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(54) Title: COMBINATION THERAPY METHODS FOR TREATING AN INFLAMMATORY BREAST CANCER

(57) Abstract: Provided are combination therapy methods of treating cancer (such as an inflammatory breast cancer) comprising administering to an individual an effective amount of paclitaxel and an effective amount of romidepsin. Also provided are pharmaceutical compositions and kits comprising same.



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COMBINATION THERAPY METHODS FOR TREATING AN INFLAMMATORY BREAST CANCER

TECHNICAL FIELD

[0001] The present invention relates to methods and compositions for the treatment of cancer comprising an administration of a combination of a taxane and romidepsin. In one embodiment, the cancer is an inflammatory breast cancer.

BACKGROUND

[0002] Cancer is a leading cause of death world wide. Despite significant advances in the field of chemotherapy, many of the most prevalent forms of cancer still resist chemotherapeutic intervention.

[0003] Breast cancer is the most prevalent form of cancer in women. In 2009, an estimated 192,370 new cases of invasive breast cancer were expected to be diagnosed in women in the U.S., along with 62,280 new cases of non-invasive (in situ) breast cancer. About 40,170 women in the U.S. were expected to die in 2009 from breast cancer.

[0004] Inflammatory breast cancer (IBC) is the most advanced type of non metastatic breast tumor. IBC is less commonly diagnosed than other forms of breast cancer, however IBC accounts for a significant percentage of the over 40,000 breast cancer-related deaths each year (Anderson *et al.*, *Breast Dis* 2005-2006; 22:9-23; Hance *et al.*, *J Natl Cancer Inst* 2005 Jul 6;97(13):966-75.). The outcome of the disease is poor. The average survival of IBC patients is 2.9 years which is significantly less than the 6.4 year survival rate of patients diagnosed with non-IBC locally advanced breast cancer and the >10 year survival rate of patients with non-T4 {i.e., non-locally advanced) breast cancer (Hance *et al.*, *supra*).

[0005] IBC is diagnosed at an earlier age than other types of breast cancers (< 52 years of age), and because it is often diagnosed during the child-bearing years, IBC is commonly misdiagnosed as an infection such as mastitis, leading to delays in accurate diagnosis and treatment.

[0006] IBC does not present as a lump but rather is first noticeable as diffuse erythema of the breast often appearing as a rash or mosquito bite, rapidly

progressing, often within days or weeks, to involvement of more than two-thirds of the skin overlying the breast, with swelling and enlargement of the breast and dimpled skin defined as "peau d'orange" (Cristofanilli *et al*, *Cancer*, 2007 Oct 1;110(7):1436-44).

[0007] Although multi-modality treatment strategies including neoadjuvant chemotherapy, surgery, and radiation have been developed over the past 30 years and has been successful in increasing the overall survival of patients with non-IBC locally advanced breast cancers, there has been no significant change in survival of IBC patients during this same time frame (Gonzalez-Angulo *et al*, *Oncologist*, 2007 Aug;12(8):904-912). Accordingly, there is a significant need for therapeutics that may be used to effectively treat patients with IBC.

[0008] Epigenetic alternations in the genome contribute to cancer initiation and progression. For example, histone hypoacetylation and abnormal DNA methylation in promoter regions of important genes can lead to gene silencing. Multiple genes are methylated and thus silenced in breast cancer (*Pu RT. Mod. Path.*, 2003). The functions of epigenetic modifiers in treating various cancers have been investigated (Cooper *et al*, *Gynecol Oncol.* 2007, 104(3):596-601; Ramalingam *et al*, *J. Clin. Oncology*, 2006 ASCO Annual Meeting Proceedings, Part I, Vol. 24 (18S); and Kim *et al*, *Cancer Res*, 2003).

[0009] The current success of HDAC in the clinical practice for various cancers encourages the pursuing of a combinational therapy in order to increase the response rate.

[0010] Taxanes (such as paclitaxel and docetaxel) have been shown to have significant antineoplastic and anticancer effects in a wide variety of cancers. For example, paclitaxel acts by interfering with the normal function of microtubule breakdown. Paclitaxel binds to the beta subunit of tubulin, the building blocks of microtubules, causing hyper-stabilization of the microtubule structures. The resulting paclitaxel/microtubule structure is unable to disassemble, thereby arresting mitosis and inhibiting angiogenesis. The poor aqueous solubility for the taxanes, however, presents significant challenges for developing effective taxane-based cancer therapeutics. Furthermore, the interaction of different taxane formulations with other therapeutic agents in the combination therapy context remains to be studied.

[0011] Albumin-based nanoparticle compositions have been developed as a drug delivery system for delivering substantially water insoluble drugs such as taxanes.

See, for example, U.S. Pat. Nos. 5,916,596; 6,506,405; 6,749,868, 6,537,579, 7,820,788, U.S. Pat. Pub. Nos. 2007/0082838, WO08/057562, WO2009126938A1, WO2009126401A1, and WO2009126175A1. The albumin-based nanoparticle technology utilizes the natural properties of the protein albumin to transport and deliver substantially water insoluble drugs to the site of disease. These nanoparticles are readily incorporated into the body's own transport processes and are able to exploit the tumors' attraction to albumin, enabling the delivery of higher concentrations of the active drug encapsulated in the nanoparticles to the target site. In addition, the albumin-based nanoparticle technology offers the ability to improve a drug's solubility by avoiding the need for toxic chemicals, such as solvents, in the administration process, thus potentially improving safety through the elimination of solvent-related side effects.

[0012] There is an urgent need for therapies to treat IBC. An effective and safe combinational therapy would be valuable in a type of cancer where few treatment alternatives exist.

BRIEF SUMMARY

[0013] The invention provides combination therapy methods of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of at least one other agent that modifies the epigenetics in a cell (also referred herein as an "epigenetic modifier" or "the other agent"). In some embodiments, the invention provides a method of treating a proliferative disease (such as cancer) in an individual comprising administering to the individual a) an effective amount of a composition comprising paclitaxel and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the other agent modifies (such as inhibits) DNA methylation. In some embodiments, the other agent modifies histone modification, which includes, but is not limited to, histone acetylation, histone methylation, histone sumoylation, and histone phosphorylation. In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin).

[0014] In some embodiments, the proliferative disease is resistant or refractory to the treatment of taxane when administered alone or in conjunction with an agent other than the epigenetic modifier. In some embodiments, the proliferative disease is resistant or refractory to the treatment when the epigenetic modifier is administered alone or in conjunction with another agent (such as a taxane including paclitaxel).

[0015] The methods of the present application are useful for the treatment of various diseases, including, for example, breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the proliferative disease is solid tumor. In some embodiments, the proliferative disease is liquid tumor.

[0016] In some embodiments, provided are compositions for use in the methods described herein. In some embodiments, the composition comprises paclitaxel and a pharmaceutically acceptable carrier. In some embodiments, the composition comprising paclitaxel and the composition comprising another agent are administered simultaneously, either in the same composition or in separate compositions. In some embodiments, the composition and the other agent are administered sequentially, *i.e.*, the composition is administered either prior to or after the administration of the other agent.

[0017] In some embodiments, the administration of the composition and the other agent is concurrent, *i.e.*, the administration period of the composition and that of the other agent overlap with each other. In some embodiments, the composition is administered for at least one cycle (for example, at least any of 2, 3, or 4 cycles) prior to the administration of the other agent. In some embodiments, the other agent is administered for at least any of one, two, three, or four weeks after the termination of the nanoparticle composition. In some embodiments, the composition and the epigenetic modifier are administered over the same treatment cycles.

[0018] In some embodiments, the administration of the composition and the other agent are non-concurrent. For example, in some embodiments, the administration of the composition is terminated before the other agent is administered. In some embodiments, the administration of the other agent is terminated before the composition is administered.

[0019] In some embodiments, the other agent is a histone deacetylase inhibitor, including, but not limited to, romidepsin, vorinostat, panobinostat, belinostat, and

entinostat. In some embodiments, the other agent is an inhibitor of DNA methyltransferase, including, but not limited to, 5-azacytidine (azacitidine or Vidaza), 5-aza-2'-deoxycytidine (decitabine or Dacogen), 1-P-D-arabinofuranosil-5-azacytosine, dihydro-5-azacytidine, antisense oligonucleotide MG98, and zebularine.

[0020] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of romidepsin. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of an azacitidine. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of a decitabine.

[0021] In some embodiments, there is provided a method of treating breast cancer in an individual, comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, there is provided a method of treating breast cancer in an individual, wherein the individual is negative for ER, PR, and HER2, comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the method further comprises conducting definitive surgery within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 following the preoperative therapy.

[0022] The methods of the invention generally comprise administration of a composition comprising a taxane (such as paclitaxel). In some embodiments, the composition comprises paclitaxel.

[0023] In some embodiments, there is provided a method of treating breast cancer (such as IBC), comprising administering to said individual a) an effective amount of paclitaxel and b) an effective amount of a histone deacetylase inhibitor. In some embodiments, there is provided a method of treating breast cancer (such as IBC), comprising administering to said individual a) an effective amount of paclitaxel and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments,

there is provided a method of treating breast cancer (such as IBC), comprising administering to said individual a) an effective amount of paclitaxel and b) an effective amount of romidepsin. In some embodiments, the method further comprises administering to the individual an effective amount of a platinum-based agent.

[0024] In some embodiments, there is provided a method of treating breast cancer (such as IBC), comprising: a) intravenously administering an effective amount of paclitaxel to the individual, and b) orally administering an effective amount of romidepsin to the individual. In some embodiments, the method further comprises intravenously administering to the individual an effective amount of a platinum-based agent (such as carboplatin). In some embodiments, there is provided a method of treating breast cancer (such as IBC), comprising: a) intravenously administering about 80 to about 200 mg/m² (such as about 100 mg/m²) of paclitaxel to the individual, and b) orally administering about 10 mg/m² to about 300 mg/m² of romidepsin to the individual. In some embodiments, the method further comprises intravenously administering to the individual an effective amount of a platinum-based agent (such as carboplatin) at the dose of AUC₂.

[0025] In some embodiments, there is provided a method of treating breast cancer (such as IBC), comprising: a) intravenously administering about 80 to about 200 mg/m² (such as about 100 mg/m²) of paclitaxel to the individual weekly, and b) orally administering about 10 to about 300 mg/m² of romidepsin to the individual three out of every seven days. In some embodiments, the method further comprises intravenously administering to the individual an effective amount of carboplatin at the dose of AUC₂ weekly. In some embodiments, the composition (and the carboplatin) is administered on day one of each week, and romidepsin is administered on days 1-3 of each week. In some embodiments, the combination treatment is repeated every four weeks for four or more cycles.

[0026] Also provided are kits and compositions useful for methods described herein.

[0027] These and other aspects and advantages of the present invention will become apparent from the subsequent detailed description and the appended claims. It is to be understood that one, some, or all of the properties of the various embodiments described herein may be combined to form other embodiments of the present invention.

BRIEF DESCRIPTION OF FIGURES

- [0028] Figure 1 shows molecular subtypes of breast cancer cell lines.
- [0029] Figure 2 shows dose dependent inhibition of proliferation, invasion, anchorage and independent growth of soft agar and clonogenic growth in breast cancer cell lines by romidepsin.
- [0030] Figure 3 shows the Mary-X model of IBC that recapitulates formation of tumor emboli with E-cadherin expression, shown as stains that invade into the skin and chest wall as cohesive aggregates of tumor cells.
- [0031] Figures 4A - 4F show induction of a dose dependent apoptosis in the Mary-X IBC tumor spheroids by romidepsin.
- [0032] Figures 5A - 5G show induction of a dose dependent apoptosis in the Mary-X IBC tumor spheroids by romidepsin.
- [0033] Figure 6 shows a dose-dependent induction of p21, acetylated histone 3 and acetylated tubulin proteins in breast cancer cell lines by romidepsin.
- [0034] Figure 7 shows an inhibition of growth of Mary-X xenografts by romidepsin. Mary-X tumor spheroids were injected into NOD.Cg-Prkdc^{scl} II-2ry^{tm1Wj}/SzJ female mice via the subcutaneous route. Animals were matched for tumor size into treatment groups at day 105 after cell injection and treated with romidepsin in a dose of 2.5 mg/kg iv in a vehicle of N-Methyl-Pyrrolidone at 2.5%, 5 % Dextrose dosed Q4D x 3 at days 105, 108, and 112. Mice were imaged weekly using bioluminescence live *in vivo* imaging techniques. Study was terminated at day 154 and tissues isolated for histological and molecular analysis.
- [0035] Figures 8A - 8B show inhibition of growth of SUM149 IBC xenografts (by tumor volume and luminescence) by romidepsin. SUM149 cells (5 x 10⁵) were injected into mammary fat pads of NOD.Cg-Prkdc^{scl} II-2ry^{tm1Wj}/SzJ female mice and treated with 2.5 mg/kg of romidepsin Q4Dx3 at days 31, 35, and 38 after tumor cell injection; 7.5 mg/kg Paclitaxel Q4D beginning at day 30 in a vehicle of 5 % cremaphor, 5 % ethanol and 5 % dextrose or the combination of these 2 agents.
- [0036] Figures 9A - 9D demonstrate inhibition of growth of SUM149 IBC xenografts by romidepsin (B), paclitaxel (C), and the combination of romidepsin and paclitaxel. Figure 9A demonstrates vehicle control.

DETAILED DESCRIPTION

[0037] The present invention provides methods of combination therapy comprising administration of a taxane (such as paclitaxel) in conjunction with a second agent that modifies the epigenetics in a cell (also referred to as an "epigenetic modifier").

[0038] The present application thus provides methods of combination therapy. It is to be understood by a person of ordinary skill in the art that the combination therapy methods described herein requires that one agent or composition be administered in conjunction with another agent. "In conjunction with" refers to administration of one treatment modality in addition to another treatment modality, such as administration of a nanoparticle composition described herein in addition to administration of the other agent to the same individual. As such, "in conjunction with" refers to administration of one treatment modality before, during or after delivery of the other treatment modality to the individual.

[0039] The methods described herein are generally useful for treatment of proliferative diseases. As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, any one or more of: alleviation of one or more symptoms, diminishment of extent of disease, preventing or delaying spread (e.g., metastasis, for example metastasis to the lung or to the lymph node) of disease, preventing or delaying recurrence of disease, delay or slowing of disease progression, amelioration of the disease state, and remission (whether partial or total). Also encompassed by "treatment" is a reduction of pathological consequence of a proliferative disease. The methods of the invention contemplate any one or more of these aspects of treatment.

