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(54) **METHODS AND COMPOSITIONS FOR TREATING CANCER**

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(57) **ABSTRACT**

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Related U.S. Application Data

(63) Continuation of application No. 14/444,513, filed on Jul. 28, 2014, which is a continuation of application No. 13/034,340, filed on Feb. 24, 2011, now Pat. No. 8,822,438, which is a continuation of application No. 11/844,440, filed on Aug. 24, 2007, now abandoned.

Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17 α -hydroxylase/C_{17,20}-lyase inhibitor, such as abiraterone acetate (i.e., 3 β -acetoxy-17-(3-pyridyl) androsta-5,16-diene), in combination with at least one additional therapeutic agent such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17 α -hydroxylase/C_{17,20}-lyase inhibitor, and at least one additional therapeutic agent, such as an anti-cancer agent or a steroid.

(60) Provisional application No. 60/921,506, filed on Aug. 25, 2006.

Amerigen Exhibit 1146
Amerigen v. Janssen
ID# 2016-00286

METHODS AND COMPOSITIONS FOR TREATING CANCER

FIELD OF THE INVENTION

[0001] Methods and compositions for treating cancer are described herein. More particularly, the methods for treating cancer comprise administering a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate (i.e., 3β -acetoxy- 17 -(3-pyridyl) androsta-5,16-diene), in combination with at least one additional therapeutic agent, such as an anti-cancer agent or a steroid. Furthermore, disclosed are compositions comprising a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, and at least one additional therapeutic agent such as an anti-cancer agent or a steroid. e.g., a corticosteroid or, more specifically, a glucocorticoid.

BACKGROUND

[0002] The number of people diagnosed with cancer has significantly increased. Of special interest are individuals diagnosed with androgen-dependent disorders, such as prostate cancer, and estrogen-dependent disorders, such as breast cancer since such diagnoses are increasing in number at an alarming rate.

[0003] Prostate cancer is currently the most common non-skin cancer and the second leading cause of cancer-related death in men after lung cancer. The primary course of treatment for patients diagnosed with organ-confined prostate cancer is usually prostatectomy or radiotherapy. Not only are these treatments highly invasive and have undesirable side effects, such localized treatments are not effective on prostate cancer after it has metastasized. Moreover, a large percent of individuals who receive localized treatments will suffer from recurring cancer.

[0004] Additionally, breast cancer incidence in women has increased from one out of every 20 women in 1960 to one out of every eight women in 2005. Moreover, it is the most common cancer among white and African-American women. Similar to treating prostate cancer, most options for women diagnosed with breast cancer are highly invasive and have significant side-effects. Such treatments include surgery, radiation and chemotherapy.

[0005] Hormone therapy is another treatment option for individuals diagnosed with prostate or breast cancer. Hormone therapy is a form of systemic treatment for prostate or breast cancer wherein hormone ablation agents are used to suppress the production or block the effects of hormones, such as estrogen and progesterone in the body, which are believed to promote the growth of breast cancer, as well as testosterone and dihydrotestosterone, which are believed to promote the growth of prostate cancer. Moreover, hormone therapy is less invasive than surgery and does not have many of the side effects associated with chemotherapy or radiation. Hormone therapy can also be used by itself or in addition to localized therapy and has shown to be effective in individuals whose cancer has metastasized.

[0006] Even though hormone therapy is less invasive and can be used on more advanced stages of cancer, some individuals administered current hormone therapy treatments may not show a significant response or may not show any response at all to such treatments. Additionally, some patients treated with current hormone therapy treatments may also

suffer from relapsing or recurring cancer. Currently, such refractory cancer patients are left with very few treatment options.

[0007] Despite the progress made in the treatment of cancer, there remains a need for more effective ways to treat cancer such as, but not limited to, prostate cancer and breast cancer. Additionally, there is a need for effective anti-cancer treatment options for patients who are not responding to current anti-cancer treatments. Also, there is a need for effective anti-cancer treatment options for patients whose cancer has recurred.

SUMMARY OF THE INVENTION

[0008] Described herein are methods for treating a cancer in which a therapeutically effective amount of a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor, such as abiraterone acetate (i.e. 3β -acetoxy- 17 -(3-pyridyl)androsta-5,16-diene), is administered to a patient. e.g., a patient in need thereof, in combination with a therapeutically effective amount of at least one additional therapeutic agent including, but not limited to, an anti-cancer agent or steroid. Such methods can also provide an effective treatment for individuals with a refractory cancer, including individuals who are currently undergoing a cancer treatment. Therefore, in certain embodiments, the method is directed to treating a refractory cancer in a patient, in which a therapeutically effective amount of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered to a patient currently receiving an anti-cancer agent.

