

[00158] In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject in the amount ranging from about 0.01 to about 1,000 mg/kg/day, from about 0.1 to about 500 mg/kg/day, from about 0.1 to about 250 mg/kg/day, or from about 0.1 to about 100 mg/kg/day. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject in the amount of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 15, about 20, about 25, about 30, about 35, about 40 about 50, about 60, about 70, about 75, about 80, about 90, about 100, about 105, about 120, about 130, about 140, about 150, about

160, about 170, about 180, about 190, about 200, about 300, about 400, about 500, about 600, about 700, about 750, about 800, about 900, or about 1,000 mg/kg/day.

[00159] The administered dose of the indazolylaminopyrrolotriazine provided herein can also be expressed in units other than the unit "mg/kg/day." For example, doses for parenteral administration can be expressed as $mg/m^2/day$. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to $mg/m^2/day$ to given either the height or weight of a subject or both (*See,* www.fda.gov/cder/cancer/animalframe.htm). For example, a dose of 1 mg/kg/day for a 65 kg human is approximately equal to 38 $mg/m^2/day$.

[00160] In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject in the amount ranging from about 1 to about 1,500 $mg/m^2/day$, about 1 to about 1,000 $mg/m^2/day$, from about 10 to about 500 $mg/m^2/day$, from about 10 to about 300 $mg/m^2/day$, or from about 20 to about 200 $mg/m^2/day$. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject in the amount of about 10, about 20, about 30, about 40, about 50, about 60, about 70, about 80, about 90, about 100, about 110, about 120, about 130, about 134, about 140, about 150, about 160, about 170, about 180, about 190, about 200, about 210, about 220, about 230, about 240, about 250, about 260, about 270, about 280, about 290, or about 300 $mg/m^2/day$.

[00161] In one embodiment, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered daily in a single dose or divided doses, where the total daily dose ranges from about 1 mg to about 2,000 mg, from about 10 mg to about 1,600 mg, from about 100 mg to about 1,200 mg, from about 200 mg to about 1,200 mg, from about 200 mg to about 1,100 mg, from about 300 mg to about 1,100 mg, from about 300 mg to about 1,000 mg, from about 300 mg to about 800 mg, from about 320 to about 800 mg, from about 320 to about 700 mg, from about 325 to about 650 mg, from about 325 mg to about 600 mg, or from about 350 mg to about 600 mg.

[00162] In another embodiment, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered daily in a single dose or

divided doses for a total daily dose of at least 200 mg, at least 250 mg, at least 300 mg, at least 320 mg, at least 325 mg, at least 350 mg, or at least 400 mg.

[00163] In yet another embodiment, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered daily in a single dose or divided doses (*e.g.*, BID) for a total daily dose of about 10 mg, about 30 mg, about 65 mg, about 100 mg, about 200 mg, about 250 mg, about 300 mg, about 320 mg, about 400 mg, about 480 mg, about 500 mg, about 600 mg, about 660 mg, about 700 mg, about 800 mg, about 900 mg, about 1,000 mg, about 1,200 mg, about 1,400 mg, or about 1,600 mg.

[00164] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered daily in a single dose or divided doses for a total daily dose sufficient to achieve a plasma concentration of the compound at steady state ranging from about 0.5 μM to about 40 μM, from about 1 μM to about 30 μM, from about 5 μM to about 25 μM or from about 10 μM to about 20 μM; in one embodiment, about 1 μM, about 2 μM, about 5 μM, about 10 μM, about 15 μM, about 30 μM, about 40 μM, or about 50 μM. As used herein, the term "plasma concentration at steady state" is the concentration reached after a period of administration of a compound. Once steady state is reached, there are minor peaks and troughs on the time dependent curve of the plasma concentration of the compound.

[00165] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered daily in a single dose or divided doses for a total daily dose calculated to achieve a plasma concentration of the compound at steady state ranging from about 0.5 μM to about 40 μM, from about 1 μM to about 30 μM, from about 5 μM to about 25 μM or from about 10 μM to about 20 μM; in one embodiment, about 1 μM, about 2 μM, about 5 μM, about 10 μM, about 15 μM, about 30

μM, about 40 μM, or about 50 μM.

[00166] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve a C_{max} from about 0.1 to about 100 μM, about 0.2 to about 50 μM, about 0.4 to about 40 μM, about 0.5 to about 10 μM, about 5 to about 40 μM, from about 10 to about 40 μM, from about 0.4 to about 4.5 μM, or from about 3.5 to about 6 μM; in one embodiment, about 0.1 μM, 0.2 μM, about 0.3 μM, about 0.4 μM, about 0.5 μM, 0.6 μM, about 0.7 μM, 0.8 μM, about 0.9 μM, about 1 μM, about 2 μM, about 3 μM, about 4 μM, about 5 μM, about 6 μM, 7 μM, about 8 μM, 9 μM, about 10 μM, about 15 μM, about 20 μM, about 30 μM, about 40 μM, about 50 μM.

[00167] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose calculated to achieve a C_{max} from about 0.1 to about 100 μM, about 0.2 to about 50 μM, about 0.4 to about 40 μM, about 0.5 to about 10 μM, about 5 to about 40 μM, from about 10 to about 40 μM, from about 0.4 to about 4.5 μM, or from about 3.5 to about 6 μM; in one embodiment, about 0.1 μM, 0.2 μM, about 0.3 μM, about 0.4 μM, about 0.5 μM, 0.6 μM, about 0.7 μM, 0.8 μM, about 0.9 μM, about 1 μM, about 2 μM, about 3 μM, about 4 μM, about 5 μM, about 6 μM, 7 μM, about 8 μM, 9 μM, about 10 μM, about 15 μM, about 20 μM, about 30 μM, about 40 μM, about 50 μM.

[00168] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve a C_{max} of about 0.1 to about 50 μg/mL, about 0.2 to about 40 μg/mL, about 2 to about 20 μg/mL, about 1.5 to about 3.2 μg/mL, or about 0.2 to about 2.2 μg/mL.

[00169] In certain embodiments, the indazolylaminopyrrolotriazine provided herein,

e.g., an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose calculated to achieve a C_{max} of about 0.1 to about 50 μg/mL, about 0.2 to about 40 μg/mL, about 2 to about 20 μg/mL, about 1.5 to about 3.2 μg/mL, or about 0.2 to about 2.2 μg/mL.

[00170] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve an AUC from about 1 to about 500, from about 5 to about 400, from about 60 to about 500, from about 125 to about 500, from about 125 to about 300, from 125 to about 200, from about 4 to about 35, or from about 40 to about 55 μg*hr/mL.

[00171] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose calculated to achieve an AUC from about 1 to about 500, from about 5 to about 400, from about 60 to about 500, from about 125 to about 500, from about 125 to about 300, from 125 to about 200, from about 4 to about 35, or from about 40 to about 55 μg*hr/mL.

[00172] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose sufficient to achieve an AUC from about 5 to about 1,000, from about 125 to about 1,000, from about 250 to about 500, from about 80 to about 110, or from about 5 to about 65 μM*hr.

[00173] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a

mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered in a single dose or divided doses for a total daily dose calculated to achieve an AUC from about 5 to about 1,000, from about 125 to about 1,000, from about 250 to about 500, from about 80 to about 110, or from about 5 to about 65 μM*hr.

[00174] Depending on the disease to be treated and the subject's condition, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; can be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, CIV, intracistemal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (*e.g.*, transdermal or local) routes of administration. The indazolylaminopyrrolotriazine provided herein may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration.

[00175] The indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; can be delivered as a single dose such as, *e.g.*, a single bolus injection, or oral tablets or pills; or over time such as, *e.g.*, continuous infusion over time or divided bolus doses over time.

[00176] The indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous, *i.e.*, every day, or intermittently. The term "intermittent" or "intermittently" as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of the compound provided herein is administration for one to six days per week, administration in cycles (*e.g.*, daily administration for two to eight consecutive weeks, then a rest period with

no administration for up to one week), or administration on alternate days.

[00177] In certain embodiments, the frequency of administration of the indazolylaminopyrrolotriazine is in the range of about a daily dose to about a monthly dose. In certain embodiments, the administration of indazolylaminopyrrolotriazine is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks. In one embodiment, the indazolylaminopyrrolotriazine provided herein is administered once a day. In another embodiment, the indazolylaminopyrrolotriazine provided herein is administered twice a day. In yet another embodiment, the indazolylaminopyrrolotriazine provided herein is administered three times a day. In still another embodiment, the indazolylaminopyrrolotriazine provided herein is administered four times a day.

[00178] In certain embodiments, the indazolylaminopyrrolotriazine is administered every week. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 1, 8, and 15 in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 1, 8, and 15 in a 21 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 2, 9, and 16 in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 2, 9, and 16 in a 21 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 3, 10, and 17 in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 3, 10, and 17 in a 21 day cycle.

[00179] In certain embodiments, the indazolylaminopyrrolotriazine is administered twice a week. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 1, 2, 8, 9, 15, and 16 in a 21 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 1, 2, 8, 9, 15, and 16 in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 2, 3, 9, 10, 16, and 17 in a 21 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 2, 3, 9, 10, 16, and 17 in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 4, 5, 11, 12, 18, and 19 in a 21 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 4, 5, 11, 12, 18, and 19 in a 28 day cycle.

[00180] In certain embodiments, the indazolylaminopyrrolotriazine is administered for 7 days in a 21 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered for 7 days in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered daily for three weeks, followed by a one-week rest in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered daily, uninterrupted for 4 weeks in a 28 day cycle. In certain embodiments, the indazolylaminopyrrolotriazine is administered on days 1 and 2 in a 21 day cycle.

[00181] In certain embodiments, the taxane is administered every three weeks. In certain embodiments, the taxane is administered every two weeks. In certain embodiments, the taxane is administered every week. In certain embodiments, the taxane is administered on days 1, 8, and 15 in a 28 day cycle. In certain embodiments, the taxane is administered on days 1, 8, and 15 in a 21 day cycle. In certain embodiments, the taxane is administered on days 3, 10, and 17 in a 28 day cycle. In certain embodiments, the taxane is administered on days 3, 10, and 17 in a 21 day cycle. In certain embodiments, the taxane is administered for 7 days in a 21 day cycle.

[00182] In certain embodiments, paclitaxel is administered every three weeks. In certain embodiments, paclitaxel is administered every two weeks. In certain embodiments, paclitaxel is administered every week. In certain embodiments, paclitaxel is administered on days 1, 8, and 15 in a 28 day cycle. In certain embodiments, paclitaxel is administered on days 1, 8, and 15 in a 21 day cycle. In certain embodiments, paclitaxel is administered on days 3, 10, and 17 in a 28 day cycle. In certain embodiments, paclitaxel is administered on days 3, 10, and 17 in a 21 day cycle. In certain embodiments, paclitaxel is administered for 7 days in a 21 day cycle.

[00183] In certain embodiments, the taxane is administered intravenously over 1 hour. In certain embodiments, the taxane is administered intravenously over 30 minutes. In certain embodiments, the taxane is administered intravenously over 3 hours. In certain embodiments, the taxane is administered intravenously over 24 hours. In certain embodiments, paclitaxel is administered intravenously over 3 hours. In certain embodiments, paclitaxel is administered intravenously over 24 hours. In certain embodiments, docetaxel is administered intravenously over 1 hour. In certain embodiments, carboplatin is administered intravenously over 30 minutes.

[00184] In one embodiment, the intravenous administration of the compound of formula I occurs before the intravenous administration of paclitaxel. In one embodiment, the intravenous administration of the compound of formula I occurs two days before the intravenous administration of paclitaxel. In one embodiment, the intravenous administration of the compound of formula I occurs a day before the intravenous administration of paclitaxel. In one embodiment, the intravenous administration of the compound of formula I occurs on the same day as the intravenous administration of paclitaxel.

[00185] In yet another embodiment, the intravenous administration of the compound of formula I occurs after the intravenous administration of paclitaxel. In yet another embodiment, the intravenous administration of the compound of formula I occurs one day after the intravenous administration of paclitaxel. In yet another embodiment, the intravenous administration of the compound of formula I occurs two days after the intravenous administration of paclitaxel.