[0040] An "agent that modifies the epigenetics in a cell" or "epigenetic modifier" refers to an agent that modifies an epigenetic status of a cell, namely, a phenotype or gene expression in the cell that is caused by mechanisms other than changes in the DNA sequence. An epigenetic status of a cell includes, for example, DNA methylation, histone modification(s) and RNA-associated silencing.

[0041] The term "triple negative breast cancer" used herein refer to individuals who are clinically negative for expression of estrogen receptor (ER), progesterone receptors (PR) and HER2 protein.

[0042] The term "inflammatory breast cancer" used herein refers to a special type of non metastatic breast tumor that is characterized by the presence of invasion of tumor cells into the lymphatics of the dermis and subdermis.

[0043] The term "effective amount" used herein refers to an amount of a compound or composition sufficient to treat a specified disorder, condition or disease such as ameliorate, palliate, lessen, and/or delay one or more of its symptoms. In reference to cancers or other unwanted cell proliferation, an effective amount comprises an amount sufficient to cause a tumor to shrink and/or to decrease the growth rate of the tumor (such as to suppress tumor growth) or to prevent or delay other unwanted cell proliferation.

[0044] The term "individual" is a mammal, including humans. An individual includes, but is not limited to, human, bovine, horse, feline, canine, rodent, or primate. In some embodiments, the individual is human.

[0045] The methods may be practiced in an adjuvant setting. "Adjuvant setting" refers to a clinical setting in which an individual has had a history of a proliferative disease, particularly cancer, and generally (but not necessarily) been responsive to therapy, which includes, but is not limited to, surgery (such as surgical resection), radiotherapy, and chemotherapy. However, because of their history of the proliferative disease (such as cancer), these individuals are considered at risk of development of the disease. Treatment or administration in the "adjuvant setting" refers to a subsequent mode of treatment. The degree of risk (i.e., when an individual in the adjuvant setting is considered as "high risk" or "low risk") depends upon several factors, most usually the extent of disease when first treated.

[0046] The methods provided herein may also be practiced in a "neoadjuvant setting," i.e., the method may be carried out before the primary/definitive therapy. In some embodiments, the individual has previously been treated. In some embodiments, the individual has not previously been treated. In some embodiments, the treatment is a first line therapy.

[0047] It is understood that aspect and embodiments of the invention described herein include "consisting" and/or "consisting essentially of" aspects and embodiments.

[0048] Reference to "about" a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

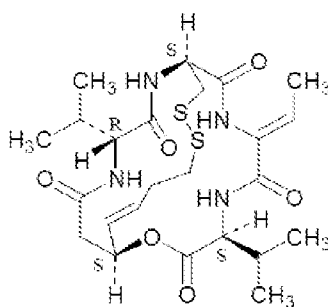
[0049] As used herein and in the appended claims, the singular forms "a," "or," and "the" include plural referents unless the context clearly dictates otherwise. It is understood that aspects and variations of the invention described herein include "consisting" and/or "consisting essentially of" aspects and variations.

Romidepsin

[0050] Romidepsin is a natural product which was isolated from *Chromobacterium violaceum* by Fujisawa Pharmaceuticals (Published Japanese Patent Application No. 64872, U.S. Patent 4,977,138, issued December 11, 1990, Ueda *et al.*, *J. Antibiot* (Tokyo) 47:301-310, 1994; Nakajima *et al.*, *Exp Cell Res* 241:126-133, 1998; and WO 02/20817; each of which is incorporated herein by reference. It is a bicyclic peptide consisting of four amino acid residues (D-valine, D-cysteine, dehydrobutyrine, and L-valine) and a novel acid (3-hydroxy-7-mercapto-4-heptenoic acid) containing both amide and ester bonds. In addition to the production from *C. violaceum* using fermentation, romidepsin can also be prepared by synthetic or semi-synthetic means. The total synthesis of romidepsin reported by Kahn *et al.* involves 14 steps and yields romidepsin in 18% overall yield (Kahn *et al.* *J. Am. Chem. Soc.* 118:7237-7238, 1996).

[0051] The chemical name of romidepsin is (1S,4S,7Z,10S,16E,21R)-7-ethylidene-4,2 1-bis(1-methylethyl)-2-oxa- 12, 13-dithia-5,8,20,23-tetrazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone. The empirical formula is $C_{24}H_{36}N_4O_6S_2$. The molecular weight is 540.71. At room temperature, romidepsin is a white powder.

[0052] It's structure is shown below:



[0053] Romidepsin has been shown to have anti-microbial, immunosuppressive, and anti-tumor activities. It was tested, for example, for use in treating patients with hematological malignancies (*e.g.* cutaneous T-cell lymphoma (CTCL), peripheral T-

cell lymphoma (PTCL), multiple myeloma, *etc*) and solid tumors (*e.g.*, prostate cancer, pancreatic cancer, *etc.*) and is thought to act by selectively inhibiting deacetylases (*e.g.*, histone deacetylase, tubulin deacetylase), thus promising new targets for the development of a new class of anti-cancer therapies (Nakajima *et al.*, *Exp Cell Res* 241 :126-133, 1998). One mode of action of romidepsin involves the inhibition of one or more classes of histone deacetylases (HDAC). Preparations and purification of romidepsin is described, for example, in U.S. Patent 4,977,138 and International PCT Application Publication WO 02/20817, each of which is incorporated herein by reference.

[0054] Exemplary forms of romidepsin include, but are not limited to, salts, esters, pro-drugs, isomers, stereoisomers (*e.g.*, enantiomers, diastereomers), tautomers, protected forms, reduced forms, oxidized forms, derivatives, and combinations thereof, with the desired activity (*e.g.*, deacetylase inhibitory activity, aggressive inhibition, cytotoxicity). In certain embodiments, romidepsin is a pharmaceutical grade material and meets the standards of the U.S. Pharmacopoeia, Japanese Pharmacopoeia, or European Pharmacopoeia. In certain embodiments, the romidepsin is at least 95%, at least 98%, at least 99%, at least 99.9%, or at least 99.95% pure. In certain embodiments, the romidepsin is at least 95%, at least 98%, at least 99%, at least 99.9%, or at least 99.95% monomeric. In certain embodiments, no impurities are detectable in the romidepsin materials (*e.g.*, oxidized material, reduced material, dimerized or oligomerized material, side products, *etc.*). Romidepsin typically includes less than 1.0%, less than 0.5%, less than 0.2%, or less than 0.1% of total other unknowns. The purity of romidepsin may be assessed by appearance, HPLC, specific rotation, NMR spectroscopy, IR spectroscopy, UV/Visible spectroscopy, powder x-ray diffraction (XRPD) analysis, elemental analysis, LC-mass spectroscopy, or mass spectroscopy.

[0055] Romidepsin is sold under the tradename Istodax® and is approved for the treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy, and for the treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

Paclitaxel

[0056] Paclitaxel is a natural product with antitumor activity. TAXOL (paclitaxel) is obtained via a semi-synthetic process from *Taxus baccata*. The chemical name for

paclitaxel is 5P,20-Epoxy-1,2a,4,7P,10p,13a-hexahydroxytax-1 l-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2iR,3S)-N-benzoyl-3-phenylisoserine.

[0057] Paclitaxel is a white to off-white crystalline powder with the empirical formula C₄₇H₅₁N₀₁₄ and a molecular weight of 853.9. It is highly lipophilic, insoluble in water, and melts at around 216-217° C.

Methods of combination therapy

[0058] The present invention provides methods of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of at least one other agent that modifies the epigenetics in a cell.

[0059] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of at least one other agent that modifies the epigenetics in a cell, wherein the composition and the other agent are administered concurrently. In some embodiments, the administrations of the composition and the other agent are initiated at about the same time (for example, within any one of 1, 2, 3, 4, 5, 6, or 7 days). In some embodiments, the administrations of the composition and the other agent are terminated at about the same time (for example, within any one of 1, 2, 3, 4, 5, 6, or 7 days). In some embodiments, the administration of the other agent continues (for example for about any one of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) after the termination of the administration of the composition. In some embodiments, the administration of the other agent is initiated after (for example after about any one of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) the initiation of the administration of the composition. In some embodiments, the administrations of the composition and the other agent are initiated and terminated at about the same time. In some embodiments, the administrations of the composition and the other agent are initiated at about the same time and the administration of the other agent continues (for example for about any one of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) after the termination of the administration of the composition. In some embodiments, the administration of the composition and the other agent stop at about the same time and the administration of the other agent is initiated after (for example after about any one of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) the

initiation of the administration of the composition. In some embodiments, the administration of the composition and the other agent stop at about the same time and the administration of the composition is initiated after (for example after about any one of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) the initiation of the administration of the other agent.

[0060] In some embodiments, the taxane is any of (and in some embodiments consisting essentially of) paclitaxel, docetaxel, and ortataxel. In some embodiments, the taxane is paclitaxel. In some embodiments, the taxane is docetaxel.

[0061] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel)); and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the composition and the other agent are administered concurrently. In some embodiments, the proliferative disease is a cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma.

[0062] In some embodiments, the other agent modifies DNA methylation or histone modification. In some embodiments, the other agent modifies (such as inhibits) DNA methylation. In some embodiments, the other agent modifies histone modification, which include, but not limited to, histone acetylation, histone methylation, histone sumoylation, and histone phosphorylation. In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin).

[0063] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that inhibits DNA methylation. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of

an inhibitor of DNA methyltransferase. Suitable agents that modify DNA methylation include, but are not limited to, 5-azacytidine (azacitidine or Vidaza), 5-aza-2'-deoxycytidine, 1-P-D-arabinofuranosil-5-azacytosine, dihydro-5-azacytidine, antisense oligonucleotide MG98, and zebularine.

[0064] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies histone modification. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies histone acetylation. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies histone methylation. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies histone sumoylation. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies histone phosphorylation.

[0065] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of an inhibitor of a histone deacetylase ("HDAC"). HDACs are classified in four groups based on their homology to yeast histone deacetylases. Class I includes HDAC1, -2, -3 and -8, which are related to yeast RPD3 gene. Class II includes HDAC4, -5, -6, -7, -9 and -10, which are related to yeast Hda1 gene. Class III, also known as the sirtuins, are related to the Sir2 gene and includes SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7. Class IV, which contains only HDAC1 1, has features of both Class I and II. The histone deacetylase inhibitors described herein in some embodiments are specific to only one specific HDAC. In

some embodiments, the histone deacetylase inhibitor is specific to one specific class of HDAC. In some embodiments, the histone deacetylase inhibitor is an inhibitor of two or more HDACs or two or more classes of HDACs. In some embodiments, the histone deacetylase inhibitor inhibits class I and II HDACs. In some embodiments, the histone deacetylase inhibitor inhibits class III HDAC.

[0066] In some embodiments, the other agent is a hydroxamic acid, including, but not limited to, vorinostat (suberoylanilide hydroxamic acid or "SAHA"), trichostatin A ("TSA"), LBH589 (panobinostat), PXD101 (belinostat), oxamflatin, tubacin, seriptaid, NVP-LAQ824, cinnamic acid hydroxamic acid (CBHA), CBHA derivatives, and ITF2357.

[0067] Vorinostat (rINN) or suberoylanilide hydroxamic acid (SAHA) is an inhibitor of histone deacetylases (HDAC). It is marketed under the name Zolinza for the treatment of cutaneous T cell lymphoma (CTCL) when the disease persists, gets worse, or comes back during or after treatment with other medicines.

[0068] Trichostatin A (TSA, 7-[4-(dimethylamino)phenyl]-N-hydroxy-4,6-dimethyl-7-oxohepta-2,4-dienamide) is an organic compound that selectively inhibits the class I and II mammalian histone deacetylase (HDAC) families of enzymes, but not class III HDACs (i.e., Sirtuins). TSA inhibits the eukaryotic cell cycle during the beginning of the growth stage.

[0069] In some embodiments, the other agent is a cyclic peptide, including, but not limited to, trapoxin B, FK228 (romidepsin), trapoxin A, apicidin, depsipeptide, and CHAP.

[0070] In some embodiments, the other agent is a benzamide, including, but not limited to, mocetinostat (MGCD0103), benzamide M344, BML-210, entinostat (SNDX-275 or MS-275), pimelic diphenylamide 4b, pimelic diphenylamide 106, MS-994, CI-994 (acetyldinaline, PD 123654, and 4-acetylamino-N-(Uaminophenyl)-benzamide. Mocetinostat (*N*-(2-Aminophenyl)-4-[[4-pyridin-3-ylpyrimidin-2-yl)amino]methyl] benzamide) works by inhibiting mainly histone deacetylase 1 (HDAC1). It also inhibits HDAC2, HDAC3, and HDAC1 1.

[0071] In some embodiments, the other agent is an electrophilic ketone, including, but not limited to, trifluoromethyl ketones and ketoamides.

[0072] In some embodiments, the other agent is an aliphatic acid compound, including, but not limited to, butyrate, phenylbutyrate, valproic acid (vpa), and phenylacetate.

[0073] In some embodiments, the other agent is selected from the group consisting of vorinostat (SAHA), belinostat (PXD101), LAQ824, panobinostat (LBH589); entinostat (MS275), CI994, and mocetinostat (MGCD0103). In some embodiments, the other agent is selected from the group consisting of vorinostat, romidepsin, panobinostat, valproic acid, and mocetinostat.

[0074] The other agents described herein can be the agents themselves, pharmaceutically acceptable salts thereof, and pharmaceutically acceptable esters thereof, as well as stereoisomer, enantiomers, racemic mixtures, and the like. The other agent or agents as described can be administered as well as a pharmaceutical composition containing the agent(s), wherein the pharmaceutical composition comprises a pharmaceutically acceptable carrier vehicle, or the like.

[0075] Reference to an agent herein applies to the other agent or its derivatives and accordingly the invention contemplates and includes either of these embodiments (agent; agent or derivative(s)). "Derivatives" or "analogs" of an agent or other chemical moiety include, but are not limited to, compounds that are structurally similar to the other agent or moiety or are in the same general chemical class as the other agent or moiety. In some embodiments, the derivative or analog of the other agent or moiety retains similar chemical and/or physical property (including, for example, functionality) of the other agent or moiety.