[0009] For example, in certain embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.1 mg/m² to about 20 mg/m² of mitoxantrone.

[0010] In another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 175 mg/m² of docetaxel.

[0011] In still other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/m² to about 100 mg/m² of docetaxel.

[0012] Furthermore, described herein is a method for the treatment of a cancer in a mammal comprising administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate; and an amount of about 0.01 mg to about 200 mg of leuprolide, wherein the leuprolide is administered over a period of about 3 days to about 12 months.

[0013] In other embodiments, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of goserelin, wherein the goserelin is administered over a period of about 28 days to about 3 months.

[0014] Additionally, in another embodiment, the method for the treatment of a cancer in a mammal comprises administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 0.01 mg to about 20 mg of triptorelin, wherein the triptorelin is administered over a period of about 1 month.

[0015] The method for the treatment of a cancer in a mammal can also comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and

an amount of about 0.1 $\mu\text{g/day}$ to about 500 $\mu\text{g/day}$ of seocalcitol, such as about 100 $\mu\text{g/day}$ of seocalcitol.

[0016] Also, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 300 mg/day of bicalutamide.

[0017] In yet another embodiment, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 0.01 mg/kg/day to about 100 mg/kg/day of abiraterone acetate and an amount of about 1 mg/day to about 2000 mg/day of flutamide.

[0018] Moreover, the method for the treatment of a cancer in a mammal can comprise administering an amount of about 50 mg/day to about 2000 mg/day of abiraterone acetate and an amount of about 0.01 mg/day to about 500 mg/day of a glucocorticoid including, but not limited to, hydrocortisone, prednisone or dexamethasone.

[0019] Also described herein are compositions for the treatment of cancer that comprise a combination of a therapeutically effective amount of at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and a therapeutically effective amount of at least one additional anti-cancer agent, such as, but not limited to, mitoxantrone, paclitaxel, docetaxel, leuprolide, goserelin, triptorelin, seocalcitol, bicalutamide, flutamide, or a steroid including, but not limited to, hydrocortisone, prednisone, or dexamethasone.

[0020] Finally, single unit dosage forms comprising abiraterone acetate and a glucocorticoid, optionally with carriers, diluents or excipients, are contemplated. Also, kits comprising at least one 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor and an additional anti cancer agent or steroid are contemplated. For example, the kit may include a vial containing abiraterone acetate and another vial containing a glucocorticoid.

DEFINITIONS

[0021] As used herein and unless otherwise defined the word “cancer,” refers to the growth, division or proliferation of abnormal cells in the body. Cancers that can be treated with the methods and the compositions described herein include, but are not limited to, prostate cancer, breast cancer, adrenal cancer, leukemia, lymphoma, myeloma, Waldenström’s macroglobulinemia, monoclonal gammopathy, benign monoclonal gammopathy, heavy chain disease, bone and connective tissue sarcoma, brain tumors, thyroid cancer, pancreatic cancer, pituitary cancer, eye cancer, vaginal cancer, vulvar cancer, cervical cancer, uterine cancer, ovarian cancer, esophageal cancer, stomach cancer, colon cancer, rectal cancer, liver cancer, gallbladder cancer, cholangiocarcinoma, lung cancer, testicular cancer, penial cancer, oral cancer, skin cancer, kidney cancers, Wilms’ tumor and bladder cancer.

[0022] As used herein, and unless otherwise defined, the terms “treat,” “treating” and “treatment” include the eradication, removal, modification, management or control of a tumor or primary, regional, or metastatic cancer cells or tissue and the minimization or delay of the spread of cancer.

[0023] As used herein, and unless otherwise defined, the term “patient” means an animal, including but not limited to an animal such as a human, monkey, cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, or guinea pig. In one embodiment, the patient is a mammal and in another embodiment the patient is a human. In certain embodiments, the patient can be an adult male or female. In

some embodiments, the patient is a mule of age about 30 years to about 85 years. In other embodiments, the patient is a female of age about 30 years to about 85 years. In a particular embodiment, the patient has or is susceptible to having (e.g., through genetic or environmental factors) cancer. In a further embodiment, the patient has or is susceptible to having (e.g., through genetic or environmental factors) a tumor. In other embodiments, the patient can be castrated or non-castrated.