[00186] In certain embodiments, the taxane provided herein is administered to the subject in a single dose or divided doses for a total daily dose ranging from about 10 to about 1,000 mg/m^2, from about 20 to about 500 mg/m^2, from about 50 to 250 mg/m^2, from about 110 to about 200 mg/m^2, from about 60 to about 175 mg/m^2, from about 60 to about 100 mg/m^2, or from about 80 to about 90 mg/m^2. In certain embodiments, the taxane provided herein is administered to the subject in a single dose or divided doses for a total daily dose in the amount of about 60, about 75, about 80, about 90, about 100, about 135, about 150, about 175, about 250 mg/m^2, or about 260 mg/m^2. . In certain embodiments, the taxane provided herein is administered to the subject in a single dose or divided doses for a total daily dose in the amount of about 60, about 75, about 80, about 90, about 100, about 135, about 150, about 170, about 175, about 200, about 210, about 225, about 250, 255, about 260, about 275, about 280 or about 300 mg/m^2.

[00187] In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 250 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 250 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 175 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 175 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is

administered intravenously to the subject in the amount of 150 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 150 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 135 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 135 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 100 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 100 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 to 90 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 to 90 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 90 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 90 mg/m^2 over 24 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 mg/m^2 over 24 hours.

[00188] In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 175 mg/m^2 over 3 hours every three weeks. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 100 mg/m^2 over 3 hours every two weeks. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 135 mg/m^2 over 3 hours. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 to 90 mg/m^2 every week. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 mg/m^2 every week. In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 80 mg/m^2 on days 1, 8, and 15 every 28 days.

[00189] In certain embodiments, paclitaxel is administered intravenously to the subject in the amount of 30 mg/m^2 or 40 mg/m^2 on five consecutive days.

[00190] In certain embodiments, albumin-bound paclitaxel is administered intravenously to the subject in the amount of 100 mg/m^2 every 28 days. In certain embodiments, albumin-bound paclitaxel is administered intravenously to the subject in the amount of 150 mg/m^2 on days 1, 8, and 15 every 28 days. In certain embodiments, albumin-

bound paclitaxel is administered intravenously to the subject in the amount of 260 mg/m^2 every 21 days. In certain embodiments, albumin-bound paclitaxel is administered intravenously to the subject in the amount of 110-200 mg/m^2.

[00191] In certain embodiments, paclitaxel is administered intravenously over 1 hour. In certain embodiments, paclitaxel is administered intravenously over 1 - 2 hours. In certain embodiments, paclitaxel is administered intravenously over 2 hours. In certain embodiments, paclitaxel is administered intravenously over 6 hours. In certain embodiments, paclitaxel is administered intravenously over 24 hours.

[00192] In certain embodiments, docetaxel is administered intravenously to the subject over 1 hour. In certain embodiments, docetaxel is administered intravenously to the subject every three weeks. In certain embodiments, docetaxel is administered intravenously to the subject over 1 hour every three weeks. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 60 to 100 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 60 to 125 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 60 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 70 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 75 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 90 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 100 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 115 mg/m^2. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 125 mg/m^2.

[00193] In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 60, 70 or 75 mg/m^2 once every three weeks. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 60, 70 or 75 mg/m^2 once every two weeks. In certain embodiments, docetaxel is administered intravenously to the subject in the amount of 60, 70 or 75 mg/m^2 once every week. In certain embodiments, docetaxel is administered on day 2 in a 21 day cycle.

[00194] In certain embodiments, the docetaxel is administered intravenously to the subject in the amount of 50 mg/m^2 on days 1 and 8 every 21 days. In certain embodiments,

the docetaxel is administered intravenously to the subject in the amount of 50 mg/m^2 on days 1 and 8 every 30 days. In certain embodiments, the docetaxel is administered intravenously to the subject in the amount of 50 mg/m^2 on days 1 and 8 every month.

[00195] In certain embodiments, the docetaxel is administered intravenously to the subject in the amount of 14 mg/m^2 for 5 consecutive days

[00196] In certain embodiments, the indazolylaminopyrrolotriazine is administered intravenously to the subject on days 1 and 2 every 21 days. In certain embodiments, the docetaxel is administered intravenously to the subject once on day 2 every 21 days. In certain embodiments, the indazolylaminopyrrolotriazine is administered intravenously to the subject in the amount of about 20, about 30, about 40, about 80, about 134, about 200, or about 280 mg/m^2/day on days 1 and 2 every 21 days. In certain embodiments, the docetaxel is administered intravenously to the subject in the amount of about 60 or about 75 mg/m^2/day on day 2 every 21 days.

[00197] In certain embodiments, the indazolylaminopyrrolotriazine is administered intravenously to the subject on days 1 and 2, and the docetaxel is administered intravenously to the subject once on day 2, both administered every 21 days. In certain embodiments, the indazolylaminopyrrolotriazine is administered intravenously to the subject in the amount of about 20, about 30, about 40, about 80, about 134, about 200, or about 280 mg/m^2/day on days 1 and 2, and the docetaxel is administered intravenously to the subject in the amount of about 60 or about 75 mg/m^2/day on day 2, both administered every 21 days.

[00198] In certain embodiments, docetaxel is administered intravenously over 1 hour. In certain embodiments, docetaxel is administered intravenously over 1 - 2 hours. In certain embodiments, docetaxel is administered intravenously over 2 hour. In certain embodiments, docetaxel is administered intravenously over 6 hours. In certain embodiments, docetaxel is administered intravenously over 24 hours. In certain embodiments, the indazolylaminopyrrolotriazine is administered intravenously over 30 min. In certain embodiments, docetaxel is administered immediately after the indazolylaminopyrrolotriazine on day 2.

[00199] In one embodiment, the method comprises an oral administration of an indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. 600 mg/day for 21 days;

b. 600 mg/day for 28 days; and

c. 400 mg/day for 21 days;

and an intravenous administration of a taxane according to a regimen selected from:

i. 260 mg/m^2 over 24 hours;

ii. 250 mg/m^2 over 24 hours;

iii. 200 mg/m^2 over 24 hours;

iv. 185 mg/m^2 over 3 hours;

v. 185 mg/m^2 over 24 hours;

vi. 175 mg/m^2 over 3 hours;

vii. 175 mg/m^2 over 24 hours;

viii. 150 mg/m^2 over 3 hours;

ix. 150 mg/m^2 over 24 hours;

x. 135 mg/m^2 over 3 hours;

xi. 135 mg/m^2 over 24 hours;

xii. 100 mg/m^2 over 3 hours;

xiii. 80-90 mg/m^2;

xiv. 80 mg/m^2;

xv. 30 mg/m^2; and

xvi. 20 mg/m^2;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00200] In another embodiment, the method comprises an oral or intravenous administration of an indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. 600 mg/day for 21 days;

b. 600 mg/day for 28 days;

c. 400 mg/day for 21 days; and

d. 40 to 300 mg/m^2/day;

and an intravenous administration of a taxane according to a regimen selected from:

i. 260 mg/m^2 over 24 hours;

ii. 250 mg/m^2 over 24 hours;

iii. 200 mg/m^2 over 24 hours;
xvii. 185 mg/m^2 over 3 hours;
xviii. 185 mg/m^2 over 24 hours;
xix. 175 mg/m^2 over 3 hours;
xx. 175 mg/m^2 over 24 hours;
xxi. 150 mg/m^2 over 3 hours;
xxii. 150 mg/m^2 over 24 hours;
xxiii. 135 mg/m^2 over 3 hours;
xxiv. 135 mg/m^2 over 24 hours;
xxv. 100 mg/m^2 over 3 hours;
xxvi. 100 mg/m^2 over 1 hour;
xxvii. 80-90 mg/m^2;
xxviii. 80 mg/m^2;
xxix. 30 mg/m^2;
xxx. 20 mg/m^2;
xxxi. 60 to 125 mg/m^2/day; and
xxxii. 135 to 250 mg/m^2/day;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00201] In yet another embodiment, the method comprises an intravenous administration of an indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. 20 mg/m^2 on days 1 and 2;
b. 30 mg/m^2 on days 1 and 2;
c. 40 mg/m^2 on days 1 and 2;
d. 80 mg/m^2 on days 1 and 2;
e. 100 mg/m^2 on days 1 and 2;
f. 134 mg/m^2 on days 1 and 2;
g. 135 mg/m^2 on days 1 and 2;
h. 150 mg/m^2 on days 1 and 2;
i. 200 mg/m^2 on days 1 and 2;
j. 250 mg/m^2 on days 1 and 2;

k. 275 mg/m^2 on days 1 and 2;

l. 280 mg/m^2 on days 1 and 2;

m. 300 mg/m^2 on days 1 and 2; and

n. 40 to 300 mg/m^2/day;

and an intravenous administration of a taxane according to a regimen selected from:

i. 260 mg/m^2 over 24 hours;

ii. 250 mg/m^2 over 24 hours;

iii. 200 mg/m^2 over 24 hours;

iv. 185 mg/m^2 over 3 hours;

v. 185 mg/m^2 over 24 hours;

vi. 175 mg/m^2 over 3 hours;

vii. 175 mg/m^2 over 24 hours;

viii. 150 mg/m^2 over 3 hours;

ix. 150 mg/m^2 over 24 hours;

x. 135 mg/m^2 over 3 hours;

xi. 135 mg/m^2 over 24 hours;

xii. 100 mg/m^2 over 3 hours;

xiii. 100 mg/m^2 over 1 hour;

xiv. 80-90 mg/m^2;

xv. 80 mg/m^2;

xvi. 75 mg/m^2;

xvii. 70 mg/m^2;

xviii. 65 mg/m^2;

xix. 60 mg/m^2;

xx. 50 mg/m^2;

xxi. 30 mg/m^2;

xxii. 20 mg/m^2;

xxiii. 60 to 125 mg/m^2/day; and

xxiv. 135 to 250 mg/m^2/day;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00202] In yet another embodiment, the method comprises an administration of an

indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. a dose sufficient to achieve a C_{max} of about 5 to about 40 μM;

b. a dose sufficient to achieve a C_{max} of about 10 to about 40 μM;

c. a dose sufficient to achieve a C_{max} of about 2 to about 20 μg/mL;

d. a dose sufficient to achieve a C_{max} of about 3.5 to about 6 μM;

e. a dose sufficient to achieve a C_{max} of about 0.4 to about 4.5 μM;

f. a dose sufficient to achieve a C_{max} of about 1.5 to about 3.2 μg/mL;

and

g. a dose sufficient to achieve a C_{max} of about 0.2 to about 2.2 μg/mL;

and an intravenous administration of a taxane according to a regimen selected from:

i. 260 mg/m^2 over 24 hours;

ii. 250 mg/m^2 over 24 hours;

iii. 200 mg/m^2 over 24 hours;

iv. 185 mg/m^2 over 3 hours;

v. 185 mg/m^2 over 24 hours;

vi. 175 mg/m^2 over 3 hours;

vii. 175 mg/m^2 over 24 hours;

viii. 150 mg/m^2 over 3 hours;

ix. 150 mg/m^2 over 24 hours;

x. 135 mg/m^2 over 3 hours;

xi. 135 mg/m^2 over 24 hours;

xii. 100 mg/m^2 over 3 hours;

xiii. 80-90 mg/m^2;

xiv. 80 mg/m^2;

xv. 30 mg/m^2;

xvi. 20 mg/m^2; and

xvii. 60 to 100 mg/m^2/day;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00203] In yet another embodiment, the method comprises an intravenous administration of an indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. a dose sufficient to achieve an AUC of about 60 to about 500 μg*hr/mL;
b. a dose sufficient to achieve an AUC of about 125 to about 500 μg*hr/mL;
c. a dose sufficient to achieve an AUC of about 125 to about 300 μg*hr/mL;
d. a dose sufficient to achieve an AUC of about 125 to about 200 μg*hr/mL;
e. a dose sufficient to achieve an AUC of about 125 to about 1,000 μM*hr;
f. a dose sufficient to achieve an AUC of about 250 to about 500 μM*hr;
g. a dose sufficient to achieve an AUC of about 4 to about 35 μg*hr/mL; and
h.. a dose sufficient to achieve an AUC of about 40 to about 55 μg*hr/mL;

and an intravenous administration of a taxane according to a regimen selected from:

i. 260 mg/m^2 over 24 hours;
ii. 250 mg/m^2 over 24 hours;
iii. 200 mg/m^2 over 24 hours;
iv. 185 mg/m^2 over 3 hours;
v. 185 mg/m^2 over 24 hours;
vi. 175 mg/m^2 over 3 hours;
vii. 175 mg/m^2 over 24 hours;
viii. 150 mg/m^2 over 3 hours;
ix. 150 mg/m^2 over 24 hours;
x. 135 mg/m^2 over 3 hours;
xi. 135 mg/m^2 over 24 hours;
xii. 100 mg/m^2 over 3 hours;
xiii. 80-90 mg/m^2;
xiv. 80 mg/m^2;
xv. 30 mg/m^2; xvi.20 mg/m^2; and
xvii. 60 to 100 mg/m^2/day;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00204] In yet another embodiment, the method comprises an administration of an indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. a dose sufficient to achieve a C_{max} of about 5 to about 40 μM;