[0076] In some embodiments, the other agent is vorinostat. Thus, for example, in some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of vorinostat. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of vorinostat. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0077] In some embodiments, the other agent is romidepsin. Thus, for example, in some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of Romidepsin. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of romidepsin. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0078] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of romidepsin, wherein the composition is administered intravenously, wherein the romidepsin is administered orally. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of romidepsin wherein the composition is administered intravenously and wherein the romidepsin is administered orally. In some embodiments, the composition and the romidepsin are administered concurrently. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0079] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as

paclitaxel), wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 10 mg/m² to about 300 mg/m² romidepsin. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 10 mg/m² to about 300 mg/m² romidepsin. In some embodiments, romidepsin is administered orally. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0080] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of azacitidine. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering an effective amount of a composition comprising paclitaxel; b) intravenously or subcutaneously administering an effective amount of azacitidine.

[0081] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as

paclitaxel); and b) an effective amount of azacitidine. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of azacitidine. In some embodiments, the composition and the azacitidine are administered concurrently. In some embodiments, the composition is administered intravenously. In some embodiments, the azacitidine is administered intravenously or subcutaneously. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0082] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of azacitidine, wherein the composition and the azacitidine are administered intravenously. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of azacitidine. In some embodiments, the composition is administered intravenously. In some embodiments, the azacitidine is administered intravenously or subcutaneously. In some embodiments, the composition and the azacitidine are administered concurrently. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0083] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), wherein the taxane is in the dosage range of about 60-300 mg/m²

(including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² for example about 50-100 mg/m² or for example about 75 mg/m²) azacitidine. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² for example about 50-100 mg/m² for example about 75 mg/m²) azacitidine. In some embodiments, the composition is administered intravenously. In some embodiments, the azacitidine is administered intravenously or subcutaneously. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0084] In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²); b) intravenously or subcutaneously administering about 20 to about 200 mg/m² (such as about 50-100 mg/m² or for example about 75 mg/m²) azacitidine. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²) weekly; b) intravenously or subcutaneously administering about 20 to about 200 mg/m² (such as about 50-100 mg/m², for example about 75 mg/m²) azacitidine daily. In some embodiments, the administrations of the composition and the azacitidine are concurrent. In some embodiments, the composition is administered three out of four weeks and the azacitidine is administered on days 1-5 on a four week cycle.

[0085] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the

individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of decitabine. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering an effective amount of a composition comprising paclitaxel; b) intravenously or intraperitoneally administering an effective amount of azacitidine.

[0086] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of decitabine. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of decitabine. In some embodiments, the composition and the decitabine are administered concurrently. In some embodiments, the composition is administered intravenously or intraperitoneally. In some embodiments, the decitabine is administered intravenously or intraperitoneally. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0087] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as

paclitaxel); and b) an effective amount of decitabine, wherein the composition and the decitabine are administered intravenously. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of decitabine. In some embodiments, the composition is administered intravenously. In some embodiments, the decitabine is administered intravenously or intraperitoneally. In some embodiments, the composition and the decitabine are administered concurrently. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0088] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² for example about 50-100 mg/m²) decitabine. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² for example about 50-100 mg/m²) decitabine. In some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² for example about 15-20 mg/m²) decitabine. In some embodiments, the composition is administered intravenously. In some embodiments, the decitabine is administered

intravenously or intraperitoneally. In some embodiments, the proliferative disease is cancer selected from the group consisting of breast cancer, lung cancer (such as small cell lung cancer and non-small cell lung cancer), renal cancer, bladder cancer, pancreatic cancer, ovarian cancer, prostate cancer, brain cancer, colorectal cancer, leukemia, lymphoma, and multiple myeloma. In some embodiments, the cancer is breast cancer, such as triple negative breast cancer. In some embodiments, the cancer is inflammatory breast cancer.

[0089] In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²); b) intravenously or intraperitoneally administering about 5 to about 200 mg/m² (such as about 15-20 mg/m²) decitabine. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²) weekly; b) intravenously or intraperitoneally administering about 5 to about 200 mg/m² (such as about 15-20 mg/m²) decitabine daily. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²) weekly; b) intravenously or intraperitoneally administering about 5 to about 200 mg/m² (such as about 15-20 mg/m²) decitabine every eight hours for three days. In some embodiments, the composition is administered three out of four weeks and the decitabine is administered on days 1-3 on a six week cycle. In some embodiments, the administrations of the composition and the decitabine are concurrent. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²) weekly; b) intravenously or intraperitoneally administering about 5 to about 200 mg/m² (such as about 15-20 mg/m²) decitabine daily for five days. In some embodiments, the administrations of the composition and the decitabine are concurrent. In some

embodiments, the composition is administered three out of four weeks and the decitabine is administered on days 1-5 on a four week cycle.

[0100] In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); and b) an effective amount of azacitidine. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, and b) an effective amount of azacitidine. In some embodiments, the composition is administered intravenously. In some embodiments, the azacitidine is administered intravenously or subcutaneously.

[0101] In some embodiments, the breast cancer is an early stage breast cancer, non-metastatic breast cancer, stage IV breast cancer, locally advanced breast cancer, metastatic breast cancer, hormone receptor positive metastatic breast cancer, breast cancer in remission, breast cancer in an adjuvant setting, ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), or breast cancer in a neoadjuvant setting. In some embodiments, the breast cancer is hormone receptor positive metastatic breast cancer. In some embodiments, the breast cancer (which may be HER2 positive or HER2 negative) is advanced breast cancer. In some embodiments, the breast cancer is ductal carcinoma in situ. In some embodiments, the individual may be a human who has a gene, genetic mutation, or polymorphism associated with breast cancer (*e.g.*, BRCA1, BRCA2, ATM, CHEK2, RAD51, AR, DIRAS3, ERBB2, TP53,

AKT, PTEN, and/or PI3K) or has one or more extra copies of a gene (*e.g.*, one or more extra copies of the HER2 gene) associated with breast cancer.

[0102] In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² or for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² or for example about 50-100 mg/m²) azacitidine. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the paclitaxel is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² or for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² or for example about 50-100 mg/m² or for example about 75 mg/m²) azacitidine. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100 mg/m², and b) about 50 mg/m² to about 100 mg/m² (such as 75 mg/m²) azacitidine. In some embodiments, the composition is administered first followed by administration of the azacitidine. In some embodiments, the azacitidine is administered first followed by administration of the composition. In some embodiments, the administrations of the composition and the azacitidine are concurrent. In some embodiments, the composition is administered three out of four weeks and the azacitidine is administered on the first, second, third, fourth, fifth, or sixth day (such as on days 1-5) on a four week cycle. In some embodiments, the azacitidine is administered on days 1-5, followed by administration of the nanoparticle composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles.

[0103] In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising

administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100 mg/m², and b) about 50 mg/m² to about 100 mg/m² (such as 75 mg/m²) azacitidine, wherein the azacitidine is administered on days 1-5 followed by administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising: a) intravenously administering to the individual an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100-150 mg/m² (such as 100 mg/m²) and b) subcutaneously administering to the individual about 50-100 mg/m² (such as 75 mg/m²) azacitidine, wherein the azacitidine is subcutaneously administered on days 1-5, followed by intravenous administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, the individual suffering from breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) has not had prior cytotoxic regimens. In some embodiments, the individual suffering from breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) has had no more than 2 prior cytotoxic regimens. In some embodiments, the individual suffering from breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) has had more than 2 prior cytotoxic regimens.

[0104] In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of decitabine. In some embodiments, there is provided a method of treating breast cancer (for example,

HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, and b) an effective amount of a DNA methyltransferase inhibitor. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel), and b) an effective amount of decitabine. In some embodiments, the composition is administered intravenously. In some embodiments, the decitabine is administered intravenously or intraperitoneally.

[0105] In some embodiments, the breast cancer is an early stage breast cancer, non-metastatic breast cancer, stage IV breast cancer, locally advanced breast cancer, metastatic breast cancer, hormone receptor positive metastatic breast cancer, breast cancer in remission, breast cancer in an adjuvant setting, ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), or breast cancer in a neoadjuvant setting. In some embodiments, the breast cancer is hormone receptor positive metastatic breast cancer. In some embodiments, the breast cancer (which may be HER2 positive or HER2 negative) is advanced breast cancer. In some embodiments, the breast cancer is ductal carcinoma in situ. In some embodiments, the individual may be a human who has a gene, genetic mutation, or polymorphism associated with breast cancer (*e.g.*, BRCA1, BRCA2, ATM, CHEK2, RAD51, AR, DIRAS3, ERBB2, TP53, AKT, PTEN, and/or PI3K) or has one or more extra copies of a gene (*e.g.*, one or more extra copies of the HER2 gene) associated with breast cancer.

[0106] In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), wherein the taxane is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² or for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² or for example about 15-20 mg/m²) decitabine. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an

individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the paclitaxel is in the dosage range of about 60-300 mg/m² (including for example about 80-200 mg/m² or for example about 100 mg/m²), and b) about 5-500 mg/m² (including for example about 10-200 mg/m² or for example about 15-20 mg/m²) decitabine. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100 mg/m², and b) about 5 mg/m² to about 100 mg/m² (such as 15 mg/m²) decitabine. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100 mg/m², and b) about 5 mg/m² to about 100 mg/m² (such as 20 mg/m²) decitabine. In some embodiments, the composition is administered first followed by administration of the decitabine. In some embodiments, the decitabine is administered first followed by administration of the composition. In some embodiments, the administrations of the composition and the decitabine are concurrent. In some embodiments, the composition is administered three out of four weeks and the decitabine is administered three times a day on the first, second, third, fourth, fifth, or sixth day (such as on days 1-3) on a four week cycle. In some embodiments, the composition is administered three out of four weeks and the decitabine is administered on the first, second, third, fourth, fifth or sixth day (such as on days 1-5) on a four week cycle. In some embodiments, the decitabine is administered three times a day on days 1-3, followed by administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, the decitabine is administered on days 1-5, followed by administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles.

[0107] In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising

paclitaxel, wherein the taxane is in the dosage range of about 100 mg/m², and b) about 5 mg/m² to about 100 mg/m² (such as 15 mg/m²) decitabine, wherein the decitabine is administered three times a day on days 1-3 followed by administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100 mg/m², and b) about 5 mg/m² to about 100 mg/m² (such as 20 mg/m²) decitabine, wherein the decitabine is administered on days 1-5 followed by administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising: a) intravenously administering to the individual an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100-150 mg/m² (such as 100 mg/m²) and b) intravenously or intraperitoneally administering to the individual about 5 mg/m² to about 100 mg/m² (such as 15 mg/m²) decitabine, wherein the decitabine is intravenously or intraperitoneally administered three times a day on days 1-3, followed by intravenous administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, there is provided a method of treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising: a) intravenously administering to the individual an effective amount of a composition comprising paclitaxel, wherein the taxane is in the dosage range of about 100-150 mg/m² (such as 100 mg/m²) and b) intravenously or intraperitoneally administering to the individual about 5-100 mg/m² (such as 20 mg/m²) decitabine, wherein the decitabine is intravenously or intraperitoneally administered on days 1-5, followed by intravenous administration of the composition on days 8, 15, and 22 of a 28-day cycle, for a total of 6 cycles. In some embodiments, the individual suffering from breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) has not had prior cytotoxic regimens. In some embodiments, the individual suffering from breast

cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) has had no more than 2 prior cytotoxic regimens. In some embodiments, the individual suffering from breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer) has had more than 2 prior cytotoxic regimens.

[0108] In some embodiments, the methods further comprise administration of one or more additional agent. In some embodiments, the additional agent is another agent that modifies the epigenetics in a cell, such as the agents described herein. In some embodiments, the additional agent is a chemotherapeutic agent, such as chemotherapeutic agents described in U.S. Patent Application No. 2006/0263434, incorporated herein in its entirety. In some embodiments, the additional agent is any one of dexamethasone, bortezomib, imatinib, sorafenib, gemcitabine, capecitabine, lenalidomide, sunitinib, paclitaxel, and docetaxel. For example, in some embodiments, there is provided a method of treating a proliferative disease, comprising: a) an effective amount of a composition comprising a taxane (such as paclitaxel), b) an effective amount of romidepsin, and c) an effective amount of an additional agent selected from the group consisting of dexamethasone, bortezomib, imatinib, sorafenib, gemcitabine, capecitabine, lenalidomide, sunitinib, paclitaxel, and docetaxel. In some embodiments, there is provided a method of treating a proliferative disease, comprising: a) an effective amount of a composition comprising a taxane (such as paclitaxel), b) an effective amount of romidepsin, and c) an effective amount of capecitabine. In some embodiments, there is provided a method of treating a proliferative disease, comprising: a) an effective amount of a composition comprising a taxane (such as paclitaxel), b) an effective amount of romidepsin, and c) an effective amount of azacitidine.

[0109] In some embodiments, the method further comprises the administration of a platinum-based agent, including for example carboplatin and cisplatin. For example, in some embodiments, there is provided a method of treating a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); b) an effective amount of a histone deacetylase inhibitor, and c) an effective amount of a platinum-based agent. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer, or for example,

inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel); b) an effective amount of a histone deacetylase inhibitor, and c) an effective amount of a platinum-based agent. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising paclitaxel; b) an effective amount of romidepsin, and c) an effective amount of carboplatin. In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising: a) intravenously administering an effective amount of a composition comprising paclitaxel; b) orally administering an effective amount of romidepsin, and c) intravenously administering an effective amount of carboplatin.

[0110] In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²); b) orally administering about 10 mg/m² to about 300 mg/m² of romidepsin, and c) intravenously administering carboplatin at the dose of AUC 2-6 (such as AUC2). In some embodiments, there is provided a method of treating cancer (such as breast cancer, including triple negative breast cancer, or for example, inflammatory breast cancer) in an individual, comprising: a) intravenously administering a composition comprising paclitaxel at the dose of about 80 to about 200 mg/m² (such as about 100 mg/m²) weekly; b) orally administering about 10 mg/m² to about 300 mg/m² of romidepsin three out of seven days, and c) intravenously administering carboplatin at the dose of AUC 2-6 (such as AUC2) weekly. In some embodiments, the administrations of the composition, the romidepsin, and the carboplatin are concurrent. In some embodiments, the composition and the carboplatin are administered on day one of each week, and the romidepsin is administered on days 1-3 of each week.