[0024] The term “ 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor” as used herein refers to an inhibitor of 17α -hydroxylase/ $C_{17,20}$ -lyase, (which is an enzyme in testosterone synthesis) an analog thereof, derivative thereof, metabolite thereof or pharmaceutically acceptable salt thereof. Also, unless otherwise noted, reference to a particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can include analogs, derivatives, metabolites or pharmaceutically acceptable salts of such particular 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0025] The term “anti-cancer agent” as used herein refers to any therapeutic agent that directly or indirectly kills cancer cells or directly or indirectly prohibits stops or reduces the proliferation of cancer cells. It should be noted that even though throughout this specification and in the claims the phrase “anti-cancer agent” is written as a singular noun, for example; “an anti-cancer agent” or “the anti-cancer agent,” the phrase “anti-cancer agent” should not be interpreted as being limited to the inclusion of a single anti-cancer agent.

[0026] As used herein, and unless otherwise defined, the phrase “therapeutically effective amount” when used in connection with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent means an amount of the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor or therapeutic agent effective for treating a disease or disorder disclosed herein, such as cancer.

[0027] As used herein and unless otherwise defined the phrase “refractory cancer.” means cancer that is not responding to an anti-cancer treatment or cancer that is not responding sufficiently to an anti-cancer treatment. Refractory cancer can also include recurring or relapsing cancer.

[0028] As used herein and unless otherwise defined the phrase “refractory patient,” means a patient who has refractory cancer.

[0029] As used herein and unless otherwise defined the phrase “relapse cancer.” means cancer that was at one time responsive to an anti-cancer treatment but has become no longer responsive to such treatment or is no longer responding sufficiently to such treatment.

[0030] As used herein and unless otherwise defined the phrase “recurring cancer,” means cancer that has returned after a patient has been earlier diagnosed with cancer, under gone treatment or had been previously diagnosed as cancer-free.

[0031] As used herein and unless otherwise defined the term “derivative” refers to a chemically modified compound wherein the chemical modification takes place at one or more functional groups of the compound. The derivative may retain or improve the pharmacological activity of the compound from which it is derived.

[0032] As used herein and unless otherwise defined the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group).

[0033] As used herein and unless otherwise defined the phrase “pharmaceutically acceptable salt” refers to any salt of

a 17-hydroxylase/C_{17,20}-lyase inhibitor which retains the biological effectiveness of the 17 α -hydroxylase/C_{17,20}-lyase inhibitor. Examples of pharmaceutically acceptable salts include, but are not limited to, acetates, sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, gamma-hydroxybutyrates, glycollates, tartarates, alkanesulfonates (e.g. methane-sulfonate or mesylate), propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates. Several of the officially approved salts are listed in Remington: The Science and Practice of Pharmacy. Mack Publ. Co., Easton.

DETAILED DESCRIPTION OF THE INVENTION

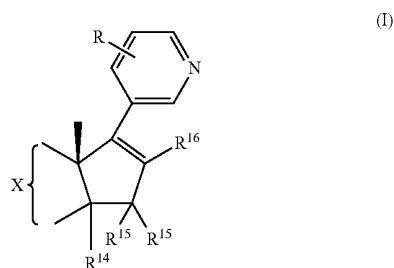
[0034] The methods described herein for treating cancer comprise administering to a mammal, preferably a human, a 17 α -hydroxylase/C_{17,20}-lyase inhibitor in addition to at least one therapeutic agent, such as an anti-cancer agent or steroid, particularly a glucocorticoid. The compositions described herein comprise a 17 α -hydroxylase/C_{17,20}-lyase inhibitor and at least one additional therapeutic agent, such as an anti-cancer agent or steroid, particularly a corticosteroid or glucocorticoid. Other anti-cancer treatments such as, administration of yet another anti-cancer agent, radiotherapy, chemotherapy, photodynamic therapy, surgery or other immunotherapy, can be used with the methods and compositions.

17 α -Hydroxylase/C_{17,20}-Lyase Inhibitors

[0035] 17 α -hydroxylase/C_{17,20}-lyase inhibitors have been shown to be useful in the treatment of cancer, specifically hormone-dependent disorders such as, androgen-dependent and estrogen-dependent disorders like prostate cancer and breast cancer respectively, as described in U.S. Pat. No. 5,604,213 to Barrie et al., which is herein incorporated by reference in its entirety.