b. a dose sufficient to achieve a C_{max} of about 10 to about 40 μM;

c. a dose sufficient to achieve a C_{max} of about 2 to about 20 μg/mL;

d. a dose sufficient to achieve a C_{max} of about 3.5 to about 6 μM;

e. a dose sufficient to achieve a C_{max} of about 0.4 to about 4.5 μM;

f. a dose sufficient to achieve a C_{max} of about 1.5 to about 3.2 μg/mL; and

g. a dose sufficient to achieve a C_{max} of about 0.2 to about 2.2 μg/mL;

and an intravenous administration of a taxane according to a regimen selected from:

i. 20–100 mg/m^2 ;

ii. 60 mg/m^2;

iii. 75 mg/m^2;

iv. 100 mg/m^2;

v. 30 mg/m^2;

vi. 20 mg/m^2; and

vii. 60 to 100 mg/m^2/day;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00205] In yet another embodiment, the method comprises an intravenous administration of an indazolylaminopyrrolotriazine provided herein according to a regimen selected from:

a. a dose sufficient to achieve an AUC of about 60 to about 500 μg*hr/mL;

b. a dose sufficient to achieve an AUC of about 125 to about 500 μg*hr/mL;

c. a dose sufficient to achieve an AUC of about 125 to about 300 μg*hr/mL;

d. a dose sufficient to achieve an AUC of about 125 to about 200 μg*hr/mL;

e. a dose sufficient to achieve an AUC of about 125 to about 1,000

μM*hr;

f. a dose sufficient to achieve an AUC of about 250 to about 500 μM*hr;

g.. a dose sufficient to achieve an AUC of about 4 to about 35 μg*hr/mL; and

h.. a dose sufficient to achieve an AUC of about 40 to about 55 μg*hr/mL;

and an intravenous administration of a taxane according to a regimen selected from:

i. 60–100 mg/m^2 ;

ii. 60 mg/m^2;

iii. 75 mg/m^2; and

iv. 100 mg/m^2;

wherein the indazolylaminopyrrolotriazine and taxane are administered simultaneously, concurrently, separately, or sequentially.

[00206] In yet another embodiment, the method provided herein further comprises an intravenous administration of carboplatin according to a regimen selected from:

1. a dose sufficient to achieve an AUC of about 2 to about 8 mg*min/mL;
2. a dose sufficient to achieve an AUC of about 3 to about 8 mg*min/mL;
3. a dose sufficient to achieve an AUC of about 3 to about 7.5 mg*min/mL;
4. a dose sufficient to achieve an AUC of about 2 mg*min/mL;
5. a dose sufficient to achieve an AUC of about 3 mg*min/mL;
6. a dose sufficient to achieve an AUC of about 5 mg*min/mL;
7. a dose sufficient to achieve an AUC of about 6 mg*min/mL; and
8. a dose sufficient to achieve an AUC of about 7.5 mg*min/mL;

wherein the indazolylaminopyrrolotriazine , taxane, and carboplatin are administered simultaneously, concurrently, separately, or sequentially.

[00207] In still another embodiment, the method provided herein further comprises an intravenous administration of carboplatin according to a regimen selected from:

1. a dose calculated to achieve an AUC of about 2 to about 8 mg*min/mL;
2. a dose calculated to achieve an AUC of about 3 to about 8 mg*min/mL;
3. a dose calculated to achieve an AUC of about 3 to about 7.5

mg*min/mL;

4. a dose calculated to achieve an AUC of about 2 mg*min/mL;
5. a dose calculated to achieve an AUC of about 3 mg*min/mL;
6. a dose calculated to achieve an AUC of about 5 mg*min/mL;
7. a dose calculated to achieve an AUC of about 6 mg*min/mL; and
8. a dose calculated to achieve an AUC of about 7.5 mg*min/mL;

wherein the indazolylaminopyrrolotriazine , taxane, and carboplatin are administered simultaneously, concurrently, separately, or sequentially.

[00208] In certain embodiments, the subject is a mammal. In certain embodiments, the mammal is a human.

[00209] In one embodiment, the proliferative disease is a tumor. In another embodiment, the proliferative disease is a solid tumor. In certain embodiments, the solid tumor is an advanced solid tumor. In certain embodiments, the solid tumor is a metastatic solid tumor. In yet another embodiment, the proliferative disease is cancer. In yet another embodiment, the proliferative disease is advanced cancer. In certain embodiments, the solid tumor is metastatic cancer.

[00210] In certain embodiments, the tumor overexpresses HER1 protein. In certain embodiments, the tumor overexpresses HER2 protein.

[00211] In certain embodiments, the cancer treatable with the methods provided herein includes, but is not limited to, (1) leukemias, including, but not limited to, acute leukemia, acute myeloid leukemia (AML), acute lymphocytic leukemia, acute myelocytic leukemias such as myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia leukemias and myelodysplastic syndrome or a symptom thereof (such as anemia, thrombocytopenia, neutropenia, bicytopenia or pancytopenia), refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), preleukemia, and chronic myelomonocytic leukemia (CMML), (2) chronic leukemias, including, but not limited to, chronic myelocytic (granulocytic) leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia (CML), and hairy cell leukemia; (3) polycythemia vera; (4) lymphomas, including, but not limited to, Hodgkin's disease and non-Hodgkin's disease; (5) multiple myelomas, including, but not limited to, smoldering multiple myeloma, nonsecretory myeloma, osteosclerotic myeloma, plasma cell leukemia, solitary

plasmacytoma, and extramedullary plasmacytoma; (6) Waldenström's macroglobulinemia; (7) monoclonal gammopathy of undetermined significance; (8) benign monoclonal gammopathy; (9) heavy chain disease; (10) bone and connective tissue sarcomas, including, but not limited to, bone sarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, malignant giant cell tumor, fibrosarcoma of bone, chordoma, periosteal sarcoma, soft-tissue sarcomas, angiosarcoma (hemangiosarcoma), fibrosarcoma, Kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, metastatic cancers, neurilemmoma, rhabdomyosarcoma, and synovial sarcoma; (11) brain tumors, including, but not limited to, glioma, astrocytoma, brain stem glioma, ependymoma, oligodendroglioma, nonglial tumor, acoustic neurinoma, craniopharyngioma, medulloblastoma, meningioma, pineocytoma, pineoblastoma, and primary brain lymphoma; (12) breast cancer, including, but not limited to, adenocarcinoma, lobular (small cell) carcinoma, intraductal carcinoma, medullary breast cancer, mucinous breast cancer, tubular breast cancer, papillary breast cancer, primary cancers, Paget's disease, and inflammatory breast cancer; (13) adrenal cancer, including, but not limited to, pheochromocytom and adrenocortical carcinoma; (14) thyroid cancer, including, but not limited to, papillary or follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer; (15) pancreatic cancer, including, but not limited to, insulinoma, gastrinoma, glucagonoma, vipoma, somatostatin-secreting tumor, and carcinoid or islet cell tumor; (16) pituitary cancer, including, but limited to, Cushing's disease, prolactin-secreting tumor, acromegaly, and diabetes insipius; (17) eye cancer, including, but not limited, to ocular melanoma such as iris melanoma, choroidal melanoma, and cilliary body melanoma, and retinoblastoma; (18) vaginal cancer, including, but not limited to, squamous cell carcinoma, adenocarcinoma, and melanoma; (19) vulvar cancer, including, but not limited to, squamous cell carcinoma, melanoma, adenocarcinoma, basal cell carcinoma, sarcoma, and Paget's disease; (20) cervical cancers, including, but not limited to, squamous cell carcinoma, and adenocarcinoma; (21) uterine cancer, including, but not limited to, endometrial carcinoma and uterine sarcoma; (22) ovarian cancer, including, but not limited to, ovarian epithelial carcinoma, borderline tumor, germ cell tumor, and stromal tumor; (23) esophageal cancer, including, but not limited to, squamous cancer, adenocarcinoma, adenoid cystic carcinoma, mucoepidermoid carcinoma, adenosquamous carcinoma, sarcoma, melanoma, plasmacytoma, verrucous carcinoma, and oat cell (small cell) carcinoma; (24) stomach cancer, including, but not limited to, adenocarcinoma, fungating (polypoid), ulcerating, superficial spreading, diffusely spreading, malignant lymphoma, liposarcoma,

fibrosarcoma, and carcinosarcoma; (25) colon cancer; (26) rectal cancer; (27) liver cancer, including, but not limited to, hepatocellular carcinoma and hepatoblastoma; (28) gallbladder cancer , including, but not limited to, adenocarcinoma; (29) cholangiocarcinomas, including, but not limited to, pappillary, nodular, and diffuse; (30) lung cancer, including, but not limited to, non-small cell lung cancer, squamous cell carcinoma (epidermoid carcinoma), adenocarcinoma, large-cell carcinoma, and small-cell lung cancer; (31) testicular cancer, including, but not limited to, germinal tumor, seminoma, anaplastic, classic (typical), spermatocytic, nonseminoma, embryonal carcinoma, teratoma carcinoma, and choriocarcinoma (yolk-sac tumor); (32) prostate cancer, including, but not limited to, adenocarcinoma, leiomyosarcoma, and rhabdomyosarcoma; (33) penal cancer; (34) oral cancer, including, but not limited to, squamous cell carcinoma; (35) basal cancer; (36) salivary gland cancer, including, but not limited to, adenocarcinoma, mucoepidermoid carcinoma, and adenoidcystic carcinoma; (37) pharynx cancer, including, but not limited to, squamous cell cancer and verrucous; (38) skin cancer, including, but not limited to, basal cell carcinoma, squamous cell carcinoma and melanoma, superficial spreading melanoma, nodular melanoma, lentigo malignant melanoma, and acral lentiginous melanoma; (39) kidney cancer, including, but not limited to, renal cell cancer, adenocarcinoma, hypernephroma, fibrosarcoma, and transitional cell cancer (renal pelvis and/or uterer); (40) Wilms' tumor; (41) bladder cancer, including, but not limited to, transitional cell carcinoma, squamous cell cancer, adenocarcinoma, and carcinosarcoma; and other cancer, including, not limited to, myxosarcoma, osteogenic sarcoma, endotheliosarcoma, lymphangio-endotheliosarcoma, mesothelioma, synovioma, hemangioblastoma, epithelial carcinoma, cystadenocarcinoma, bronchogenic carcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, and papillary adenocarcinomas (*See* Fishman *et al.*, 1985, *Medicine*, 2d Ed., J.B. Lippincott Co., Philadelphia and Murphy *et al.*, 1997, *Informed Decisions: The Complete Book of Cancer Diagnosis, Treatment, and Recovery*, Viking Penguin, Penguin Books U.S.A., Inc., United States of America).

[00212] In certain embodiments, the cancer that is treatable with the methods provided herein includes, but is not limited to, bladder cancer, breast cancer, cervical cancer, colon cancer (*e.g.*, colorectal cancer), endometrial cancer, esophageal cancer, gastric cancer, glioma (*e.g.*, glioblastoma), head and neck cancer, liver cancer, lung cancer (*e.g.*, small cell and non-small cell lung cancers), melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic

cancer, prostate cancer, renal cancer, sarcoma (*e.g.*, osteosarcoma), skin cancer (*e.g.*, squamous cell carcinoma), stomach cancer, testicular cancer, thyroid cancer, and uterine cancer.

[00213] In certain embodiments, the cancer that is treatable with the methods provided herein includes, but is not limited to, bladder cancer, breast cancer, cervical cancer, colon cancer (*e.g.*, colorectal cancer), endometrial cancer, gastric cancer, glioma (*e.g.*, glioblastoma), head and neck cancer, liver cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, and prostate cancer.

[00214] In certain embodiments, the cancer is non-small cell lung cancer. In certain embodiments, the cancer is non-small cell lung cancer which overexpresses HER1 protein. In certain embodiments, the cancer is non-small cell lung cancer which overexpresses HER2 protein. In certain embodiments, the cancer is non-small cell lung cancer which overexpresses HER1 and HER2 proteins. In certain embodiments, the cancer is metastatic non-small cell lung cancer. In certain embodiments, the cancer is metastatic non-small cell lung cancer which overexpresses HER1 protein. In certain embodiments, the cancer is metastatic non-small cell lung cancer which overexpresses HER2 protein. In certain embodiments, the cancer is metastatic non-small cell lung cancer which overexpresses HER1 and HER2 proteins.