[0111] The present invention in some embodiments provides a method of treating a proliferative disease in an individual comprising administering to the individual: a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b)

an effective amount of at least one other agent that modifies the epigenetics in a cell. The other agent can be an inhibitor of histone deacetylase (such as romidepsin) or an inhibitor of DNA methyltransferase (such as azacitidine or decitabine). In some embodiments, the method further comprises administering to said individual a platinum-based agent. In some embodiments of any of the methods described herein, the proliferative disease is cancer, such as breast cancer. In some embodiments, the individual is negative for ER, PR, or HER2. In some embodiments, individual is negative for ER, PR, and HER2. In some embodiments, the proliferative disease is ovarian cancer. In some embodiments, the proliferative disease is lung cancer (such as non-small cell lung cancer). In some embodiments of any of the methods described above, the composition comprising taxane and the other agent are administered simultaneously. In some embodiments of any of the methods described above, the composition comprising taxane and the other agent are administered sequentially. In some embodiments of any of the methods described above, the composition comprising taxane and the other agent are administered concurrently.

[0112] In some embodiments of any of the methods described above, the taxane is paclitaxel. In some embodiments of any of the methods described above, the individual is a human.

[0113] The present application also provides pharmaceutical compositions comprising a taxane (such as paclitaxel) for use in the treatment of a proliferative disease (such as cancer), wherein said use comprises simultaneous, sequential, and/or concurrent administration of an agent that modifies the epigenetics in a cell. In some embodiments, the invention provides a pharmaceutical composition comprising an agent that modifies the epigenetics in a cell for use in the treatment of a proliferative disease (such as cancer), wherein said use comprises simultaneous, sequential, and/or concurrent administration of a composition comprising a taxane (such as paclitaxel). In some embodiments, the invention provides taxane-containing compositions and compositions comprising an agent that inhibits prosurvival and/or inflammatory signal for simultaneous, sequential, and/or concurrent use for treatment of a proliferative disease (such as cancer).

[0114] In some embodiments, there is provided a kit comprising: a) a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In one embodiment, the other agent is romidepsin. In some embodiments, there is provided a medicine comprising: a) a

composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. . In one embodiment, the other agent is romidepsin.

Methods of treating proliferative diseases

[0115] The combination therapy methods described herein are useful for treating proliferative diseases. The methods require administration of the composition and the other agent in effective amounts. In some embodiments, an effective amount is an amount sufficient to delay development. In some embodiments, an effective amount is an amount sufficient to prevent or delay recurrence. An effective amount can be administered in one or more administrations. In the case of cancer, the effective amount of the drug or composition may: (i) reduce the number of cancer cells; (ii) reduce tumor size; (iii) inhibit, retard, slow to some extent and preferably stop cancer cell infiltration into peripheral organs; (iv) inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; (v) inhibit tumor growth; (vi) prevent or delay occurrence and/or recurrence of tumor; and/or (vii) relieve to some extent one or more of the symptoms associated with the cancer.

[0116] Thus, in some embodiments, there is provided a method of inhibiting cell proliferation (such as tumor growth) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the effective amounts of the taxane composition and the other agent synergistically inhibit cell proliferation (such as tumor cell growth). In some embodiments, at least about 10% (including for example at least about any of 20%, 30%, 40%, 60%, 70%, 80%, 90%, or 100%) cell proliferation is inhibited. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0117] In some embodiments, there is provided a method of inhibiting tumor metastasis (such as metastasis of breast cancer, pulmonary metastasis or metastasis to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the effective amounts of the taxane composition and the other agent synergistically inhibit tumor metastasis. In some embodiments, at least about 10% (including for example at least about any of 20%, 30%, 40%, 60%, 70%, 80%, 90%, or 100%) metastasis is inhibited. In some embodiments, method of inhibiting metastasis to lymph node is provided. In some embodiments, method of inhibiting metastasis to the lung is provided. In some embodiments, the taxane is paclitaxel. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0118] In some embodiments, there is provided a method of reducing (such as eradicating) pre-existing tumor metastasis (such as pulmonary metastasis or metastasis to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the effective amounts of the taxane composition and the other agent synergistically reduces (such as eradicates) tumor metastasis. In some embodiments, at least about 10% (including for example at least about any of 20%, 30%, 40%, 60%, 70%, 80%, 90%, or 100%) metastasis is reduced. In some embodiments, method of reducing metastasis to lymph node is provided. In some embodiments, method of reducing metastasis to the lung is provided. In some embodiments, the taxane is paclitaxel. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as

decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0119] In some embodiments, there is provided a method of reducing incidence or burden of preexisting tumor metastasis (such as pulmonary metastasis or metastasis to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0120] In some embodiments, there is provided a method of reducing tumor size in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the effective amounts of the taxane composition and the other agent synergistically reduces tumor size. In some embodiments, the tumor size is reduced at least about 10% (including for example at least about any of 20%, 30%, 40%, 60%, 70%, 80%, 90%, or 100%). In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0121] In some embodiments, there is provided a method of prolonging time to disease progression of a proliferative disease (such as cancer) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the method prolongs the time to disease progression by at least any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0122] In some embodiments, there is provided a method of prolonging survival of an individual having a proliferative disease (such as cancer), comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the method prolongs the survival of the individual by at least any of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, or 24 month. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the other agent is administered intravenously or subcutaneously.

[0123] It is understood that any of the embodiments in this section apply to the embodiments provided in the section "methods of combination therapy." For example, in some embodiments, there is provided a method of reducing (such as eradicating) pre-existing tumor metastasis (such as pulmonary metastasis or metastasis

to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of a vorinostat, wherein the composition and the romdiepsin are administered concurrently. In some embodiments, there is provided a method of reducing (such as eradiating) pre-existing tumor metastasis (such as pulmonary metastasis or metastasis to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of paclitaxel, and b) an effective amount of th romidepsin, wherein the composition and the romidepsin are administered concurrently. In some embodiments, there is provided a method of reducing (such as eradiating) pre-existing tumor metastasis (such as pulmonary metastasis or metastasis to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of a composition comprising taxane, and b) an effective amount of a histone deacetylase inhibitor, wherein the composition and the histone deacetylase inhibitor are administered concurrently. In some embodiments, there is provided a method of reducing (such as eradiating) pre-existing tumor metastasis (such as pulmonary metastasis or metastasis to the lymph node) in an individual, comprising administering to the individual: a) an effective amount of paclitaxel, and b) an effective amount of a histone deacetylase inhibitor, wherein the composition and the bcl-2 are administered concurrently.

[0124] The effectiveness of the methods of the present invention can be assessed by one or more criteria, which include, but are not limited to, markers of proliferation and/or apoptosis, gene methylation, gene expression profile, and tissue histone acetylation. In some embodiments, the effectiveness of the method can be assessed by functional imaging, such as PET/CT scans and/or fludeoxyglucose F 18-position emission tomography (FDG-PET) (Sun, X. et al. J. Nucl. Med. (201 1) 52(1): 140-146).

[0125] Thus, for example, in some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel) and b) an effective amount of at least one other agent that modifies the epigenetics in a cell, wherein the standard uptake value (SUV) determined in a FDG-PET scan in the individual is decreased by at least about any of 10%, 20%>, 30%>, 40%>, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such

asromidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the method further comprises determining a baseline SUV value in the individual prior to the treatment. In some embodiments, the method further comprises determining the SUV value in the individual after the treatment.

[0126] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell, wherein the level of C1D15 is decreased by at least about any of 10%, 20%>, 30%>, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the method further comprises determining a baseline C1D15 level in the individual prior to the treatment. In some embodiments, the method further comprises determining the C1D15 level in the individual after the treatment.

[0127] In some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell, wherein the level of DNA methylation in one or more genes in the individual is decreased by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some

embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the method further comprises determining a baseline DNA methylation level in the individual prior to the treatment. In some embodiments, the method further comprises determining the DNA methylation level in the individual after the treatment. In some embodiments, the level of DNA methylation is determined based on the methylation of one or more target genes, such as ER-alpha, APC-1, RAR-beta, cyclin D2, Twist, RASSF1A, and HIN-1. The levels of methylation can be determined, for example, by quantitative multiplex methylation-specific PCR.

[0128] In some embodiments, the responsiveness of the method is determined by gene expression profile. For example, in some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell, wherein the level of expression in one or more genes in the individual is changed by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the method further comprises determining a baseline gene expression profile in the individual prior to the treatment. In some embodiments, the method further comprises determining the gene expression profile in the individual after the treatment. Changes of gene expression can be determined, for example, by RT-PCR or immunohistochemistry.

[0129] In some embodiments, the responsiveness of the method is determined by the level of histone deacetylation. For example, in some embodiments, there is provided a method of treating a proliferative disease (such as cancer), comprising administering to the individual a) an effective amount of a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell, wherein the level of histone deacetylation in the individual is decreased by at least about any of 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or 95%. In some embodiments, the taxane is paclitaxel. In some embodiments, the other agent is an inhibitor of a histone deacetylase (such as romidepsin). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as azacitidine). In some embodiments, the other agent is an inhibitor of DNA methyltransferase (such as decitabine). In some embodiments, the taxane in the composition is administered by intravenous administration. In some embodiments, the other agent is administered by intraperitoneal administration. In some embodiments, the other agent is administered by oral administration. In some embodiments, the method further comprises determining a baseline histone acetylation level in the individual prior to the treatment. In some embodiments, the method further comprises determining the histone acetylation level in the individual after the treatment. Level of histone acetylation can be determined, for example, by determination of histone acetylation level in tissue and/or peripheral blood mononuclear cells.

[0130] The treatment methods can also be evaluated for safety and toxicity, for example, based on NCI CTCAE analyses.

[0131] The methods described herein are useful for treating various diseases. In some embodiments, the proliferative disease is a non-cancerous disease, including, but not limited to, fibrosis (especially pulmonary, but also other types of fibrosis, such as renal fibrosis), angiogenesis, psoriasis, atherosclerosis and smooth muscle proliferation in the blood vessels, such as stenosis or restenosis following angioplasty. In some embodiments, there is provided a method of treating any of the following diseases: restenosis, stenosis, fibrosis, angiogenesis, psoriasis, atherosclerosis, and proliferation of smooth muscle cells.

[0132] In some embodiments, the proliferative disease is cancer. In some embodiments, the proliferative disease is a benign or malignant tumor. Where hereinbefore and subsequently a tumor, a tumor disease, a carcinoma or a cancer are

mentioned, also metastasis in the original organ or tissue and/or in any other location are implied alternatively or in addition, whatever the location of the tumor and/or metastasis is.

[0133] In some embodiments, the method is used to treat a primary tumor. In some embodiments, a method of treating metastatic cancer (that is, cancer that has metastasized from the primary tumor) is provided. In some embodiments, the method is for the treatment of an advanced disease or a lesser extent of disease, such as low tumor burden. In some embodiments, there is provided a method of treating cancer at an advanced stage. In some embodiments, the method is for the treatment of an early stage breast cancer. The methods may be practiced in an adjuvant setting. The methods provided herein may also be practiced in a neoadjuvant setting, *i.e.*, the method may be carried out before the primary/definitive therapy. In some embodiments, the method further comprises conducting surgery on the individual following the completion of the treatment. For example, in some embodiments when the cancer is breast cancer, breast conserving surgery or mastectomy can be carried out within about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 weeks after completion of the neoadjuvant chemotherapy.

[0134] In some embodiments, the individual has previously been treated. In some embodiments, the individual has not previously been treated. In some embodiments, the treatment is a first line therapy. In some embodiments, the breast cancer has reoccurred after a remission.

[0135] In some embodiments, the cancer is breast cancer. These methods can be used, for example, to treat, stabilize, prevent, and/or delay any type or stage of breast cancer, such as early stage breast cancer, non-metastatic breast cancer, advanced breast cancer, stage IV breast cancer, locally advanced breast cancer, metastatic breast cancer, breast cancer in remission, breast cancer in an adjuvant setting, or breast cancer in a neoadjuvant setting. In some embodiments, the method is useful for preoperative systemic therapy (PST).

[0136] In some embodiments, there is provided a method of treating breast cancer (which may be HER2 positive or HER2 negative), including, for example, advanced breast cancer, stage IV breast cancer, locally advanced breast cancer, and metastatic breast cancer. In some embodiments, the breast cancer is inflammatory breast cancer. In some embodiments, the breast cancer is basal cell breast cancer. In some embodiments, the individual is diagnosed with T2, T3, or T4 lesion, or a stage N, M0

or Tic, N1-3 and MO. In some embodiments, the individual has an ECOG performance status of 0-1. In some embodiments, the individual has skin metastasis to the ipsilateral breast. In some embodiments, the individual has undergone prior therapy (such as hormonal therapy). In some embodiments, the individual has not undergone prior therapy (such as hormonal therapy). In some embodiments, the individual is awaiting definitive surgery. In some embodiments, the breast cancer is resected breast cancer. In some embodiments, the breast cancer is unresected breast cancer, such as unresected stage II or III breast cancer.

[0137] In some embodiments, the method is for treating an individual having one or more of these risk factors resulting in a higher probability of developing breast cancer than an individual without these risk factor(s). These risk factors include, but are not limited to, age, sex, race, diet, history of previous disease, presence of precursor disease, genetic (i.e., hereditary) considerations, and environmental exposure. In some embodiments, the individual may be a human who is genetically or otherwise predisposed to developing breast cancer who has or has not been diagnosed with breast cancer. Individuals at risk for breast cancer include, e.g., those having relatives who have experienced this disease, and those whose risk is determined by analysis of genetic or biochemical markers. For example, the individual may be a human who has a gene, genetic mutation, or polymorphism associated with breast cancer (e.g., BRCA1, BRCA2, ATM, CHEK2, RAD51, AR, DIRAS3, ERBB2, and/or TP53) or has one or more extra copies of a gene (e.g., one or more extra copies of the HER2 gene) associated with breast cancer. In some embodiments, the breast cancer is HER2 negative. In some embodiments, the breast cancer is ER negative. In some embodiments, the breast cancer is PR negative. In some embodiments, the breast cancer is EP negative and HER2 negative. In some embodiments, the breast cancer is PR negative and HER2 negative. In some embodiments, the breast cancer is ER negative and PR negative. In some embodiment, the breast cancer is ER negative, PR negative, and HER2 negative.