[0036] In certain embodiments, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can be 17-(3-pyridyl)androsta-5,16-dien-3 β -ol; 17-(3-pyridyl)androsta-3,5,16-triene; 17-(3-pyridyl)androsta-4,16-dien-3-one; 17-(3-pyridyl)estra-1,3,5[10],16-tetraen-3-ol; 17-(3-pyridyl)-5 α -androst-16-en-3 α -ol; 17-(3-pyridyl)-5 α -androst-16-en-3-one; 17-(3-pyridyl)-androsta-4,16-diene-3,11-dione; 17-(3-pyridyl)-androsta-3,5,16-trien-3-ol; 6 α - and 6 β -fluoro-17-(3-pyridyl)androsta-4,16-dien-3-ol; 17-(3-pyridyl)androsta-4,16-dien-3 β -dione; 3 α -trifluoromethyl-17-(3-pyridyl)androst-16-en-3 β -ol or their acid addition salts and 3-esters as well as metabolites, analogs, derivatives or a pharmaceutically acceptable salt thereof.

[0037] In certain embodiments, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can have the structure of formula (I):



wherein X represents the residue of the A, B and C rings of a steroid which can be, without limitation, androstan-3 α - or 3 β -ol; androst-5-en-3 α - or 3 β -ol; androst-4-en-3-one; androst-2-ene; androst-4-ene; androst-5-ene; androsta-5,7-dien-3 α or 3 β -ol; androsta-1,4-dien-3-one; androsta-3,5-diene; androsta-3,5-diene-3-ol; estra-1,3,5[10]-triene; estra-1,3,5[10]-trien-3-ol; 5 α -androstan-3-one; androst-4-ene-3,11-dione; 6-fluoroandrost-4-ene-3-one; or androstan-4-ene-3,6-dione; each of which, where structurally permissible, can be further derivatized in one or more of the following ways, including, but not limited to, to form 3-esters; to have one or more carbon or carbon ring double bonds in any of the 5,6-, 6,7-, 7,8-, 9,11- and 11,12-positions; as 3-oximes; as 3-methylenes; as 3-carboxylates; as 3-nitriles; as 3-nitros; as 3-desoxy derivatives; to have one or more hydroxy, halo, C₁₋₄-alkyl, trifluoromethyl, C₁₋₄-alkoxy, C₁₋₄-alkanoyloxy, benzoyloxy, oxo, methylene or alkenyl substituents in the A, B, or C-ring; or to be 19-nor;

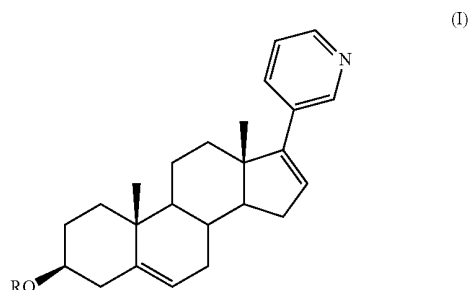
[0038] R represents a hydrogen atom or an alkyl group of 1-4 carbon atoms;

[0039] R¹⁴ represents a hydrogen atom, a halogen atom or an alkyl group of 1 to 4 carbon atoms;

[0040] each of the R¹⁵ substituents independently represents a hydrogen atom or an alkyl or alkoxy group of 1-4 carbon atoms, a hydroxy group or an alkylcarbonyloxy group of 2 to 5 carbon atoms or together represent an oxo or methylene group or R¹⁴ and one of the R¹⁵ groups together represent a double bond and the other R¹⁵ group represents a hydrogen atom or an alkyl group of 1 to 4 carbon atoms; and

[0041] R¹⁶ represents a hydrogen atom, halogen atom, or an alkyl group of 1 to 4 carbon atoms, in the form of the tree bases or pharmaceutically acceptable acid addition salts, but excluding 3 β -acetoxy-17-(3-pyridyl)androsta-5,14,16-triene, 3 β ,15 α - and 3 β ,15 β -diacetoxy-17-(3-pyridyl)androsta-5,16-diene and 3 β -methoxy-17-(3-pyridyl)-5 α -androst-16-ene. Suitable inhibitors also include metabolites, derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

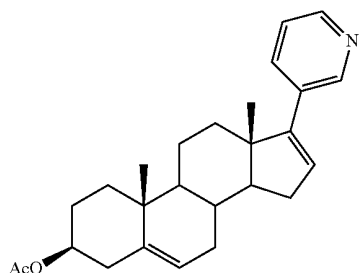
[0042] In another embodiment, the 17 α -hydroxylase/C_{17,20}-lyase inhibitor can have the structure of formula (I):



wherein R represents hydrogen or a lower acyl group having 1 to 4 carbons. Suitable inhibitors also include derivatives, analogs, or pharmaceutically acceptable salts of formula (I).