[00215] In certain embodiments, the cancer is breast cancer. In certain embodiments, the cancer is breast cancer which overexpresses HER1 protein. In certain embodiments, the cancer is breast cancer which overexpresses HER2 protein. In certain embodiments, the cancer is breast cancer which overexpresses HER1 and HER2 proteins. In certain embodiments, the cancer is metastatic breast cancer. In certain embodiments, the cancer is metastatic breast cancer which overexpresses HER1 protein. In certain embodiments, the cancer is metastatic breast cancer which overexpresses HER2 protein. In certain embodiments, the cancer is metastatic breast cancer which overexpresses HER1 and HER2 proteins.

[00216] In certain embodiments, the cancer is head and neck cancer. In certain embodiments, the cancer is lung cancer. In certain embodiments, the cancer is lung adenocarcinoma. In certain embodiments, the cancer is esophogeal or upper GI cancer.

[00217] In certain embodiments, the subject to be treated with one of the methods provided herein has not been treated with anticancer therapy. In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with anticancer therapy.

[00218] The methods provided herein encompass treating a subject regardless of patient's age, although some diseases or disorders are more common in certain age groups. Further provided is a method for treating a subject who has undergone surgery in an attempt to treat the disease or condition at issue, as well as the one who have not. Because the subjects with cancer have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a particular subject may vary, depending on his/her prognosis.

[00219] The combination regimen can be administered repetitively if necessary, for example, until the patient experiences stable disease or regression, or until the patient experiences disease progression or unacceptable toxicity. For example, stable disease for solid tumors generally means that the perpendicular diameter of measurable lesions has not increased by 25% or more from the last measurement. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, *Journal of the National Cancer Institute* **2000**, *92*, 205-216. Stable disease or lack thereof is determined by methods known in the art such as evaluation of patient symptoms, physical examination, visualization of the tumor that has been imaged using X-ray, CAT, PET, or MRI scan and other commonly accepted evaluation modalities.

[00220] In certain embodiments, the combination regimen is administered to the subject over an extended period of time, ranging from 1 day to about 12 months, from 2 days to about 6 months, from 3 days to about 5 months, from 3 days to about 4 months, from 3 days to about 12 weeks, from 3 days to about 10 weeks, from 3 days to about 8 weeks, from 3 days to about 6 weeks, from 3 days to about 5 weeks, from 3 days to about 4 weeks, from 3 days to about 3 weeks, from 3 days to about 2 weeks, or from 3 days to about 10 days.

[00221] In certain embodiments, the combination regimen is administered in a 21 day cycle. In certain embodiments, the combination regimen is administered in a 28 day cycle. In certain embodiments, the combination regimen is administered in a monthly cycle.

[00222] In certain embodiments, the combination regimen is cyclically administered to

the subject. Cycling therapy involves the administration of the combination regimen provided herein for a period of time, followed by a rest for a period of time, and repeating this sequential administration. Cycling therapy can reduce the development of resistance to one or more of the therapies, avoid or reduce the side effects of one of the therapies, and/or improves the efficacy of the treatment.

[00223] Consequently, in one embodiment, the combination regimen provided herein is administered daily for one week, two weeks, three weeks, four weeks, five weeks, six weeks, eight weeks, ten weeks, fifteen weeks, or twenty weeks, followed by a rest period of about 1 day to about ten weeks. For example, the methods contemplate using cycling of one week, two weeks, three weeks, four weeks, five weeks, six weeks, eight weeks, ten weeks, fifteen weeks, or twenty weeks. In another embodiment, the combination regimen provided herein is administered daily for one week, two weeks, three weeks, four weeks, five weeks, or six weeks with a rest period of 1, 3, 5, 7, 9, 12, 14, 16, 18, 20, 22, 24, 26, 28, 29 or 30 days. In certain embodiments, the rest period is 14 days. In certain embodiments, the rest period is 28 days. In one embodiment, the rest period is a period that is sufficient for bone marrow recovery. The frequency, number and length of dosing cycles can be increased or decreased.

[00224] As used herein, the term "combination regimen" includes the use of more than one therapies (*e.g.*, one or more prophylactic and/or therapeutic agents). However, the use of the term "combination regimen" does not restrict the order in which therapies (*e.g.*, prophylactic and/or therapeutic agents) are administered to the subject. A first therapy (*e.g.*, a prophylactic or therapeutic agent such as an indazolylaminopyrrolotriazine provided herein) can be administered prior to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (*e.g.*, 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (*e.g.*, a prophylactic or therapeutic agent such as the taxane described herein) to the subject. Triple therapy is also contemplated herein (*e.g.*, a platinum agent as a third therapy).

[00225] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a

mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered to the subject prior to the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject about 2 days, about 1 day, about 12 hrs, about 6 hrs, about 4 hrs, about 2 hrs, about 60 min, about 30 min, about 20 min, about 10 min before the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject about 2 days before the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject about 1 day before the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject in the same day as the administration of the taxane.

[00226] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered to the subject after the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject about 2 days, about 1 day, about 12 hrs, about 6 hrs, about 4 hrs, about 2 hrs, about 60 min, about 30 min, about 20 min, about 10 min after the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject about 2 days after the administration of the taxane. In certain embodiments, the indazolylaminopyrrolotriazine provided herein is administered to the subject about 1 day after the administration of the taxane.

[00227] In certain embodiments, the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; is administered to the subject concurrently with the administration of the taxane.

[00228] In each embodiment provided herein, the method may further comprise a diagnostic step for determining the expression level of HER1 protein on the cells of the tumor. In one embodiment, the diagnostic step is carried out prior to the administration of the combination regimen provided herein. If the subject has a tumor with overexpressed HER1,

the combination regimen provided herein is then administered. In another embodiment, the diagnostic step is carried out during the course of the treatment.

[00229] In each embodiment provided herein, the method may further comprise a diagnostic step for determining the expression level of HER2 protein on the cells of the tumor. In one embodiment, the diagnostic step is carried out prior to the administration of the compounds. In another embodiment, the diagnostic step is carried out during the course of the treatment.

[00230] The methods provided herein may further comprise administering other therapeutic agents useful in the treatment and/or prevention of a disease described herein.

[00231] In certain embodiments, each method provided herein may independently further comprise the step of administering an additional therapeutic agent. The additional therapeutic agents that may be used in combination with the combination regimen herein include, but are not limited to, surgery, endocrine therapy, biologic response modifiers (*e.g.*, interferons, interleukins, and tumor necrosis factor (TNF)), hyperthermia and cryotherapy, agents to attenuate any adverse effects (*e.g.*, antiemetics), and other approved chemotherapeutic drugs, including, but not limited to, alkylating drugs (mechlorethamine, chlorambucil, cyclophosphamide, melphalan, and ifosfamide), antimetabolites (cytarabine (also known as cytosine arabinoside or Ara-C), HDAC (high dose cytarabine), and methotrexate), purine antagonists and pyrimidine antagonists (6-mercaptopurine, 5-fluorouracil, cytarbine, and gemcitabine), spindle poisons (vinblastine, vincristine, and vinorelbine), podophyllotoxins (etoposide, irinotecan, and topotecan), antibiotics (daunorubicin, doxorubicin, bleomycin, and mitomycin), nitrosoureas (carmustine and lomustine), enzymes (asparaginase), and hormones (tamoxifen, leuprolide, flutamide, and megestrol), imatinib, adriamycin, dexamethasone, and cyclophosphamide. For a more comprehensive discussion of updated cancer therapies; *See*, http://www.nci.nih.gov/, a list of the FDA approved oncology drugs at http://www.fda.gov/cder/cancer/druglistframe.htm, and The Merck Manual, Seventeenth Ed. 1999, the entire contents of which are hereby incorporated by reference.

[00232] In certain embodiments, the additional therapeutic agents that may be used in combination with the combination regimen herein include, but are not limited to, vinorelbine, vinblastine, erlotinib, gemcitabine, mitomycin, bevacizumab, etoposide, ifosfamide,

cetuximab, irinotecan, and pemetrexed.

[00233] In another embodiment, provided herein is a method of inhibiting the growth of a cell, comprising contacting the cell with an effective amount of a taxane and an indazolylaminopyrrolotriazine described herein, *e.g.,* an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

[00234] In certain embodiments, the cell is a mammalian cell. In certain embodiments, the mammal is a human cell. In certain embodiments, the cell is a tumor cell. In certain embodiments, the cell is mammalian tumor cell. In certain embodiments, the cell is a human tumor cell. In certain embodiments, the cell is a cancerous cell. In certain embodiments, the cell is mammalian cancerous cell. In certain embodiments, the cell is a human cancerous cell.

[00235] In certain embodiments, the tumor cell overexpresses HER1 protein. In certain embodiments, the tumor cell overexpresses HER2 protein.

[00236] In certain embodiments, the cancerous cell that can be treated with the methods provided herein includes, but is not limited to, cells of bladder cancer, breast cancer, cervical cancer, colon cancer (*e.g.*, colorectal cancer), endometrial cancer, esophageal cancer, gastric cancer, glioma (*e.g.*, glioblastoma), head and neck cancer, liver cancer, lung cancer (*e.g.*, small cell and non-small cell lung cancers), melanoma, myeloma, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, sarcoma (*e.g.*, osteosarcoma), skin cancer (*e.g.*, squamous cell carcinoma), stomach cancer, testicular cancer, thyroid cancer, and uterine cancer.

[00237] In certain embodiments, the cell is a cell of bladder cancer, breast cancer, cervical cancer, colon cancer (*e.g.*, colorectal cancer), endometrial cancer, gastric cancer, glioma (*e.g.*, glioblastoma), head and neck cancer, liver cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, or prostate cancer.

[00238] In certain embodiments, the cell is treated by contacting the cell with the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of

diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; prior to contacting the cell with the taxane. In certain embodiments, the cell is treated with the indazolylaminopyrrolotriazine provided herein, about 2 days, about 1 day, about 12 hrs, about 6 hrs, about 4 hrs, about 2 hrs, about 60 min, about 30 min, or about 10 min before contacting the cell with the taxane.

[00239] In certain embodiments, the cell is treated by contacting the cell with the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; concurrently by contacting the cell with the taxane.

[00240] In certain embodiments, the cell is treated by contacting the cell with the indazolylaminopyrrolotriazine provided herein, *e.g.*, an indazolylaminopyrrolotriazine of Formula I or II, including a single enantiomer, a mixture of enantiomers, or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; after contacting the cell with the taxane. In certain embodiments, the cell is treated with the indazolylaminopyrrolotriazine provided herein, about 2 days, about 1 day, about 12 hrs, about 6 hrs, about 4 hrs, about 2 hrs, about 60 min, about 30 min, or about 10 min after contacting the cell with the taxane.

[00241] The inhibition of cell growth can be gauged by, *e.g.*, counting the number of cells contacted with compounds of interest, comparing the cell proliferation with otherwise identical cells not contacted with the compounds, or determining the size of the tumor that encompasses the cells. The number of cells, as well as the size of the cells, can be readily assessed using any method known in the art (*e.g.*, trypan blue exclusion and cell counting, measuring incorporation of ^{3}H-thymidine into nascent DNA in a cell).

[00242] The combination regimes provided herein can also be provided as an article of manufacture using packaging materials well known to those of skill in the art. *See*, *e.g.*, U.S. Pat. Nos. 5,323,907; 5,052,558; and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[00243] Provided herein also are kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the kit provided herein includes containers and dosage forms of the compounds in the combination regimens provided herein.

[00244] In certain embodiments, the kit includes a container comprising dosage forms of the compounds in the combination regimens provided herein, in one or more containers.

[00245] Kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[00246] Kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

[00247] The disclosure will be further understood by the following non-limiting examples.

EXAMPLES

Example 1

MX-1 Human Breast Carcinoma Mouse Xenograft Study

[00248] The human breast carcinoma cell line MX-1 was from frozen stock that was passed serially in vivo for no more than 10 continual passages.

[00249] Nude mice (Taconic Labs) were inoculated with MX-1 cells as trocar fragments subcutaneously in the axillary region. The tumors were grown to about 100 mg size, which was measured by electronic caliper measurement through the skin), and the mice were then randomized among control and the various treatment groups, with eight mice per group in the efficacy arms. During the treatment period, the solid tumors were measured three times weekly. Body weights were also measured three times weekly.