[0138] The methods described herein are also useful for treating other solid tumors (such as advanced solid tumors). In some embodiments, there is provided a method of treating lung cancer, including, for example, non-small cell lung cancer (NSCLC, such as advanced NSCLC), small cell lung cancer (SCLC, such as advanced SCLC), and advanced solid tumor malignancy in the lung. In some embodiments, there is provided a method of treating any of ovarian cancer, head and neck cancer,

gastric malignancies, melanoma (including metastatic melanoma and malignant melanoma), ovarian cancer, colorectal cancer, and pancreatic cancer.

[0139] In some embodiments, the method is useful for treating one or more of the following: cutaneous T cell lymphoma (CTCL), leukemia, follicular lymphoma, Hodgkin lymphoma, and acute myeloid leukemia.

[0140] In some embodiments, the disease is a cancer of any one of the following: basal cell carcinoma, medulloblastoma, glioblastoma, multiple myeloma, chronic myelogenous leukemia (CML), acute myelogenous leukemia, pancreatic cancer, lung cancer (small cell lung cancer and non-small cell lung cancer), esophageal cancer, stomach cancer, biliary cancer, prostate cancer, liver cancer, hepatocellular cancer, gastrointestinal cancer, gastric cancer, and ovarian and bladder cancer. In some embodiments, the cancer is selected from the group consisting of pancreas ductal adenocarcinoma, colon adenocarcinoma, and ovary cystadenocarcinoma. In some embodiments, the cancer is pancreas ductal adenocarcinoma. In some embodiments, the cancer is a tumor that is poorly perfused and/or poorly vascularized.

[0141] In some embodiments, the cancer is pancreatic cancer, including for example pancreatic adenocarcinoma, pancreatic adenosquamous carcinoma, pancreatic squamous cell carcinoma, and pancreatic giant cell carcinoma. In some embodiments, the pancreatic cancer is exocrine pancreatic cancer. In some embodiments, the pancreatic cancer is endocrine pancreatic cancer (such as islet cell carcinoma). In some embodiments, the pancreatic cancer is advanced metastatic pancreatic cancer.

[0142] Other examples of cancers that may be treated by the methods of the invention include, but are not limited to, adenocortical carcinoma, agnogenic myeloid metaplasia, AIDS-related cancers (e.g., AIDS-related lymphoma), anal cancer, appendix cancer, astrocytoma (e.g., cerebellar and cerebral), basal cell carcinoma, bile duct cancer (e.g., extrahepatic), bladder cancer, bone cancer, (osteosarcoma and malignant fibrous histiocytoma), brain tumor (e.g., glioma, brain stem glioma, cerebellar or cerebral astrocytoma (e.g., pilocytic astrocytoma, diffuse astrocytoma, anaplastic (malignant) astrocytoma), malignant glioma, ependymoma, oligodenglioma, meningioma, craniopharyngioma, haemangioblastomas, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, and glioblastoma), breast cancer, bronchial adenomas/carcinoids, carcinoid tumor (e.g., gastrointestinal carcinoid tumor),

carcinoma of unknown primary, central nervous system lymphoma, cervical cancer, colon cancer, colorectal cancer, chronic myeloproliferative disorders, endometrial cancer (e.g., uterine cancer), ependymoma, esophageal cancer, Ewing's family of tumors, eye cancer (e.g., intraocular melanoma and retinoblastoma), gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, (e.g., extracranial, extragonadal, ovarian), gestational trophoblastic tumor, head and neck cancer, hepatocellular (liver) cancer (e.g., hepatic carcinoma and hepatoma), hypopharyngeal cancer, islet cell carcinoma (endocrine pancreas), laryngeal cancer, leukemia, lip and oral cavity cancer, oral cancer, liver cancer, lung cancer (e.g., small cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung, and squamous carcinoma of the lung), lymphoid neoplasm (e.g., lymphoma), medulloblastoma, ovarian cancer, mesothelioma, metastatic squamous neck cancer, mouth cancer, multiple endocrine neoplasia syndrome, myelodysplasia syndromes, myelodysplastic/myeloproliferative diseases, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, neuroendocrine cancer, oropharyngeal cancer, ovarian cancer (e.g., ovarian epithelial cancer, ovarian germ cell tumor, ovarian low malignant potential tumor), pancreatic cancer, parathyroid cancer, penile cancer, cancer of the peritoneal, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, pleuropulmonary blastoma, lymphoma, primary central nervous system lymphoma (microglioma), pulmonary lymphangiomyomatosis, rectal cancer, renal cancer, renal pelvis and ureter cancer (transitional cell cancer), rhabdomyosarcoma, salivary gland cancer, skin cancer (e.g., non-melanoma (e.g., squamous cell carcinoma), melanoma, and Merkel cell carcinoma), small intestine cancer, squamous cell cancer, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, tuberous sclerosis, urethral cancer, vaginal cancer, vulvar cancer, Wilms' tumor, and post-transplant lymphoproliferative disorder (PTLD), abnormal vascular proliferation associated with phakomatoses, edema (such as that associated with brain tumors), and Meigs' syndrome.

[0143] In some embodiments, the cancer is a solid tumor (such as advanced solid tumor). Solid tumor includes, but is not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma,

lymphangioendotheliosarcoma, Kaposi's sarcoma, soft tissue sarcoma, uterine sacronomasynovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma (including for example adenocarcinoma, clear cell renal cell carcinoma, papillary renal cell carcinoma, chromophobe renal cell carcinoma, collecting duct renal cell carcinoma, granular renal cell carcinoma, mixed granular renal cell carcinoma, renal angiomyolipomas, or spindle renal cell carcinoma.), hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, and retinoblastoma.

[0144] In some embodiments the lymphoid neoplasm (*e.g.*, lymphoma) is a B-cell neoplasm. Examples of B-cell neoplasms include, but are not limited to, precursor B-cell neoplasms (*e.g.*, precursor B-lymphoblastic leukemia/lymphoma) and peripheral B-cell neoplasms (*e.g.*, B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/small lymphocytic lymphoma (small lymphocytic (SL) NHL), lymphoplasmacytoid lymphoma/immunocytoma, mantle cell lymphoma, follicle center lymphoma, follicular lymphoma (*e.g.*, cytologic grades: I (small cell), II (mixed small and large cell), III (large cell) and/or subtype: diffuse and predominantly small cell type), low grade/follicular non-Hodgkin's lymphoma (NHL), intermediate grade/follicular NHL, marginal zone B-cell lymphoma (*e.g.*, extranodal (*e.g.*, MALT-type +/- monocytoid B cells) and/or Nodal (*e.g.*, +/- monocytoid B cells)), splenic marginal zone lymphoma (*e.g.*, +/- villous lymphocytes), Hairy cell leukemia, plasmacytoma/plasma cell myeloma (*e.g.*, myeloma and multiple myeloma), diffuse large B-cell lymphoma (*e.g.*, primary mediastinal (thymic) B-cell lymphoma), intermediate grade diffuse NHL, Burkitt's lymphoma, High-grade B-cell lymphoma, Burkitt-like, high grade immunoblastic NHL, high grade lymphoblastic NHL, high grade small non-cleaved cell NHL, bulky disease NHL, AIDS-related lymphoma, and Waldenstrom's macroglobulinemia).

[0145] In some embodiments the lymphoid neoplasm (*e.g.*, lymphoma) is a T-cell and/or putative NK-cell neoplasm. Examples of T-cell and/or putative NK-cell neoplasms include, but are not limited to, precursor T-cell neoplasm (precursor T-lymphoblastic lymphoma/leukemia) and peripheral T-cell and NK-cell neoplasms (*e.g.*, T-cell chronic lymphocytic leukemia/prolymphocytic leukemia, and large granular lymphocyte leukemia (LGL) (*e.g.*, T-cell type and/or NK-cell type), cutaneous T-cell lymphoma (*e.g.*, mycosis fungoides/Sezary syndrome), primary T-cell lymphomas unspecified (*e.g.*, cytological categories (*e.g.*, medium-sized cell, mixed medium and large cell), large cell, lymphoepitheloid cell, subtype hepatosplenic $\gamma\delta$ T-cell lymphoma, and subcutaneous panniculitic T-cell lymphoma), angioimmunoblastic T-cell lymphoma (AILD), angiocentric lymphoma, intestinal T-cell lymphoma (*e.g.*, +/- enteropathy associated), adult T-cell lymphoma/leukemia (ATL), anaplastic large cell lymphoma (ALCL) (*e.g.*, CD30+, T- and null-cell types), anaplastic large-cell lymphoma, and Hodgkin's like).

[0146] In some embodiments the lymphoid neoplasm (*e.g.*, lymphoma) is Hodgkin's disease. For example, the Hodgkin's disease may be lymphocyte predominance, nodular sclerosis, mixed cellularity, lymphocyte depletion, and/or lymphocyte-rich.

[0147] In some embodiments, the cancer is leukemia. In some embodiments, the leukemia is chronic leukemia. Examples of chronic leukemia include, but are not limited to, chronic myelocytic I (granulocytic) leukemia, chronic myelogenous, and chronic lymphocytic leukemia (CLL). In some embodiments, the leukemia is acute leukemia. Examples of acute leukemia include, but are not limited to, acute lymphoblastic leukemia (ALL), acute myeloid leukemia, acute lymphocytic leukemia, and acute myelocytic leukemia (*e.g.*, myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia).

[0148] In some embodiments, the cancer is liquid tumor or plasmacytoma. Plasmacytoma includes, but is not limited to, myeloma. Myeloma includes, but is not limited to, an extramedullary plasmacytoma, a solitary myeloma, and multiple myeloma. In some embodiments, the plasmacytoma is multiple myeloma.

[0149] In some embodiments, the cancer is multiple myeloma. Examples of multiple myeloma include, but are not limited to, IgG multiple myeloma, IgA multiple myeloma, IgD multiple myeloma, IgE multiple myeloma, and nonsecretory multiple myeloma. In some embodiments, the multiple myeloma is IgG multiple

myeloma. In some embodiments, the multiple myeloma is IgA multiple myeloma. In some embodiments, the multiple myeloma is a smoldering or indolent multiple myeloma. In some embodiments, the multiple myeloma is progressive multiple myeloma. In some embodiments, multiple myeloma may be resistant to a drug, such as, but not limited to, bortezomib, dexamethasone (Dex-), doxorubicin (Dox-), and melphalan (LR).

Modes of administration

[0150] The composition comprising taxane (also referred to as "composition") and the other agent can be administered simultaneously (i.e., simultaneous administration) and/or sequentially (i.e., sequential administration).

[0151] In some embodiments, the composition and the other agent (including the specific agents described herein) are administered simultaneously. The term "simultaneous administration," as used herein, means that the composition and the other agent are administered with a time separation of no more than about 15 minute(s), such as no more than about any of 10, 5, or 1 minutes. When the drugs are administered simultaneously, the drug and the other agent may be contained in the same composition (e.g., a composition comprising both the drug and the other agent) or in separate compositions (e.g., the drug is contained in one composition and the other agent is contained in another composition).

[0152] In some embodiments, the composition and the other agent are administered sequentially. The term "sequential administration" as used herein means that the drug in the composition and the other agent are administered with a time separation of more than about 15 minutes, such as more than about any of 20, 30, 40, 50, 60 or more minutes. Either the composition or the other agent may be administered first. The composition and the other agent are contained in separate compositions, which may be contained in the same or different packages.

[0153] In some embodiments, the administration of the composition and the other agent are concurrent, i.e., the administration period of the composition and that of the other agent overlap with each other. In some embodiments, the composition is administered for at least one cycle (for example, at least any of 2, 3, or 4 cycles) prior to the administration of the other agent. In some embodiments, the other agent is administered for at least any of one, two, three, or four weeks. In some embodiments, the administrations of the composition and the other agent are initiated at about the

same time (for example, within any one of 1, 2, 3, 4, 5, 6, or 7 days). In some embodiments, the administrations of the composition and the other agent are terminated at about the same time (for example, within any one of 1, 2, 3, 4, 5, 6, or 7 days). In some embodiments, the administration of the other agent continues (for example for about any one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) after the termination of the administration of the composition. In some embodiments, the administration of the other agent is initiated after (for example after about any one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or we months) the initiation of the administration of the composition. In some embodiments, the administrations of the composition and the other agent are initiated and terminated at about the same time. In some embodiments, the administrations of the composition and the other agent are initiated at about the same time and the administration of the other agent continues (for example for about any one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months) after the termination of the administration of the composition. In some embodiments, the administration of the composition and the other agent stop at about the same time and the administration of the other agent is initiated after (for example after about any one of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or we months) the initiation of the administration of the composition.

[0154] In some embodiments, the administration of the composition and the other agent are non-concurrent. For example, in some embodiments, the administration of the composition is terminated before the other agent is administered. In some embodiments, the administration of the other agent is terminated before the composition is administered. The time period between these two non-concurrent administrations can range from about two to eight weeks, such as about four weeks.

[0155] The dosing frequency of the drug-containing composition and the other agent may be adjusted over the course of the treatment, based on the judgment of the administering physician. When administered separately, the drug-containing composition and the other agent can be administered at different dosing frequency or intervals. For example, the drug-containing composition can be administered weekly, while another agent can be administered more or less frequently. In some embodiments, sustained continuous release formulation of the composition or an agent may be used. Various formulations and devices for achieving sustained release are known in the art. Exemplary dosing frequencies are further provided herein.

[0156] The composition and the other agent can be administered using the same route of administration or different routes of administration. Exemplary administration routes are further provided herein. In some embodiments (for both simultaneous and sequential administrations), the taxane in the composition and the other agent are administered at a predetermined ratio. For example, in some embodiments, the ratio by weight of the taxane in the composition and the other agent is about 1 to 1. In some embodiments, the weight ratio may be between about 0.001 to about 1 and about 1000 to about 1, or between about 0.01 to about 1 and 100 to about 1. In some embodiments, the ratio by weight of the taxane in the composition and the other agent is less than about any of 100:1, 50:1, 30:1, 10:1, 9:1, 8:1, 7:1, 6:1, 5:1, 4:1, 3:1, 2:1, and 1:1. In some embodiments, the ratio by weight of the taxane in the composition and the other agent is more than about any of 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 30:1, 50:1, 100:1. Other ratios are contemplated.

[0157] The doses required for the taxane and/or the other agent may (but not necessarily) be lower than what is normally required when each agent is administered alone. Thus, in some embodiments, a subtherapeutic amount of the drug in the composition and/or the other agent are administered. "Subtherapeutic amount" or "subtherapeutic level" refer to an amount that is less than therapeutic amount, that is, less than the amount normally used when the drug in the composition and/or the other agent are administered alone. The reduction may be reflected in terms of the amount administered at a given administration and/or the amount administered over a given period of time (reduced frequency).