[0043] In still another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor can be a 3β -alkanoyloxy-17-(3-pyridyl) androsta-5,16-diene in which the alkanoyloxy group has from 2 to 4 carbon atoms.

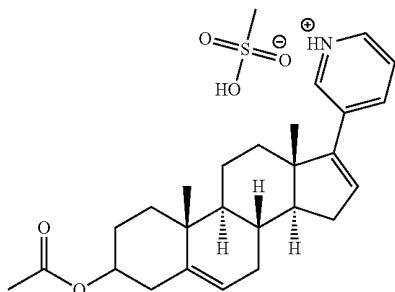
[0044] In a preferred embodiment, the 17α -hydroxylase $C_{17,20}$ -lyase inhibitor comprises abiraterone acetate or 3β -acetoxy-17-(3-pyridyl)androsta-5,16-diene which has the following structural formula:



(II)

and pharmaceutically acceptable salts thereof.

[0045] Preferred salts of abiraterone acetate and methods of making such salts are also disclosed in U.S. Provisional Application No. 60/603,559) to Hunt, which is incorporated by reference in its entirety. Preferred salts include, but are not limited to, acetates, citrates, lactates, alkanesulfonates (e.g. methane-sulfonate or mesylate) and tartarates. Of special interest is the abiraterone acetate mesylate salt (i.e. 3β -acetoxy-17-(3-pyridyl)androsta-5,16-diene mesylate salt) which has the following structural formula:



(III)

[0046] The 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors can be made according to any method known to one skilled in the art. For example, such inhibitors can be synthesized according to the method disclosed in U.S. Pat. Nos. 5,604,213 and 5,618,807 to Barrie et al., herein incorporated by reference. Another method of making 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors is disclosed in U.S. provisional application 60/603,558 to Bury, herein incorporated by reference.

[0047] The amount of 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor administered to a mammal having cancer is an amount that is sufficient to treat the cancer, whether the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered alone or in

combination with an additional anti-cancer treatment, such as an additional anti-cancer agent.

Additional Therapeutic Agents

[0048] Suitable compounds that can be used in addition to 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitors as an anti-cancer agent include, but are not limited to, hormone ablation agents, anti-androgen agents, differentiating agents, anti-neoplastic agents, kinase inhibitors, anti-metabolite agents, alkylating agents, antibiotic agents, immunological agents, interferon-type agents, intercalating agents, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, mitotic inhibitors, matrix metalloprotease inhibitors, genetic therapeutics, and anti-androgens. The amount of the additional anti-cancer agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor. Below are lists of examples of some of the above classes of anti-cancer agents. The examples are not all inclusive and are for purposes of illustration and not for purposes of limitation. Many of the examples below could be listed in multiple classes of anti-cancer agents and are not restricted in any way to the class in which they are listed in.

[0049] Suitable hormonal ablation agents include, but are not limited to, androgen ablation agents and estrogen ablation agents. In preferred embodiments, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor is administered with a hormonal ablation agent, such as deslorelin, leuprolide, goserelin or triptorelin. Even though throughout this specification and in the claims the phrase "hormonal ablation agent" is written as a singular noun, for example, "a hormonal ablation agent" or "the hormonal ablation agent," the phrase "hormonal ablation agent" should not be interpreted as being limited to the inclusion of a single hormonal ablation agent. The amount of the hormonal ablation agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0050] Suitable anti-androgen agents include but are not limited to bicalutamide, flutamide and nilutamide. The amount of the anti-androgen agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0051] In another embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with a differentiating agent. Suitable differentiating agents include, but are not limited to, polyamine inhibitors; vitamin D and its analogs, such as, calcitriol, doxerealeiferol and seocalcitol; metabolites of vitamin A, such as, ATRA, retinoic acid, retinoids; short-chain fatty acids; phenylbutyrate; and nonsteroidal anti-inflammatory agents. The amount of the differentiating agent administered to a mammal having cancer is an amount that is sufficient to treat the cancer whether administered alone or in combination with a 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor.

[0052] In another preferred embodiment, the 17α -hydroxylase/ $C_{17,20}$ -lyase inhibitor may be administered with an anti-neoplastic agent, including, but not limited to, tubulin interacting agents, topoisomerase inhibitors and agents, actretin, alstonine, amonafide, amphetamine, ampicillin, ankinomycin, anti-neoplaston, aphidicolin glycinate, asparaginase, baccharin, batracylin, benfluron, benzotript,

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