[00250] AC480 (Ambit Biosciences, San Diego, CA) was formulated in aqueous 50% propylene glycol at a concentration of 30 mg/ml, and administered orally (PO) once daily (QD). Paclitaxel (Hauser Pharmaceuticals, Denver, CO) was formulated in aqueous 10% ethanol/10% CREMOPHOR® EL (Sigma, St. Louis, MO) at a concentration of 2 mg/ml, and administered once daily (QD) by intraperitoneal injection (IP). The animals were grouped and dosed as shown in Table 1.

TABLE 1.

Group	Compounds	Dosing Schedule
1	Untreated control	N/A
2	Vehicle treated control	The vehicle (0.2 mL/20 g) of AC480 formulation was administered PO/QD from Day 1 through 21.
3	Paclitaxel only	Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17.
4	AC480 only	AC480 (300 mg/kg) was administered PO/QD at Day 1, 2, 8, 9, 15, & 16.
5	AC480 only	AC480 (180 mg/kg) was administered PO/QD from Day 1 through 21
6	AC480 + Paclitaxel	AC480 (300 mg/kg) was administered PO/QD at Day 1, 2, 8, 9, 15, & 16. Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17.
7	AC480 + Paclitaxel	AC480 (180 mg/kg) was administered PO/QD at Day 1, 2, 8, 9, 15, & 16. Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17.

8	Paclitaxel + AC480	Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17. AC480 (300 mg/kg) was administered PO/QD at Day 4, 5, 11, 12, 18, & 19.
9	Paclitaxel + AC480	Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17. AC480 (180 mg/kg) was administered PO/QD at Day 4, 5, 11, 12, 18, & 19.
10	AC480 + Paclitaxel	AC480 (300 mg/kg) was administered PO/QD at Day 2, 3, 9, 10, 16, & 17. Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17.
11	AC480 + Paclitaxel	AC480 (180 mg/kg) was administered PO/QD at Day 2, 3, 9, 10, 16, & 17. Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17.
12	Gefitinib + Paclitaxel	Gefitinib (150 mg/kg) was administered PO/QD at Day 1, 2, 8, 9, 15, & 16. Paclitaxel (35 mg/kg) was administered IP/QD at Day 3, 10, & 17.

[00251] The results of this study are summarized in FIGS. 1 to 3. The combination of AC480 and paclitaxel appears to be well tolerated.

Example 2

MX-1 Human Breast Carcinoma Mouse Xenograft Study

[00252] A second mouse xenograft study was conducted to study alternative dosage combinations and schedules. The same protocol as described in Example 1 was followed for body weight and tumor size measurements. The same compound formulations were also used, but paclitaxel dose was adjusted down to 25 mg/kg and administered intravenously (IV) for this study.

TABLE 2.

Group	Compounds	Dosing Schedule
2	Vehicle treated control	The vehicle (0.2 mL/20 g) of AC480 formulation was administered PO/QD from Day 1 through 21.
3	Paclitaxel only	Paclitaxel (25 mg/kg) was administered IP/QD at Day 3, 10, & 17.
4	AC480 only	AC480 (300 mg/kg) was administered PO/QD at Day 1, 2, 8, 9, 15, & 16.
5	AC480 + Paclitaxel	AC480 (300 mg/kg) was administered PO/QD at Day 1, 2, 8, 9, 15, & 16. Paclitaxel (25 mg/kg) was administered IP/QD at Day 3, 10, & 17.
6	AC480 + Paclitaxel	AC480 (300 mg/kg) was administered PO/QD at Day 2, 3, 9, 10, 16, & 17. Paclitaxel (25 mg/kg) was administered IP/QD at Day 3, 10, & 17.
7	AC480 + Paclitaxel	AC480 (180 mg/kg) was administered PO/QD at Day 2, 3, 9, 10, 16, & 17. Paclitaxel (25 mg/kg) was administered IP/QD at Day 3, 10, & 17.
10	AC480 + Paclitaxel	AC480 (300 mg/kg) was administered PO/QD at Day 3, 10, & 17. Paclitaxel (25 mg/kg) was administered IP/QD at Day 3, 10, & 17.

[00253] The results of this study are shown in FIG. 4.

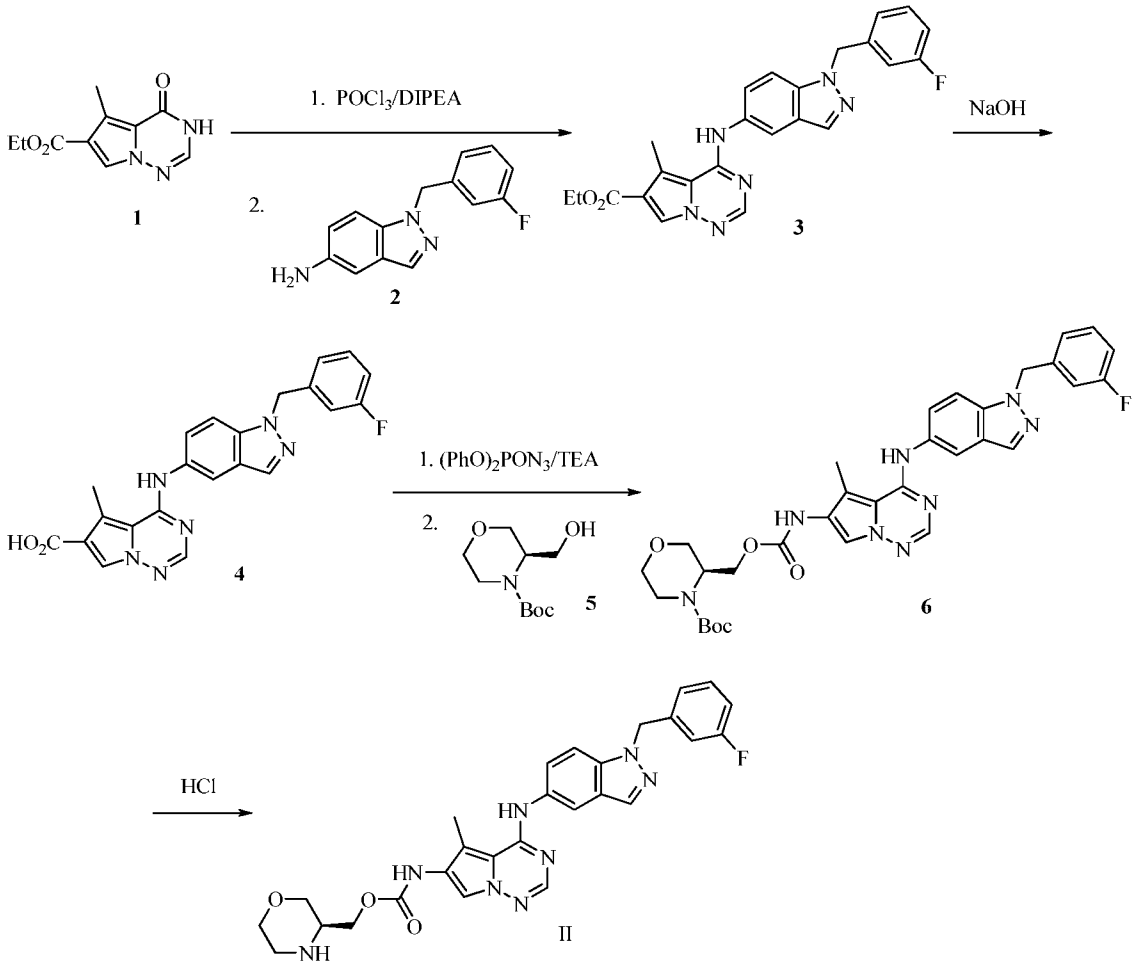
Example 3

Synthesis of [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester (AC480)

[00254] The synthesis of AC480 is shown in Scheme 1. Compound **1** was chlorinated, followed by coupling with compound **2** to form compound **3**. Saponification of compound **3** afforded acid **4**, which was first converted to an acyl azide and then underwent Curtius rearrangement in the present of compound **5** to form compound **6**. Removal of Boc (*N-tert-*

butoxycarbonyl) group with hydrochloride acid, formation of a hydrochloride salt, and subsequent neutralization gave free base compound **II**, which was then purified *via* crystallization.

Scheme 1



Example 4

Synthesis of [4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester, ethanesulfonate (AC480 esylate) in crystalline Form II-B

[00255] A mixture of free base compound **II** and ethanesulfonic acid in ethanol was heated at 78 ± 5 °C for at least one hour. The reaction mixture was then cooled to 20 ± 5 °C and AC480 esylate precipated. After filtration, the filter caske was washed with ethanol cooled to 0 ± 5 °C. The resulting solid was then dried to constant weight in a vacuum oven at

≤ 30 °C to yield AC480 esylate in crystalline Form II_B, which has a melting point of about 202 °C.

TABLE 3. Stability of AC480 Esylate at 5 °C

Parameter	Initial	1 Month	3 Month
Appearance	Conformed[a]	Conformed[a]	Conformed[a]
AC480 content (HPLC)	100%	102%	99%
Total impurities (HPLC)	0.3%	0.4%	0.33%
Nitrosamine (LC/MS/MS)	0 ppm	0 ppm	0 ppm
Moisture content (KF)	0.9%	0.9%	0.6%

a. AC480 esylate is white to pale-yellow or pale-pink powder, which may contain lumps.

TABLE 4. Stability of AC480 Esylate at 25 °C/60%RH

Parameter	Initial	1 Month	3 Month
Appearance	Conformed[a]	Conformed[a]	Conformed[a]
AC480 content (HPLC)	100%	101%	100%
Total impurities (HPLC)	0.3%	0.4%	0.33%
Nitrosamine (LC/MS/MS)	0 ppm	0 ppm	0 ppm
Moisture content (KF)	0.9%	0.8%	0.6%

a. AC480 esylate is white to pale-yellow or pale-pink powder, which may contain lumps.

[00256] The stability of AC480 esylate in crystalline Form II-B was determined under three different storage conditions: i) 5 °C; ii) 25 °C and 60% RH; and iii) 40 °C and 75% RH. Results are summarized in Tables 3 to 5.

Example 5

Preparation of a pharmaceutical formulation comprising AC480 esylate

[00257] A pharmaceutical formulation comprising AC480 esylate was prepared through an aseptic lyophilization process. The composition of the pharmaceutical formulation and the amount water used in the preparation are summarized in Table 6.

TABLE 5. Stability of AC480 Esylate at 40 °C/75%RH

Parameter	Initial	1 Month	3 Month
Appearance	Conformed[a]	Conformed[a]	Conformed[a]
AC480 content (HPLC)	100%	102%	100%
Total impurities (HPLC)	0.3%	0.4%	0.33%
Nitrosamine (LC/MS/MS)	0 ppm	0 ppm	0 ppm
Moisture content (KF)	0.9%	0.9%	0.6%

a. AC480 esylate is white to pale-yellow or pale-pink powder, which may contain lumps.

[00258] In preparation of the pharmaceutical formulation, 75% of the required amount of sterile water for injection was added to a clean depyrogenated glass vessel. The required amounts of powdered mannitol (2% by weight), hydroxypropyl-β-cyclodextrin (HPβCD) (15% by weight), and AC480 esylate were added to the vessel, and mixed until dissolved. The solution was brought to its final batch weight with sterile water for injection, that is, the remaining 25%. The solution was then sterile filtered and filled into 30 cc amber glass vials at 12 mL/vial. The vials were partially stoppered, and lyophilized. Once lyophilization was completed, the vials were backfilled with sterile filtered nitrogen, and stoppers were fully inserted. The vials were then crimp sealed using 20 mm White Flip-Off Crimp seals.

TABLE 6

Component	Amount (%)	Composition per 300 mg Unit Dose	Amount for 12 L (12,000 g) Batch
AC480 Esylate[a]	3.025%	363 mg	363 g
Hydroxypropyl-β-cyclodextrin	15%	1,800 mg	1,800 g
Mannitol	2%	240 mg	240 g
Water for injection USP[b]	79.975%	9,597 mg	9,597 g

a. AC480 Esylate (363 mg) contained 300 mg of AC480 free base.
b. Water was removed during lyophilization.

[00259] Before administration to a patient, each vial will be reconstituted with water to 25 mg/mL of AC480 free base

Example 6

Phase I Clinical Trial of AC480 Esylate in Combination with Docetaxel

[00260] AC480 esylate will be tested in a Phase I trial in human patients having a broad range of advanced solid malignancies. This Phase I study is an open-label, dose escalation study of 2-day pulsed IV administration of AC480 esylate given as monotherapy, then in combination with docetaxel once every 3 weeks in patients with advanced solid tumors. In this Phase I study, the safety and PK parameters of a 2-day pulse of AC480 esylate as monotherapy and also in combination with docetaxel once every 3 weeks are determined.