[0158] In some embodiments, enough other agent is administered so as to allow reduction of the normal dose of the drug in the composition required to effect the same degree of treatment by at least about any of 5%, 10%, 20%, 30%>, 50%>, 60%>, 70%>, 80%>, 90%>, or more. In some embodiments, enough drug in the composition is administered so as to allow reduction of the normal dose of the other agent required to effect the same degree of treatment by at least about any of 5%>, 10%>, 20%>, 30%>, 50%, 60%, 70%, 80%, 90%, or more.

[0159] In some embodiments, the dose of both the taxane in the composition and the other agent are reduced as compared to the corresponding normal dose of each when administered alone. In some embodiments, both the taxane in the composition and the other agent are administered at a subtherapeutic, i.e., reduced, level. In some embodiments, the dose of the composition and/or the other agent is substantially less

than the established maximum toxic dose (MTD). For example, the dose of the composition and/or the other agent is less than about 50%, 40%>, 30%>, 20%>, or 10%> of the MTD.

[0160] In some embodiments, the dose of taxane and/or the dose of the other agent is higher than what is normally required when each agent is administered alone. For example, in some embodiments, the dose of the composition and/or the other agent is substantially higher than the established maximum toxic dose (MTD). For example, the dose of the composition and/or the other agent is more than about 50%, 40%, 30%, 20%, or 10% of the MTD of the agent when administered alone.

[0161] In some embodiments, the amount of a taxane (e.g., paclitaxel) in the composition is included in any of the following ranges: about 0.5 to about 5 mg, about 5 to about 10 mg, about 10 to about 15 mg, about 15 to about 20 mg, about 20 to about 25 mg, about 20 to about 50 mg, about 25 to about 50 mg, about 50 to about 75 mg, about 50 to about 100 mg, about 75 to about 100 mg, about 100 to about 125 mg, about 125 to about 150 mg, about 150 to about 175 mg, about 175 to about 200 mg, about 200 to about 225 mg, about 225 to about 250 mg, about 250 to about 300 mg, about 300 to about 350 mg, about 350 to about 400 mg, about 400 to about 450 mg, or about 450 to about 500 mg. In some embodiments, the amount of a taxane (e.g., paclitaxel) or derivative thereof in the effective amount of the composition (e.g., a unit dosage form) is in the range of about 5 mg to about 500 mg, such as about 30 mg to about 300 mg or about 50 mg to about 200 mg. In some embodiments, the concentration of the taxane (e.g., paclitaxel) in the composition is dilute (about 0.1 mg/ml) or concentrated (about 100 mg/ml), including for example any of about 0.1 to about 50 mg/ml, about 0.1 to about 20 mg/ml, about 1 to about 10 mg/ml, about 2 mg/ml to about 8 mg/ml, about 4 to about 6 mg/ml, about 5 mg/ml. In some embodiments, the concentration of the taxane (e.g., paclitaxel) is at least about any of 0.5 mg/ml, 1.3 mg/ml, 1.5 mg/ml, 2 mg/ml, 3 mg/ml, 4 mg/ml, 5 mg/ml, 6 mg/ml, 7 mg/ml, 8 mg/ml, 9 mg/ml, 10 mg/ml, 15 mg/ml, 20 mg/ml, 25 mg/ml, 30 mg/ml, 40 mg/ml, or 50 mg/ml.

[0162] Exemplary effective amounts of a taxane (e.g., paclitaxel) in the composition include, but are not limited to, at least about any of 25 mg/m², 30 mg/m², 50 mg/m², 60 mg/m², 75 mg/m², 80 mg/m², 90 mg/m², 100 mg/m², 120 mg/m², 125 mg/m², 150 mg/m², 160 mg/m², 175 mg/m², 180 mg/m², 200 mg/m², 210 mg/m², 220 mg/m², 250 mg/m², 260 mg/m², 300 mg/m², 350 mg/m², 400 mg/m², 500 mg/m², 540

mg/m², 750 mg/m², 1000 mg/m², or 1080 mg/m² of a taxane (e.g., paclitaxel). In various embodiments, the composition includes less than about any of 350 mg/m², 300 mg/m², 250 mg/m², 200 mg/m², 150 mg/m², 120 mg/m², 100 mg/m², 90 mg/m², 50 mg/m², or 30 mg/m² of a taxane (e.g., paclitaxel). In some embodiments, the amount of the taxane (e.g., paclitaxel) per administration is less than about any of 25 mg/m², 22 mg/m², 20 mg/m², 18 mg/m², 15 mg/m², 14 mg/m², 13 mg/m², 12 mg/m², 11 mg/m², 10 mg/m², 9 mg/m², 8 mg/m², 7 mg/m², 6 mg/m², 5 mg/m², 4 mg/m², 3 mg/m², 2 mg/m², or 1 mg/m². In some embodiments, the effective amount of a taxane (e.g., paclitaxel) in the composition is included in any of the following ranges: about 1 to about 5 mg/m², about 5 to about 10 mg/m², about 10 to about 25 mg/m², about 25 to about 50 mg/m², about 50 to about 75 mg/m², about 75 to about 100 mg/m², about 100 to about 125 mg/m², about 125 to about 150 mg/m², about 150 to about 175 mg/m², about 175 to about 200 mg/m², about 200 to about 225 mg/m², about 225 to about 250 mg/m², about 250 to about 300 mg/m², about 300 to about 350 mg/m², or about 350 to about 400 mg/m². In some embodiments, the effective amount of a taxane (e.g., paclitaxel) in the composition is about 5 to about 300 mg/m², such as about 20 to about 300 mg/m², about 50 to about 250 mg/m², about 100 to about 150 mg/m², about 120 mg/m², about 130 mg/m², or about 140 mg/m², or about 260 mg/m².

[0163] In some embodiments of any of the above aspects, the effective amount of a taxane (e.g., paclitaxel) in the composition includes at least about any of 1 mg/kg, 2.5 mg/kg, 3.5 mg/kg, 5 mg/kg, 6.5 mg/kg, 7.5 mg/kg, 10 mg/kg, 15 mg/kg, or 20 mg/kg. In various embodiments, the effective amount of a taxane (e.g., paclitaxel) in the composition includes less than about any of 350 mg/kg, 300 mg/kg, 250 mg/kg, 200 mg/kg, 150 mg/kg, 100 mg/kg, 50 mg/kg, 25 mg/kg, 20 mg/kg, 10 mg/kg, 7.5 mg/kg, 6.5 mg/kg, 5 mg/kg, 3.5 mg/kg, 2.5 mg/kg, or 1 mg/kg of a taxane (e.g., paclitaxel).

[0164] Exemplary dosing frequencies for the composition (and as indicated below for the other agent) include, but are not limited to, weekly without break; weekly, three out of four weeks; once every three weeks; once every two weeks; weekly, two out of three weeks. In some embodiments, the composition is administered about once every 2 weeks, once every 3 weeks, once every 4 weeks, once every 6 weeks, or once every 8 weeks. In some embodiments, the composition is administered at least about any of 1x, 2x, 3x, 4x, 5x, 6x, or 7x (i.e., daily) a week, or three times daily, two times

daily. In some embodiments, the intervals between each administration are less than about any of 6 months, 3 months, 1 month, 20 days, 15 days, 12 days, 10 days, 9 days, 8 days, 7 days, 6 days, 5 days, 4 days, 3 days, 2 days, or 1 day. In some embodiments, the intervals between each administration are more than about any of 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 8 months, or 12 months. In some embodiments, there is no break in the dosing schedule. In some embodiments, the interval between each administration is no more than about a week.

[0165] In some embodiments, the taxane in the composition is administered weekly. In some embodiments, the taxane in the composition is administered every two weeks. In some embodiments, the taxane in the composition is administered every three weeks. In some embodiments, the other agent is administered 1x, 2x, 3x, 4x, 5x, 6x, or 7 times a week. In some embodiments, the other agent is administered every two weeks or two out of three weeks. In some embodiments, the taxane is paclitaxel. In some embodiment, the other agent is romidepsin. In some embodiments of the above dosages and/or administrations, the taxane is paclitaxel and the other agent is vorinostat.

[0166] The administration of the composition (and for the other agent) can be extended over an extended period of time, such as from about a month up to about seven years. In some embodiments, the composition is administered over a period of at least about any of 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 18, 24, 30, 36, 48, 60, 72, or 84 months. In some embodiments, the taxane (e.g., paclitaxel) is administered over a period of at least one month, wherein the interval between each administration is no more than about a week, and wherein the dose of the taxane (e.g., paclitaxel) at each administration is about 0.25 mg/m² to about 75 mg/m², such as about 0.25 mg/m² to about 25 mg/m² or about 25 mg/m² to about 50 mg/m².

[0167] In some embodiments, the dosage of a taxane (e.g., paclitaxel) in a composition can be in the range of 5-400 mg/m² when given on a 3 week schedule, or 5-250 mg/m² when given on a weekly schedule. For example, the amount of a taxane (e.g., paclitaxel) can be about 60 to about 300 mg/m² (e.g., about 260 mg/m²) when given on a three week schedule.

[0168] Other exemplary dosing schedules for the administration of the composition include, but are not limited to, 100 mg/m², weekly, without break; 75 mg/m² weekly, 3 out of four weeks; 100 mg/m², weekly, 3 out of 4 weeks; 125 mg/m², weekly, 3 out of 4 weeks; 125 mg/m², weekly, 2 out of 3 weeks; 130 mg/m²,

weekly, without break; 175 mg/m², once every 2 weeks; 260 mg/m², once every 2 weeks; 260 mg/m², once every 3 weeks; 180-300 mg/m², every three weeks; 60-175 mg/m², weekly, without break; 20-150 mg/m², twice a week; and 150-250 mg/m² twice a week. The dosing frequency of the composition may be adjusted over the course of the treatment based on the judgment of the administering physician.

[0169] In some embodiments, the individual is treated for at least about any of one, two, three, four, five, six, seven, eight, nine, or ten treatment cycles. The compositions described herein allow infusion of the composition to an individual over an infusion time that is shorter than about 24 hours. For example, in some embodiments, the composition is administered over an infusion period of less than about any of 24 hours, 12 hours, 8 hours, 5 hours, 3 hours, 2 hours, 1 hour, 30 minutes, 20 minutes, or 10 minutes. In some embodiments, the composition is administered over an infusion period of about 30 minutes.

[0170] Other exemplary dose of the taxane (in some embodiments paclitaxel) in the nanoparticle composition include, but is not limited to, about any of 50 mg/m², 60 mg/m², 75 mg/m², 80 mg/m², 90 mg/m², 100 mg/m², 120 mg/m², 160 mg/m², 175 mg/m², 200 mg/m², 210 mg/m², 220 mg/m², 260 mg/m², and 300 mg/m². For example, the dosage of paclitaxel in a composition can be in the range of about 100-400 mg/m² when given on a 3 week schedule, or about 50-250 mg/m² when given on a weekly schedule.

[0171] The dosing frequency of the other agent can be the same or different from that of the composition. Exemplary frequencies are provided above. As further example, the other agent can be administered three times a day, two times a day, daily, 6 times a week, 5 times a week, 4 times a week, 3 times a week, two times a week, weekly. In some embodiments, the other agent is administered twice daily or three times daily. Exemplary amounts of the other agent include, but are not limited to, any of the following ranges: about 0.5 to about 5 mg, about 5 to about 10 mg, about 10 to about 15 mg, about 15 to about 20 mg, about 20 to about 25 mg, about 20 to about 50 mg, about 25 to about 50 mg, about 50 to about 75 mg, about 50 to about 100 mg, about 75 to about 100 mg, about 100 to about 125 mg, about 125 to about 150 mg, about 150 to about 175 mg, about 175 to about 200 mg, about 200 to about 225 mg, about 225 to about 250 mg, about 250 to about 300 mg, about 300 to about 350 mg, about 350 to about 400 mg, about 400 to about 450 mg, or about 450 to about 500 mg, about 500 to about 550 mg, about 550 to about 600 mg, about 600 to about

650 mg, about 650 to about 700 mg, about 700 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, about 950 mg to about 1000 mg. For example, the other agent can be administered at a dose of about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). For example, in some embodiments, romidepsin is administered (for example by oral administration) at about 10-300 mg/m² (including for example 50 mg/m², 100 mg/m², 150 mg/m², 200 mg/m², or 250 mg/m²), on days 1, 8 and 15 of the 28 day cycle. In some embodiments, azacitidine is administered (for example by intraperitoneal administration) at about 20-200 mg/kg/day (including for example 50 mg/kg/day, 80 mg/kg/day, 100 mg/kg/day, 120 mg/kg/day, 140 mg/kg/day, 180 mg/kg/day). In some embodiments, decitabine is administered (for example by intraperitoneal administration) at about 0.75-4 mg/kg/day (including for example 1.0 mg/kg/day, 1.5 mg/kg/day, 2.00 mg/kg/day, 2.5 mg/kg/day, 3.0 mg/kg/day, 3.5 mg/kg/day).

[0172] In some embodiments, the effective amount of taxane in the composition is between about 45 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane in the composition is between about 80 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane in the composition is between about 80 mg/m² to about 300 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80

mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane in the composition is between about 150 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane in the composition is between about 80 mg/m² to about 150 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane (e.g., paclitaxel) in the composition is about 100 mg/m². In some embodiments, the effective amount of taxane in the composition is between about 170 mg/m² to about 200 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane in the composition is between about 200 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 1 mg/kg to about 200 mg/kg (including for example about 1 mg/kg to about 20 mg/kg, about 20 mg/kg to about 40 mg/kg, about 40 mg/kg to about 60 mg/kg, about 60 mg/kg to about 80 mg/kg, about 80 mg/kg to about 100 mg/kg, about 100 mg/kg to about 120 mg/kg, about 120 mg/kg to about 140 mg/kg, about 140 mg/kg to about 200 mg/kg). In some embodiments, the effective amount of taxane (e.g., paclitaxel) in the composition is about 260 mg/m². In some embodiments of any of the above methods, the effective amount of the other agent is about 20-30 mg/kg, about 30-40 mg/kg, about 40-50 mg/kg, about 50-60 mg/kg, about 60-70 mg/kg, about 70-80 mg/kg, about 80-100 mg/kg, or about 100-120 mg/kg.

[0173] In some embodiments, the effective amount of taxane in the composition is between about 45 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400 mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane in the composition is between about 80 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400 mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane in the composition is between about 80 mg/m² to about 300 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400 mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane in the composition is between about 150 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400 mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane in the composition is between about 80 mg/m² to about 150 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400 mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane in the composition is between about 170 mg/m² to about 200 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400

mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane in the composition is between about 200 mg/m² to about 350 mg/m² and the effective amount of the other agent is about 80 mg to about 1000 mg (including for example about 80 to about 100 mg, about 100 to about 200 mg, about 200 to about 300 mg, about 300 to about 400 mg, about 400 to about 500 mg, about 500 to about 600 mg, about 600 to about 700 mg, about 700 to about 800 mg, about 800 to about 900 mg, about 900 mg to about 1000 mg). In some embodiments, the effective amount of taxane (e.g., paclitaxel) in the composition is about 100 mg/m². In some embodiments of any of the above methods, the effective amount of the other agent is about 100-200 mg, about 200-300 mg, about 300-400 mg, about 400-500 mg.

[0174] In some embodiments, the effective amount of paclitaxel in the composition is about 100 mg/m² and the effective amount of the other agent (such as romidepsin) is about 10 to 300 mg/m².

[0175] In some embodiments, the effective amount of paclitaxel in the composition is about 50-300 mg/m² (including for example about 100 mg/m²) and the effective amount of the other agent (such as azacitidine) is about 10-200 mg/mw (including for example about 50-100 mg/m² or for example about 75 mg/m²). In some embodiments, the effective amount of paclitaxel in the composition is about 50-300 mg/m² (including for example about 100 mg/m²) and the effective amount of the other agent (such as decitabine) is about 10-200 mg/m² (including for example about 50-100 mg/m² or for example about 75 mg/m²).

[0176] The composition (and the other agent) described herein can be administered to an individual (such as human) via various routes, including, for example, intravenous, intra-arterial, intraperitoneal, intrapulmonary, oral, inhalation, intravesicular, intramuscular, intra-tracheal, subcutaneous, intraocular, intrathecal, transmucosal, and transdermal. In some embodiments, sustained continuous release formulation of the composition may be used.

[0177] A combination of the administration configurations described herein can be used. The combination therapy methods described herein may be performed alone or in conjunction with another therapy, such as surgery, radiation, chemotherapy, immunotherapy, gene therapy, and the like. Additionally, a person having a greater

risk of developing the proliferative disease may receive treatments to inhibit or and/or delay the development of the disease.

[0178] As will be understood by those of ordinary skill in the art, the appropriate doses of other agents will be approximately those already employed in clinical therapies wherein the other agent are administered alone or in combination with other agents. Variation in dosage will likely occur depending on the condition being treated. As described above, in some embodiments, the other agents may be administered at a reduced level.

Compositions

[0179] Romidepsin and paclitaxel can be used as compositions when combined with an acceptable carrier or excipient. Such compositions are useful in the methods provided herein.

[0180] Provided herein are pharmaceutical compositions comprising romidepsin as an active ingredient, including an enantiomer, a mixture of enantiomers, a mixture of two or more diastereomers, a tautomer, a mixture of two or more tautomers, or an isotopic variant thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[0181] Provided herein are pharmaceutical compositions comprising paclitaxel as an active ingredient or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug in combination with a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof.

[0182] Suitable excipients are well known to those skilled in the art, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art, including, but not limited to, the method of administration. For example, oral dosage forms such as tablets may contain excipients not suited for use in parenteral dosage forms. The suitability of a particular excipient may also depend on the specific active ingredients in the dosage form. For example, the decomposition of some active ingredients may be accelerated by some excipients such as lactose, or when exposed to water. Active ingredients that comprise primary or secondary amines are particularly susceptible to such accelerated decomposition. Consequently, provided herein are pharmaceutical compositions and

dosage forms that contain little, if any, lactose other mono- or disaccharides. As used herein, the term "lactose-free" means that the amount of lactose present, if any, is insufficient to substantially increase the degradation rate of an active ingredient. In one embodiment, lactose-free compositions comprise an active ingredient provided herein, a binder/filler, and a lubricant. In another embodiment, lactose-free dosage forms comprise an active ingredient, microcrystalline cellulose, pre-gelatinized starch, and magnesium stearate.

[0183] Like the amounts and types of excipients, the amounts and specific types of active ingredients in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. In one embodiment, dosage forms provided herein comprise romidepsin or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of from about 0.5 mg/m² to 28 mg/m². In another embodiment, dosage forms provided herein comprise romidepsin or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an amount of about 8 mg/m², 10 mg/m², 12 mg/m², or 14 mg/m².

[0184] In one embodiment, dosage forms provided herein comprise paclitaxel or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in a dose of from about 60-300 mg/m² (including for example about 80-200 mg/m² for example about 100 mg/m²),. In another embodiment, dosage forms provided herein comprise paclitaxel or a pharmaceutically acceptable salt, solvate, hydrate, stereoisomer, clathrate, or prodrug thereof in an dose of about 60, 80, 100, 150, 200, 250 mg/m². In a specific embodiment, a preferred dosage form of paclitaxel is 100 mg/m².

[0185] Pharmaceutical compositions provided herein can be used in the preparation of individual, single unit dosage forms. Single unit dosage forms are suitable for oral, mucosal (*e.g.*, nasal, sublingual, vaginal, buccal, or rectal), parenteral (*e.g.*, subcutaneous, intravenous, bolus injection, intramuscular, or intraarterial), topical (*e.g.*, eye drops or other ophthalmic preparations), transdermal or transcutaneous administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; powders; aerosols (*e.g.*, nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (*e.g.*, aqueous or non-aqueous liquid suspensions, oil-

in-water emulsions, or a water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; eye drops or other ophthalmic preparations suitable for topical administration; and sterile solids (*e.g.*, crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

[0186] In one embodiment, the pharmaceutical compositions provided herein formulated in various dosage forms for oral administration.

[0187] In one embodiment, the pharmaceutical compositions provided herein formulated in various dosage forms for parenteral administration.

[0188] In one embodiment, the pharmaceutical compositions are provided in a dosage form for oral administration, which comprise romidepsin or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers. In one embodiment, a dosage form is a capsule or tablet comprising romidepsin in an amount of about 10 mg/m², 25 mg/m², 50 mg/m², 100 mg/m², 200 mg/m², or 300 mg/m². In another embodiment, capsule or tablet dosage form comprises romidepsin in an amount of about 50 mg/m² or 75 mg/m².

[0189] In one embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise romidepsin or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers. In one embodiment, a dosage form is a syringe or vial comprising romidepsin in an amount of about 0,5 mg/m², 2,5 mg/m², 7,5 mg/m², 15 mg/m², 20 mg/m², or 28 mg/m². In another embodiment, syringe or vial dosage form comprises romidepsin in an amount of about 8 mg/m², 10 mg/m², 12 mg/m², or 14 mg/m².

[0190] In one embodiment, the pharmaceutical compositions are provided in a dosage form for parenteral administration, which comprise paclitaxel or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; and one or more pharmaceutically acceptable excipients or carriers. In one embodiment, a dosage form is a syringe or vial comprising paclitaxel in a dose of about 60-300 mg/m².

[0191] The pharmaceutical compositions provided herein can be provided in a unit-dosage form or multiple-dosage form. Examples of a unit-dosage form include an ampoule, syringe, and individually packaged tablet and capsule. For example, a 100 mg unit dose contains about 100 mg of an active ingredient in a packaged tablet

or 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.

[0192] The pharmaceutical compositions provided herein can 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

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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; polacrillin 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.

[0197] 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.

[0198] 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.

[0199] Suitable preservatives include, but are not limited to, glycerin, methyl and propylparaben, benzoic acid, 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.

[0200] It should be understood that many carriers and excipients may serve a plurality of functions, even within the same formulation.

[0201] 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.

[0202] 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.

[0203] 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.

[0204] 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.

[0205] 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.

[0206] 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.

[0207] 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.

[0208] Coloring and flavoring agents can be used in all of the above dosage forms.

[0209] 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

[0210] 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.

[0211] 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*).

[0212] 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.

[0213] 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.

[0214] 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 carboxymethylcellulose, 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 -P-cyclodextrin, sulfobutylether -P-cyclodextrin, and sulfobutylether 7-p-cyclodextrin (CAPTISOL[®], CyDex, Lenexa, KS).

[0215] 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.

[0216] 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.

[0217] 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.

[0218] 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.

[0219] 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.

[0220] 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. *Delayed Release Dosage Forms*

[0221] Pharmaceutical compositions comprising romidepsin and paclitaxel can be administered by controlled release means or by delivery devices that are well known to those of ordinary skill in the art. Examples include, but are not limited to, those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, 5,674,533, 5,059,595, 5,591,767, 5,120,548, 5,073,543, 5,639,476, 5,354,556, and 5,733,566, each of which is incorporated herein by reference. Such dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydropropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof to provide the desired release profile in varying proportions. Suitable controlled-release formulations known to those of ordinary skill in the art, including those described herein, can be readily selected for use with the active ingredients of the invention. The invention thus encompasses single unit dosage forms suitable for oral administration such as, but not limited to, tablets, capsules, gelcaps, and caplets that are adapted for controlled-release.

[0222] All controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include extended activity of the drug, reduced dosage frequency, and increased patient compliance. In addition, controlled-release formulations can be

used to affect the time of onset of action or other characteristics, such as blood levels of the drug, and can thus affect the occurrence of side (*e.g.*, adverse) effects.

[0223] Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release of other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, temperature, enzymes, water, or other physiological conditions or compounds.

Romidepsin formulation

[0224] In one embodiment, romidepsin is formulated for injection as a sterile lyophilized white powder and is supplied in a single-use vial containing 10 mg romidepsin and 20 mg povidone, USP. The diluent is a sterile clear solution and is supplied in a single-use vial containing a 2 ml deliverable volume. The diluent for romidepsin contains 80% (v/v) propylene glycol, USP and 20% (v/v) dehydrated alcohol, USP. Romidepsin is supplied as a kit containing two vials.

Romidepsin for injection is intended for intravenous infusion after reconstitution with the supplied Diluent and after further dilution with 0.9% Sodium Chloride, USP.

Paclitaxel formulation

[0225] In one embodiment, TAXOL (paclitaxel) is formulated for injection as a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

Kits, medicines, and compositions

[0226] The invention also provides compositions (such as pharmaceutical compositions), medicine, kits, and unit dosages useful for methods described herein.

Also provided are any use described herein whether in the context of use as a medicament and/or use for manufacture of a medicament.

[0227] Kits of the invention include one or more containers comprising taxane-containing compositions (or unit dosage forms and/or articles of manufacture) and/or at least one other agent that modifies the epigenetics in a cell, and in some embodiments, further comprise instructions for use in accordance with any of the methods described herein. The kit may further comprise a description of selection an individual suitable or treatment. Instructions supplied in the kits of the invention are typically written instructions on a label or package insert (e.g., a paper sheet included in the kit), but machine-readable instructions (e.g., instructions carried on a magnetic or optical storage disk) are also acceptable.

[0228] In some embodiments, the kit comprises a) a composition comprising a taxane (such as paclitaxel), and b) an effective amount of at least one other agent that modifies the epigenetics in a cell. In some embodiments, the kit comprises a) a composition comprising a taxane (such as paclitaxel), b) an effective amount of at least one other agent that modifies the epigenetics in a cell, and c) instructions for administering the composition and the other agents simultaneously, sequentially, or concurrently for treatment of a proliferative disease (such as cancer). In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the kit comprises a) a composition comprising paclitaxel, b) an effective amount of at least one other agent that modifies the epigenetics in a cell, and c) instructions for administering the composition and the other agents simultaneously, sequentially, and/or concurrently, for the effective treatment of a proliferative disease (such as cancer).

[0229] In some embodiments, the kit comprises a) a composition comprising a taxane (such as paclitaxel), b) a composition comprising at least one other agent that modifies the epigenetics in a cell and a carrier protein (such as albumin), and c) instructions for administering the compositions simultaneously, sequentially, and/or concurrently, for treatment of a proliferative disease (such as cancer). In some embodiments, the kit comprises a) a composition comprising paclitaxel, b) a composition comprising at least one other agent that modifies the epigenetics in a cell and a carrier protein (such as albumin), and c) instructions for administering the compositions simultaneously, sequentially, and/or concurrently, for the effective treatment of a proliferative disease (such as cancer).

[0230] The other agents can be present in separate containers or in a single container. It is understood that the kit may comprise one distinct composition or two or more compositions wherein one composition comprises paclitaxel and one composition comprises an other agent.

[0231] The kits of the invention are in suitable packaging. Suitable packaging include, but is not limited to, vials, bottles, jars, flexible packaging (e.g., sealed Mylar or plastic bags), and the like. Kits may optionally provide additional components such as buffers and interpretative information. The present application thus also provides articles of manufacture, which include vials (such as sealed vials), bottles, jars, flexible packaging, and the like.

[0232] The instructions relating to the use of the compositions generally include information as to dosage, dosing schedule, and route of administration for the intended treatment. The containers may be unit doses, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of the taxane (such as taxane) as disclosed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the taxane and pharmaceutical compositions and instructions for use and packaged in quantities sufficient for storage and use in pharmacies, for example, hospital pharmacies and compounding pharmacies.

[0233] Also provided are medicines for treating proliferative diseases. In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the kit comprises a) a composition comprising paclitaxel, and b) at least one other agent that modifies the epigenetics in a cell, and c) instructions for administering the composition and the other agents simultaneously, sequentially, and/or concurrently, for the effective treatment of a proliferative disease (such as cancer).

[0234] Also provided are medicines for treating a lymphoid neoplasm (for example, CLL/SLL or lymphoma, such as refractory DLBC lymphoma). In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In

some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, and b) azacitidine, and c) instructions for administering the nanoparticles and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of lymphoid neoplasm (for example, CLL/SLL or lymphoma, such as refractory DLBC lymphoma). In some embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, and b) decitabine, and c) instructions for administering the compositions and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of lymphoid neoplasm (for example, CLL/SLL or lymphoma, such as refractory DLBC lymphoma).

[0235] Also provided are medicines for treating ovarian cancer. In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, and b) azacitidine, and c) instructions for administering the nanoparticles and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of ovarian cancer. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, and b) decitabine, and c) instructions for administering the composition and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of ovarian cancer.