[00261] AC480 esylate is administered intravenously on days 1 and 2, and docetaxel on day 2 of each 21-day treatment cycle. Dose escalation is guided by careful monitoring of toxicities with pre-specified escalation and stopping rules. The study population includes adult subjects with metastatic or locally advanced solid cancers, whose disease has progressed on or following currently available standard therapies or for which no standard therapy exists. Subjects with tumors that are known or likely to be HER1 and/or HER2+ expressing, including head and neck, lung adenocarcinoma, upper GI/esophageal, and breast cancers, and that may respond and derive clinical benefit from treatment with AC480 are included.

[00262] Phase I is divided into three parts. Part 1: The safety and tolerability of AC480 esylate as monotherapy are established first, along with the determination of the MTD (MTD1) of a 2-day pulse of IV dosing of AC480 esylate. Part 2: The PK parameters of docetaxel monotherapy at a reduced dose of 60 mg/m^2 (80% standard dose due to potential overlapping hepatic toxicity) are determined. Then, the safety and tolerability of the combination of AC480 esylate (administered on days 1 and 2) and docetaxel (administered immediately after AC480 esylate on day 2 at same reduced dose) are determined, where the starting dose of AC480 esylate is one dose level below MTD1 as determined in Part 1. The MTD of AC480 esylate in combination with reduced dose docetaxel (MTD2) is also determined. Part 3: The MTD (MTD3) of the combination of AC480 esylate (administered on days 1 and 2) and docetaxel (administered immediately after AC480 esylate on day 2 at the standard full dose of 75 mg/m^2) is determined.

Part 1:

[00263] Based on preclinical monkey data, the starting IV dose of AC480 esylate in Part 1 is 40 mg/m^2 given over an approximately 30 minute period. During Part 1, patients receive AC480 esylate as monotherapy on days 1 and 2. PK blood samples are drawn at pre-specified time points. Patients are then followed weekly for 21 days to evaluate toxicity. Efficacy is assessed after Cycle 1 and every two cycles (six weeks) thereafter. The DLT evaluation period for AC480 esylate monotherapy is the first 21 days.

[00264] Dose escalation utilizes an accelerated design for Part 1 and a standard 3 + 3 cohort design for Parts 2 and 3. In the first two dose cohorts of Part 1, there is only one patient initially and there is an opportunity to dose escalate if the first patient in each cohort completes the first 21-day period without DLT. This applies only to the first two dose-escalation cohorts (40 and 80 mg/m^2). Thus, if the first patient in the first cohort (40 mg/m^2) completes the 21-day peroid with no DLT, the next patient begins the trial in the second cohort (80 mg/m^2). For only these first two patients in their respective cohorts, DLT is defined as any Grade $\geq$ 2 toxicity (based on National Cancer Institute Common Toxicity Criteria for Adverse Events Version 4.0 [CTCv4]) at any point during the first 21 days that is considered related to study drug. If the first patient in the second cohort (80 mg/m^2) also does not experience DLT in the 21-day period, then the next patient begins the trial in the third cohort (134 mg/m^2), and a standard 3 + 3 cohort design is used thereafter.

[00265] If either the first patient in the first or second cohort experiences a DLT, dose escalation is changed immediately to a standard 3 + 3 cohort design. If this occurs in either the first or second cohort, and for the third dose cohort and all subsequent dose cohorts in Part 1 and for all cohorts in Parts 2 and 3 of the study, AC480 esylate is dose escalated in standard 3 + 3 cohorts (explained below). For the 3 + 3 cohorts, if there is CTCv4 non-hematological Grade $\geq$ 3 and/or hematological Grade $\geq$ 4 (or Grade 3 neutropenic fever) toxicity at any point during the first 21 days that is considered related to study drug, this is defined as the DLT for AC480 esylate monotherapy. Further administration of AC480IV is permanently discontinued and the patient comes off study. Also, if the first cohort becomes a 3 + 3 cohort and more than one of six patients has a DLT, then the dose is reduced to the -1 dose level (Table 7). A similar approach is used if a dose reduction to the -2 dose level is necessary.

TABLE 7. Dose Escalation Schedule for Part 1, AC480 as Monotherapy

Dose-Level	AC480 Esylate IV Dose (mg/m^2)	%Change from Starting Dose (40 mg/m^2)
-2	20	-50
-1	30	-25
1 (Start)	40	0
2	80	100
3	134	335
4	200	500
5	280	700

[00266] Dose escalation by dose cohort is done in a standard modified Fibonacci design for Phase 1 studies. Each dose level is increase by 100%-33%, employing smaller increments as dose increases. When the dose escalation proceeds to the standard 3 + 3 cohort, at least 21 days of treatment and toxicity data must be available for all three patients in a single cohort before the next cohort can open at the next dose level. If zero of three patients in a cohort experience DLT, the next cohort is enrolled at the next higher dose level. If one of three patients experiences a DLT, the cohort is expanded to a total of six patients. If more than one of six patients has a DLT, then there is no further dose escalation and the current dose is defined as the Maximum Administered Dose (MAD). In that case, the next lower dose level is expanded to a total of six patients or an intermediate dose level (between MAD and the next lower level) is opened for evaluation. The highest dose level in which ≥five of six patients in the cohort tolerates the dose is defined as the MTD. In Part 1, this is referred to as MTD1. Once MTD1 is confirmed in six total patients, at least an additional three patients are enrolled at the MTD for additional PK data. Thus, the MTD of AC480 esylate monotherapy is determined in a total of at least nine patients.

Part 2:

[00267] Part 2 begins with the administrate of a single dose of docetaxel 60 mg/m^2 (80% of the standard dose, reduced in this part of study due to the potential for overlapping hepatic toxicity in combination with AC480 esylate) on day 1 of a 21-day cycle. Blood samples for docetaxel PK studies are drawn at pre-specified time points during this cycle of

docetaxel monotherapy (Cycle 1 of Part 2). The regimen for all cycles after Cycle 1 consists of infusions of AC480 esylate on days 1 and 2 in combination with docetaxel at 60 mg/m^2 on day 2, administered after AC480 esylate. Each cycle may be repeated every 3 weeks (21 days). The starting dose for AC480 esylate in Part 2 is the MTD from Part 1 minus one dose level (MTD1 – 1). Patients continue on therapy as long as they are not experiencing intolerable toxicities and there is no evidence of disease progression. All subsequent cycles in Part 2 are identical to Cycle 2, but with no further PK assessments. Efficacy is assessed after Cycle 1 immediately prior to Cycle 2, and every two cycles (six weeks) thereafter. The DLT but with no further PK assessments. The DLT evaluation period for Part 2 is the first 21 days of combination therapy of AC480 esylate and docetaxel (Cycle 2).

[00268] The AC480 esylate IV dose may be escalated or reduced in Part 2 according to Table 8; however, the maximum dose of AC480 esylate can be no higher than the MTD found in Part 1 (MTD1). As in Part 1, the AC480 esylate IV dose in Part 2 is dose escalated in cohorts of 3. If zero of three patients in a cohort experience DLT, then the next cohort is enrolled at the next higher dose level. If patients cannot tolerate the assigned AC480 esylate IV dose with the 60 mg/m^2 docetaxel dose, the AC480 esylate IV dose is lowered until ≥ five of six patients tolerate the dose. Dose levels for escalation or reduction of AC480 esylate are those used in Part 1. The highest dose level in which ≥ five of six patients in the cohort tolerates the dose is defined as the MTD of combination therapy. In Part 2, this is referred to as MTD2. Once MTD2 is confirmed in six total patients, an additional three patients are enrolled at MTD2 for additional PK data.

TABLE 8. Dose Escalation Schedule for Part 2

Dose-Level	**AC480 Esylate IV Dose (mg/m^2)**	**Docetaxel Dose (mg/m^2)**
-2	MTD1-3	60
-1	MTD1-2	60
1 (Start)	MTD1-1	60
2	MTD1	60

Part 3:

[00269] Once the MTD of AC480 esylate with 60 mg/m^2 docetaxel is established (MTD2), the MTD of AC480 esylate with a full standard dose of docetaxel (75 mg/m^2) is to

be determined (MTD3). The starting AC480 esylate IV dose in Part 3 is the MTD from Part 2 minus one dose level (MTD2–1). The first dose level of docetaxel is 75 mg/m^2. AC480 esylate is administered on days 1 and 2 of each cycle. Docetaxel is administered immediately following the AC480 esylate infusion on day 2. Each cycle is 21 days long. If zero of three patients experience DLT, the next cohort receives AC480 esylate at MTD2, and the docetaxel dose remains at 75 mg/m^2. Patients continue on therapy as long as they are not experiencing intolerable toxicities and there is no evidence of disease progression. All subsequent cycles in Part 3 of the study are to Cycle 2, but without the PK assessments. Efficacy is assessed after Cycle 1 immediately prior to Cycle 2, and every two cycles (six weeks) thereafter. The DLT evaluation period for Part 3 is the first 21 days of combination therapy of AC480 esylate and docetaxel (Cycle 2).

[00270] The dose escalation and reduction schedule for Part 3 is similar to Part 2 (*see*, Table 9). Starting dose for AC480 esylate is MTD2-1 and starting dose for docetaxel is 75 mg/m^2. The dose of AC480 esylate is increased or decreased based on patient tolerability; the maximum dose of AC480 esylate, however, can be no higher than the MTD found in Part 2 (MTD2). Dose levels for escalation or reduction of AC480IV are those used in Part 1. The dose of docetaxel remains fixed at 75 mg/m^2.

TABLE 9. Dose Escalation Schedule for Part 3

Dose-Level	**AC480 Esylate IV Dose (mg/m^2)**	**Docetaxel Dose (mg/m^2)**
-2	MTD2-3	75
-1	MTD2-2	75
1 (Start)	MTD2-1	75
2	MTD2	75

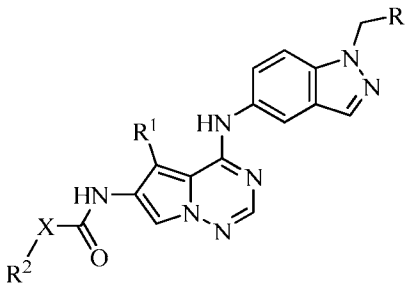
* * * * *

[00271] The examples set forth above are provided to give those of ordinary skill in the art with a complete disclosure and description of how to make and use the claimed embodiments, and are not intended to limit the scope of what is disclosed herein. Modifications that are obvious to persons of skill in the art are intended to be within the scope of the following claims. All publications, patents, and patent applications cited in this specification are incorporated herein by reference as if each such publication, patent or patent

application were specifically and individually indicated to be incorporated herein by reference.

What is claimed is:

1. A method of treating a proliferative disease in a subject, comprising administering to the subject a taxane and an indazolylaminopyrrolotriazine of Formula I:



(I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R is C_{6-14} aryl, heteroaryl, or heterocyclyl;

R^1 is C_{1-6} alkyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

X is a bond, –O–, –S–, $–C(R^3R^4)–$, or $–N(R^3)–$; and

each R^3 and R^4 is independently hydrogen, C_{1-6} alkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

wherein each alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q selected from the group consisting of (a) cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, and heterocyclyl; and (c) $–C(O)R^a$, $–C(O)OR^a$, $–C(O)NR^bR^c$, $–C(=NR^a)NR^bR^c$, $–OR^a$, $–OC(O)R^a$, $–OC(O)OR^a$, $–OC(O)NR^bR^c$, $–OC(=NR^a)NR^bR^c$, $–OS(O)R^a$, $–OS(O)_2R^a$, $–OS(O)NR^bR^c$, $–OS(O)_2NR^bR^c$, $–NR^aR^d$, $–NR^aC(O)R^b$, $–NR^aC(O)OR^b$, $–NR^aC(O)NR^bR^c$, $–NR^aC(=NR^d)NR^bR^c$, $–NR^aS(O)R^b$, $–NR^aS(O)_2R^b$, $–NR^aS(O)NR^bR^c$, $–NR^aS(O)_2NR^bR^c$, $–SR^a$, $–S(O)R^a$, and $–S(O)_2R^a$; wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl; or (ii) R^b and R^c together with the N atom to which they are attached form heterocyclyl or heteroaryl.

2. The method claim 1, wherein the taxane is paclitaxel.

3. The method of claim 2, wherein the paclitaxel is albumin-bound paclitaxel.

4. The method claim 1, wherein the taxane is docetaxel.

5. The method of any of claims 1 to 4, wherein the taxane is administered intravenously.

6. The method of claim 5, wherein the taxane is administered according to a regimen selected from:

i. 260 mg/m^2 over 24 hours;
ii. 250 mg/m^2 over 24 hours;
iii. 200 mg/m^2 over 24 hours;
iv. 185 mg/m^2 over 3 hours;
v. 185 mg/m^2 over 24 hours;
vi. 175 mg/m^2 over 3 hours;
vii. 175 mg/m^2 over 24 hours;
viii. 150 mg/m^2 over 3 hours;
ix. 150 mg/m^2 over 24 hours;
x. 135 mg/m^2 over 3 hours;
xi. 135 mg/m^2 over 24 hours;
xii. 100 mg/m^2 over 3 hours;
xiii. 60–100 mg/m^2 ;
xiv. 100 mg/m^2;
xv. 80-90 mg/m^2;
xvi. 80 mg/m^2;
xvii. 75 mg/m^2; and
xviii. 60 mg/m^2.

7. The method of any of claims 1 to 6, wherein the taxane is administered on days 3, 10, and 17 in a 21 or 28 day cycle.

8. The method of any of claims 1 to 6, wherein the taxane is administered on day 2 in a 21 day cycle.

9. The method any of claims 1 to 8, wherein the indazolylaminopyrrolotriazine is administered orally.

10. The method of claim 9, wherein the indazolylaminopyrrolotriazine is administered according to a regimen selected from:

a. 600 mg/day;

b. 400 mg/day; and

d. 40 to 300 mg/m^2/day.

11. The method claim 9 or 10, wherein the indazolylaminopyrrolotriazine is administered according to a regimen selected from:

a. a dose sufficient to achieve a C_{max} of about 5 to about 40 μM;

b. a dose sufficient to achieve a C_{max} of about 10 to about 40 μM;

c. a dose sufficient to achieve a C_{max} of about 2 to about 20 μg/mL;

d. a dose sufficient to achieve a C_{max} of about 3.5 to about 6 μM;

e. a dose sufficient to achieve a C_{max} of about 0.4 to about 4.5 μM;

f. a dose sufficient to achieve a C_{max} of about 1.5 to about 3.2 μg/mL; and

g. a dose sufficient to achieve a C_{max} of about 0.2 to about 2.2 μg/mL.

12. The method of any of claims 1 to 8, wherein the indazolylaminopyrrolotriazine is administered intravenously.

13. The method any of claims 1 to 12, wherein the indazolylaminopyrrolotriazine is administered according to a regimen selected from:

a. a dose sufficient to achieve an AUC of about 60 to about 500 μg*hr/mL;

b. a dose sufficient to achieve an AUC of about 125 to about 500 μg*hr/mL;

c. a dose sufficient to achieve an AUC of about 125 to about 300 μg*hr/mL;

d. a dose sufficient to achieve an AUC of about 125 to about 200 μg*hr/mL;

e. a dose sufficient to achieve an AUC of about 125 to about 1,000 μM*hr;

f. a dose sufficient to achieve an AUC of about 250 to about 500 μM*hr;

g. a dose sufficient to achieve an AUC of about 4 to about 35 μg*hr/mL;

and

h.. a dose sufficient to achieve an AUC of about 40 to about 55 μg*hr/mL.

14. The method of any of claims 1 to 13, wherein the indazolylaminopyrrolotriazine is administered on days 1 and 2 in a 21 day cycle.

15. The method of any of claims 1 to 14, wherein the indazolylaminopyrrolotriazine is administered prior to the administration of the taxane.

16. The method of claim 15, wherein the indazolylaminopyrrolotriazine is administered on days 2, 9, and 16 in a 21 or 28 day cycle.

17. The method of any of claims 1 to 14, wherein the indazolylaminopyrrolotriazine is administered concurrently with the taxane.

18. The method of any of claims 1 to 14, wherein the indazolylaminopyrrolotriazine is administered after the administration of the taxane.

19. The method of any of claims 1 to 18, wherein the indazolylaminopyrrolotriazine is administered on days 3, 10, and 17 in a 21 or 28 day cycle.

20. The method of any of claims 1 to 19, wherein the proliferative disease is a tumor.

21. The method of claim 20, wherein the tumor is a solid tumor.

22. The method of claim 20 or 21, wherein the tumor is a malignant tumor.

23. The method of claim 22, wherein the malignant tumor is bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, gastric cancer, glioma, head and neck cancer, liver cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, or prostate cancer.

24. The method of any of claims 20 to 23, wherein the tumor overexpresses HER1 protein.

25. The method of claim 24, wherein the tumor overexpresses HER2 protein.

26. The method of any of claims 1 to 25, further comprising administering to the

subject a platinum agent.

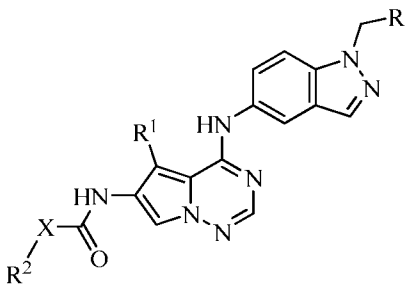
27. The method of claim 26, wherein the platinum agent is cisplatin, carboplatin, oxaliplatin, satraplatin (JM-216), or CI-973.

28. The method of claim 26 or 27, wherein the platinum agent is carboplatin.

29. The method of any of claims 26 to 28, wherein the platinum agent is administered according to a regimen selected from:

i. a dose sufficient to achieve an AUC of about 2 to about 8 mg*min/mL;
ii. a dose sufficient to achieve an AUC of about 3 to about 8 mg*min/mL;
iii. a dose sufficient to achieve an AUC of about 3 to about 7.5 mg*min/mL;
iv. a dose sufficient to achieve an AUC of about 2 mg*min/mL;
v. a dose sufficient to achieve an AUC of about 3 mg*min/mL;
vi. a dose sufficient to achieve an AUC of about 5 mg*min/mL;
vii. a dose sufficient to achieve an AUC of about 6 mg*min/mL; and
viii. a dose sufficient to achieve an AUC of about 7.5 mg*min/mL.

30. A method of inhibiting the growth of a cell, comprising contacting the cell with a taxane and an indazolylaminopyrrolotriazine of Formula I:



(I)

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R is C_{6-14} aryl, heteroaryl, or heterocyclyl;

R^1 is C_{1-6} alkyl;

R^2 is hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

X is a bond, –O–, –S–, –C(R^3R^4)–, or –N(R^3)–; and

each R^3 and R^4 is independently hydrogen, C_{1-6} alkyl, C_{6-14} aryl, C_{7-20} aralkyl, heteroaryl, or heterocyclyl;

wherein each alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, and heterocyclyl is optionally substituted with one or more substituents Q selected from the group consisting of (a) cyano, halo, and nitro; (b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, and heterocyclyl; and (c) –C(O)R^a, –C(O)OR^a, –C(O)N$R^b$$R^c$, –C(=N$R^a$)N$R^b$$R^c$, –O$R^a$, –OC(O)$R^a$, –OC(O)O$R^a$, –OC(O)N$R^b$$R^c$, –OC(=N$R^a$)N$R^b$$R^c$, –OS(O)$R^a$, –OS(O)$_2$$R^a$, –OS(O)N$R^b$$R^c$, –OS(O)$_2NR^b$$R^c$, –N$R^a$$R^d$, –N$R^a$C(O)$R^b$, –N$R^a$C(O)O$R^b$, –N$R^a$C(O)N$R^b$$R^c$, –N$R^a$C(=N$R^d$)N$R^b$$R^c$, –N$R^a$S(O)$R^b$, –N$R^a$S(O)$_2$$R^b$, –N$R^a$S(O)N$R^b$$R^c$, –N$R^a$S(O)$_2NR^b$$R^c$, –S$R^a$, –S(O)$R^a$, and –S(O)$_2$$R^a$; wherein each R^a, R^b, R^c, and R^d is independently (i) hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} cycloalkyl, C_{6-14} aryl, heteroaryl, or heterocyclyl; or (ii) R^b and R^c together with the N atom to which they are attached form heterocyclyl or heteroaryl.

31. The method of claim 30, wherein the indazolylaminopyrrolotriazine is contacted with the cell before the taxane.

32. The method of claim 30, wherein the indazolylaminopyrrolotriazine is contacted with the cell concurrently with the taxane.

33. The method of claim 30, wherein the indazolylaminopyrrolotriazine is contacted with the cell after the taxane.

34. The method of any of claims 30 to 33, wherein the cell is a tumor cell.

35. The method of claim 34, wherein the tumor cell is a solid tumor cell.

36. The method of any of claims 30 to 35, wherein the cell is a cancerous cell.

37. The method of claim 36, wherein the cancerous cell is a cell of bladder cancer, breast cancer, cervical cancer, colon cancer, endometrial cancer, gastric cancer, glioma, head and neck cancer, liver cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, or prostate cancer.

38. The method of any of claims 30 to 37, wherein the cell overexpresses HER1

protein.

39. The method of claim 38, wherein the cell overexpresses HER2 protein.

40. The method of any of claims 1 to 39, wherein R is C_{6-14} aryl, and R^1 is C_{1-4} alkyl, each optionally substituted with one or more substituents Q.

41. The method of any of claims 1 to 40, wherein X is O, and R^2 is cycloalkyl or heterocyclyl, each optionally substituted with one or more substituents Q.

42. The method of any of claims 1 to 41, wherein the compound is selected from the group consisting of:

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*)-2-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-[(3*S*)-3-hydroxy-1-pyrrolidinyl]propyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-[(3*S*)-3-hydroxy-1-piperidinyl]propyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-[(3*R*)-3-hydroxy-1-pyrrolidinyl]propyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, [(2*S*)-1-methyl-2-pyrrolidinyl]methyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-pyrrolidinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-

yl]-carbamic acid, (2*R*)-2-morpholinylmethyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, [(3*R*)-1-methyl-3-pyrrolidinyl]methyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *trans*-4-aminocyclohexyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-piperidinyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-piperidinyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-aminocyclohexyl;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*,4*R*)-2-(hydroxymethyl)-4-piperidinyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-(hydroxymethyl)-4-piperidinyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-(aminomethyl)cyclohexyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-amino-4-methylcyclohexyl ester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, [(2*R*,4*R*)-4-(hydroxy-2-piperidinyl]methylester;

[5-ethyl-4-[[(1-phenylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *trans*-4-(aminomethyl)cyclohexyl ester;

[5-ethyl-4-[[1-(2-oxazolylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(2-thienylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(4-thiazolylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(3-thienylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(2-pyridinylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(2-thiazolylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(3-pyridinylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[5-ethyl-4-[[1-(pyrazinylmethyl)-1*H*-indazol-5-yl]amino]pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *trans*-4-aminocyclohexyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*,4*R*)-2-(hydroxymethyl)-4-piperidinyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*,4*S*)-2-(hydroxymethyl)-4-piperidinyl ester;

[4-[[-1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]-triazin-6-yl]-carbamic acid, *cis*-4-aminocyclohexyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, *cis*-4-amino-4-methyl-cyclohexyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*R*)-2-aminopropyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (2*S*)-2-aminopropyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-morpholinylmethyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-piperidinyl ester;

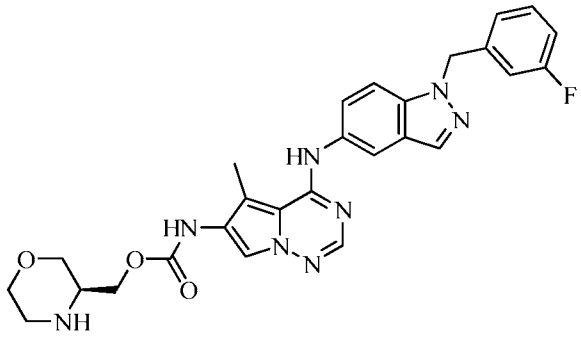
[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*S*)-3-piperidinyl ester;

3-[[[[[4-[[1[(3-fluorophenyl)methyl]-1*H*-indazol-5-yl]amino]-5-methylpyrrolo[2,1-f][1,2,4]-triazin-6-yl]amino]carbonyl]oxy]methyl]-4-morpholinecarboxylic acid, (3*S*)-1,1-dimethylethyl ester;

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, 3-morpholinylmethyl ester; and

[4-[[1-(3-fluorophenyl)methyl]-1*H*-indazol-5-ylamino]-5-methyl-pyrrolo[2,1-f][1,2,4]triazin-6-yl]-carbamic acid, (3*R*)-3-morpholinylmethyl ester;
and pharmaceutically acceptable salts, solvates, hydrates, or prodrugs thereof.

43. The method of any of claims 1 to 42, wherein the indazolylaminopyrrolotriazine is



(II)

or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof.

FIG. 1

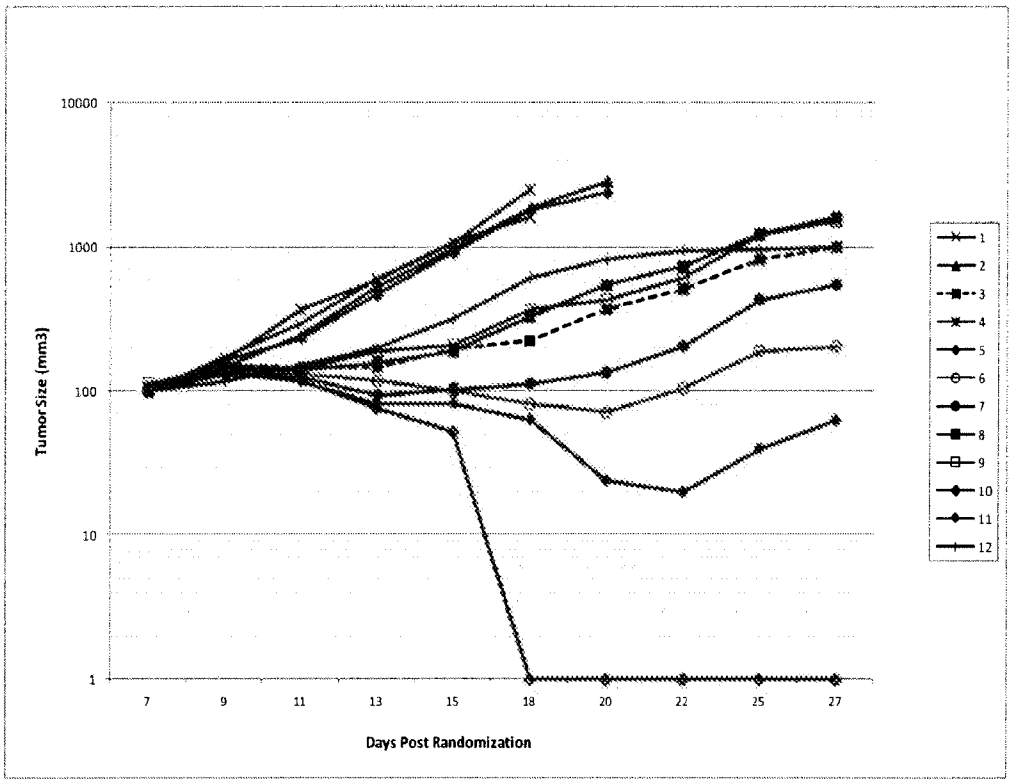

10000
1000
100
10
1
Tumor Size (mm3)
7
9
11
13
15
18
20
22
25
27
Days Post Randomization
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 2

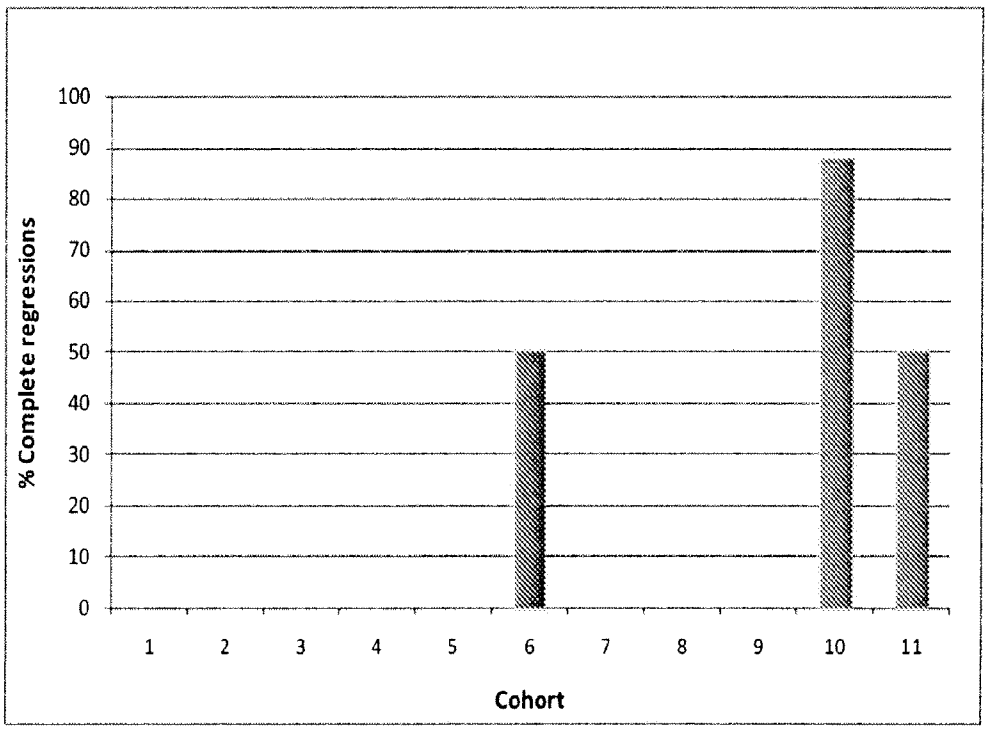

100
90
80
70
60
50
40
30
20
10
0
% Complete regressions
1
2
3
4
5
6
7
8
9
10
11
Cohort

FIG. 3

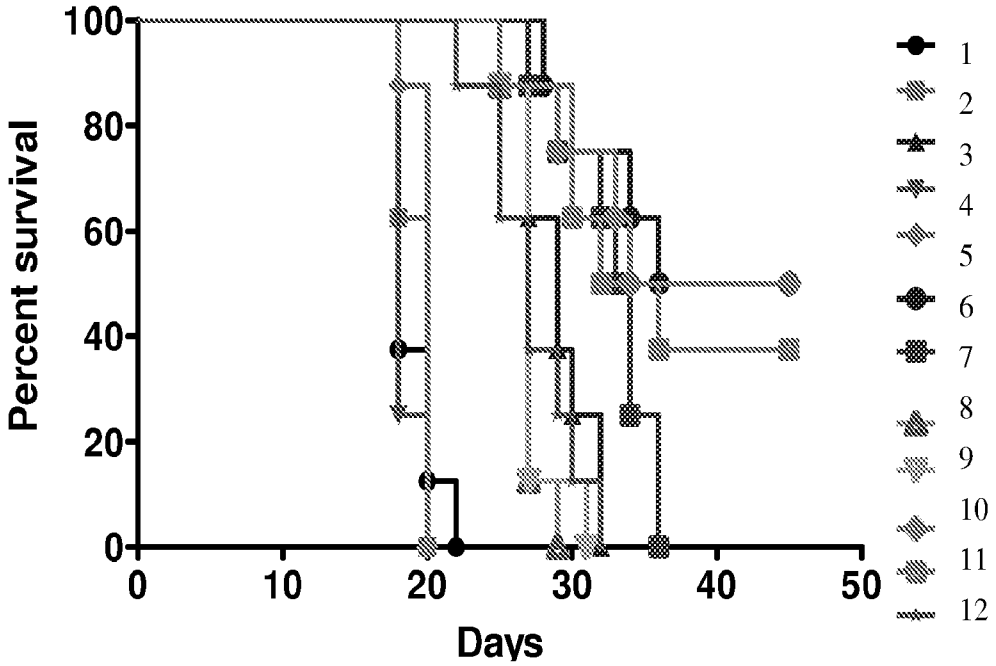
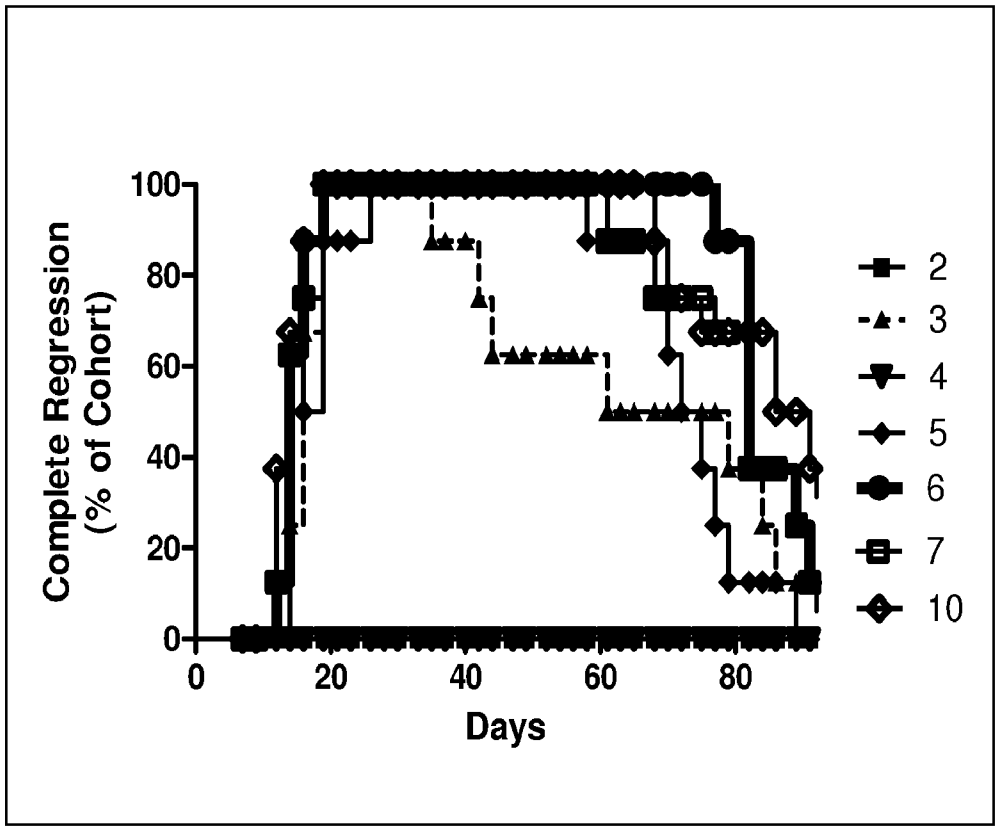

Percent survival
100
80
60
40
20
0
0
10
20
30
40
50
Days
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 4


Complete Regression
(% of Cohort)
100
80
60
40
20
0
0
20
40
60
80
Days
2
3
4
5
6
7
10

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/026916

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61P35/00 A61K31/337 A61K9/00 A61K31/222
A61K31/395
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	page 2, line 19 - page 5, line 33 page 6, line 18 - page 9, line 18 page 17, line 3 page 18, line 6 page 19, line 12 - page 23, line 7 page 23 page 77, lines 19/20, 28-31; claim 5	2-6, 20-29, 31-39

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 May 2010	18/05/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Hörtner, Michael

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WONG TAI W ET AL: "Preclinical antitumor activity of BMS-599626, a pan-HER kinase inhibitor that inhibits HER1/HER2 homodimer and heterodimer signaling." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH 15 OCT 2006 LNKD-PUBMED:17062696, vol. 12, no. 20 Pt 1, 15 October 2006 (2006-10-15), pages 6186-6193, XP007913003 ISSN: 1078-0432 the whole document	1-43
A	"1453 ORAL SB-497115, a novel, oral platelet growth factor, increases platelet counts in healthy subjects" EUROPEAN JOURNAL OF CANCER. SUPPLEMENT, PERGAMON, OXFORD, GB, vol. 3, no. 2, 1 October 2005 (2005-10-01), page 420, XP005133563 ISSN: 1359-6349 the whole document	1-43

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/026916

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ERIKA MARTINELLI ET AL: "Combination of epidermal growth factor receptor inhibitors and antiangiogenic drugs: a model for treatment" TARGETED ONCOLOGY, SPRINGER-VERLAG, PA LNKD- DOI:10.1007/S11523-006-0022-5, vol. 1, no. 3, 19 May 2006 (2006-05-19), pages 123-129, XP019415242 ISSN: 1776-260X the whole document	1-43
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Information on patent family members

International application No
PCT/US2010/026916

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		JP 2008543777 T	04-12-2008
		KR 20080026602 A	25-03-2008
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