[0236] Also provided are medicines for treating endometrial cancer (e.g. uterine cancer). In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, and b) azacitidine, and c)

instructions for administering the composition and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of endometrial cancer (e.g. uterine cancer). In some embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, and b) decitabine, and c) instructions for administering the composition and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of endometrial cancer (e.g. uterine cancer).

[0237] Also provided are medicines for treating lung cancer. In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) azacitidine, and c) instructions for administering the composition and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of lung cancer. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) decitabine, and c) instructions for administering the composition and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of lung cancer.

[0238] Also provided are medicines for treating sarcoma. In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) azacitidine, and c) instructions for administering the composition and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of sarcoma. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) decitabine, and

c) instructions for administering the composition and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of sarcoma.

[0239] Also provided are medicines for treating pancreatic cancer. In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) azacitidine, and c) instructions for administering the composition and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of pancreatic cancer. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) decitabine, and c) instructions for administering the composition and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of pancreatic cancer.

[0240] Also provided are medicines for treating breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer). In some embodiments, the medicine comprises a) a composition comprising a taxane (such as paclitaxel), and b) at least one other agent that modifies the epigenetics in a cell. In some embodiments, the taxane is any of paclitaxel, docetaxel, and ortataxel. In some embodiments, the at least one other agent that modifies the epigenetics in a cell is romidepsin. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) romidepsin, and c) instructions for administering the composition and the romidepsin simultaneously, sequentially, and/or concurrently, for the effective treatment of breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer). In some embodiments, the at least one other agent that modifies the epigenetics in a cell is azacitidine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) azacitidine, and c) instructions for administering the composition and the azacitidine simultaneously, sequentially, and/or concurrently, for the effective treatment of breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer). In some

embodiments, the at least one other agent that modifies the epigenetics in a cell is decitabine. In some embodiments there is provided a kit comprising a) a composition comprising paclitaxel, b) decitabine, and c) instructions for administering the composition and the decitabine simultaneously, sequentially, and/or concurrently, for the effective treatment of breast cancer (for example, HER2 negative breast cancer or for example, triple negative breast cancer, or for example, inflammatory breast cancer).

[0241] The compositions and the other agents can be present in separate containers or in a single container. It is understood that the medicine may comprise one distinct composition or two or more compositions wherein one composition comprises paclitaxel and one composition comprises another agent.

[0242] The kits, medicines, and compositions of this invention may include any one or more aspects or parameters described herein.

[0243] Those skilled in the art will recognize that several embodiments are possible within the scope and spirit of this invention. The invention will now be described in greater detail by reference to the following non-limiting examples. The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

EXAMPLES

Example 1. The Combined Effect of Romidepsin and Paclitaxel on IBC cells *in Vitro*

[0244] Two cell lines available for studies focused on IBC are the SUM149 and SUM190 cell lines. For *in vitro* studies to determine the inhibitory concentrations at 50% (IC₅₀) for romidepsin for proliferation, invasion and anchorage independent growth, human breast cancer cell lines of different molecular subtypes, were included, *i.e.*, breast cancer cells that differ with respect to hormone receptor (ER/PR) and Her-2 oncogene status. The cell lines included were MDA-MB-231 breast cancer cells and SUM149 IBC cells, which are both basal like (triple negative; ER/PR⁻/Her-2⁻), AU565 cells, which are Her-2 amplified (ER/PR⁻/Her-2⁺), SUM190 IBC cells which are luminal B subtype (ER/PR⁺/Her-2⁺), and MCF-7 cells, which are luminal A (ER/PR⁺/Her-2⁻). The characterization of molecular subtypes of breast cancer cell lines is provided in Table 1 below.

Table 1

Cell Lines	Origin	Clinical Type	Molecular Subtype
MCF-7	Non-IBC	ER ⁺ /PR ⁺ /Her-2 ⁻	Luminal A
MDA-IBC-3	IBC	ER ⁺ /PR ⁻ /Her-2 ⁺	Luminal B
AU565	Non-IBC	ER-, PR-, Her-2 ⁺	Her-2 ⁺
KPL-4	IBC	ER-, PR-, Her-2 ⁺	Her-2 ⁺
SUM190	IBC	Triple Negative	Her-2 ⁺
Mary-X	IBC	Triple Negative	Basal B
MDA-MB-231	Non-IBC	Triple Negative	Basal B
SUM149	IBC	Triple Negative	Basal B
SUM159	Non-IBC	Triple Negative	Basal B

[0245] Cell proliferation. Cells were seeded in six-well culture dish, harvested at 24-120 hrs after plating and cell proliferation was determined by total live cell counts and by MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; Life Technologies/Invitrogen] assay. MTT solution (5 mg/ml) was added to cells and incubated at 37°C until the appearance of colored formazan product, which then was dissolved in DMSO, and subjected to colorimetric measurement at 570 nm using a plate reader. DMSO will be used as the solvent control. The IC₅₀ value was defined as the drug concentration at which half of the maximum growth inhibition is achieved and was determined using CalcuSyn v 2.0 software (Biosoft). Agents tested is in stock solutions in DMSO or appropriate solvents depending upon chemical characteristics. Experiments were performed in triplicate and repeated twice. Results were plotted as isobolograms showing potential for additive, synergistic or antagonist activities of the combinations. IC₅₀ for each agent will be established based on results of studies analyzing dose dependent effect of agents on cell proliferation.

[0246] Clonogenicity/Self Renewal of IBC multi-cellular tumor spheroids.

Single cell suspensions of SUM149 and SUM190 were plated into ultralow attachment plates or flasks (Corning Life Sciences, Corning, NY) and maintained to enrich for spheroid formation. Spheroids were treated with either DMSO as the solvent control or with romidepsin at concentrations of 0-25 µM, with each concentration run in triplicate. After 10 days in culture, 0.5% thiazolyl blue tetrazolium bromide (MTT) was added to each well to visualize the tumor spheroids, and samples were returned to the incubator for 1 hr. Spheroid formation was measured with an Optronix Scanner (Oxford, UK) and the data was analyzed using

GelCount software. The IC₅₀ concentrations was calculated using nonlinear regression analysis of average spheroid formation.

[0247] Invasion of IBC tumor cells *in vitro* as assessed by modified Boyden chamber technique was performed. These studies showed the effect of romidepsin alone (0-25 μ M) and in combination with paclitaxel (Taxol®; 0-1000 nM) on the ability of IBC tumor cells SUM 149 and SUM 190 compared to MCF-7 and MDA-MB-23 1 breast cancer cells to invade across an artificial basement membrane as determined using the Matrigel invasion assay.

[0248] Anchorage-independent growth was assessed based on the ability of cells to grow as colonies in soft agar. This assay was performed in six-well plates with a base of 2 ml of medium containing 1% fetal bovine serum and 0.5% Bacto agar. Breast cancer cell lines described above (5 x 10⁴ cell concentration) were layered onto the base in 2 ml of medium containing 1% fetal bovine serum and 0.35% agar. The experiments were performed in triplicate and repeated twice.

[0249] In addition to culture and analysis of tumor cells grown in serum containing culture medium on a plastic substrate, we used the *in vitro* culture models of IBC tumor cells propagated under low adherence conditions, which support the formation of the multi-cellular 3 dimensional tumor spheroids which mimic tumor emboli that are visible in the skin of IBC patients and in Mary-X xenografts. These 3D tumor spheroid systems were used to evaluate the response of IBC cell lines to romidepsin based on analysis of clonogenic growth when IBC cells are cultured as multi-cellular tumor spheroids that serve as an *in vitro* surrogate for IBC tumor emboli. The results of a dose-dependent inhibition of proliferation, invasion and anchorage independent growth in soft agar and clonogenic growth in breast cancer cell lines by romidepsin are shown in Table 2 below.

Table 2

	MTT	AIG	CLONOGENIC ASSAY	INVASION
MCF-7	0.001290 μ M	0.0000030 μ M	-	-
MDA-MB-231	0.000830 μ M	0.0000011 μ M	-	0.000130 μ M
SUM159	0.007012 μ M	0.0000020 μ M	-	0.003800 μ M
SUM149	0.002368 μ M	0.0000900 μ M	0.0000000800 μ M	0.000080 μ M
SUM190	0.021650 μ M	0.0021000 μ M	0.0000039000 μ M	-
IMDA-BC-3	0.006016 μ M	0.0000090 μ M	0.0011800000 μ M	-
AU565	0.006437 μ M	0.0001300 μ M	0.0000304000 μ M	-
MARY X Spheroids	-	-	0.0016000000 μ M	-
3D SUM149 Spheroids	-	-	0.0000002415 μ M	-

3D SUM190 Spheroids	-	-	0.0040000000 μ M	-
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[0250] Induction of apoptosis, induction of p21 and acetylated Histone 3 and acetylated tubulin. The effects of romidepsin alone and in combination with paclitaxel on cell survival and apoptosis were assessed. Morphologic changes in the cell nucleus, namely nuclear condensation and fragmentation evaluated. Identification of nuclear fragmentation was achieved by seeding cells in 2-well chamber slides (I X 104 cells/chamber) using the Chromogenic TUNEL-POD assay ("In Situ Death Detection Kit, POD", Boehringer Mannheim). These studies were compared to the induction of p21 protein in cell lines. The dose dependent effects of romidepsin on p21 induction and acetylation of Histone 3 and tubulin were assessed using standard Western blotting methods. The results are shown in Figures 4-6. The results demonstrate a synergistic effect of romidepsin and paclitaxel on proliferation, invasion and anchorage independent growth in soft agar and clonogenic growth in breast cancer cell lines.

Example 2. The Combined Effect of Romidepsin and Paclitaxel in IBC *in Vivo*.

[0251] For the *in vivo* studies, to evaluate the effects of romidepsin alone and in combination with paclitaxel, 10 female 6-8 week old Nod.Scid IL-2 gamma knockout mice per treatment group were used. Studies were performed using the SUM149 and the Mary-X xenograft model of IBC. The SUM149 cell line was used to evaluate the therapeutic effects of romidepsin. The Mary-X tumor model was used to evaluate the effects of romidepsin on the IBC tumor emboli within the dermis.

[0252] In Vivo Imaging to Track Tumor Size and Response to Therapy. The SUM149 cells and Mary-X tumor spheroids were engineered to contain a luciferase construct which imparts a bioluminescent signal to the cells, allowing for *in vivo* live imaging to identify tumor location and relative volume in real time during the time course of the *in vivo* studies. To initiate tumors, 10^6 SUM149 cells were injected into the left lower mammary fat pad (i.m.) using using 26 gauge needle and 1 cc tuberculin syringe following euthanasia using isoflurane. The injection of SUM149 cells resulted in development of primary SUM149 tumors within the mammary fat pad. For studies using Mary-X, 10^6 Mary-X tumor spheroids were injected into the right hind flank of Nod.Scid mice using 26 gauge needle and 1 cc tuberculin syringe. The presence of the luciferase tag in the SUM149 and Mary-X tumor cells allowed to define the specific

effects of romidepsin and paclitaxel used alone and in combination. Animals were imaged using live *in vivo* imaging at the time of first palpable tumors were detectable. Animals were imaged for the second time at day 42 and 60 day, at which times mice had primary tumors.

[0253] In Vivo Analysis of Effects of Romidepsin Alone and/or in Combination with Paclitaxel in Pre-clinical Models of IBC. SUM149 cells (10⁶/100 ul sterile PBS) and Mary-X tumor spheroids (10⁶/100 ul sterile PBS) were injected into Nod.Scid mice at day 0. When tumors reached approximately 200-300 mm³, treatment with romidepsin and/or paclitaxel initiated. Tumor diameters were serially measured using digital calipers as an independent measure of tumor size. Study was terminated at 90-120 days after treatment was initiated, depending upon the extent of the anti-tumor effects of the single agents and the combinations. If at any time the weight of the animals fell below 20% of starting body weight, mice were euthanized using CO₂ and cervical dislocation. Based on IUCAC guidelines, mice bearing primary tumors that reached a size greater than 10% body mass of mouse were euthanized.

[0254] Primary tumors were initiated in mice as follows: SUM149 cells [10⁶] were injected into intramammary fat pad of Nod.Scid mice; and Mary-X tumor spheroids [10⁶] were injected into the hind flank of Nod.Scid mice. At the time the tumors were 200-300 mm³, mice were randomly assigned to one of the treatment groups, with the total numbers of mice as described below.

[0255] Treatment groups consisted of the following:

A). Romidepsin treatment group: romidepsin was injected with 100 ul 10% polyethylated hydrogenated castor oil in physiological saline (Cremophor EL; BASF) at a concentration of 2.5 mg/kg via the i.p. 3 times weekly into Nod.Scid mice bearing primary SUM149 xenografts and Nod.Scid mice bearing Mary-X tumor spheroids injected subcutaneously into the right hind flank of mice.

B). Paclitaxel treatment group: paclitaxel at a concentration of 15 mg/kg in Cremophor was injected via the i.p. route 3 times weekly into Nod.Scid mice bearing primary SUM149 xenografts and Nod.Scid mice bearing Mary-X tumor spheroids injected subcutaneously into the right hind flank of mice.

C). The effects of romidepsin in combination with paclitaxel were assessed using the same treatment strategy as described above.

D). Vehicle Control groups: SUM149 and Mary-X models were injected with solvent used for romidepsin, and SUM149 and Mary-X models were injected with CremafonEthanol 50:50 volume for paclitaxel vehicle control. Romidepsin was injected with 100 ul 10% polyethylated hydrogenated castor oil in physiological saline (Cremophor EL; BASF). At the time of initiation of treatment of mice, mice were treated with Cremafor vehicle control using the same schedule and concentrations used for each of the therapeutic agents being evaluated. For studies evaluating effects of paclitaxel, Cremaphor:Ethanol (50:50) was used as the vehicle control. Significant differences between groups were determined using unpaired two-tailed Student's t-test. Comparisons of three or more groups were conducted using ANOVA on ranks for non-parametric comparisons, with Student-Newman-Keuls posthoc analysis.

[0256] The results are shown in Figures 7-9. The obtained results demonstrated that romidepsin effectively inhibited tumor growth and metastasis in the SUM149 model of IBC, blocked tumor emboli survival in Mary-X model of IBC and was synergistic with Paclitaxel, resulting in significant inhibition of IBC tumors.

[0257] Collectively, these results suggest that romidepsin in combination with paclitaxel can be useful for the treatment of patients with IBC.

[0258] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

[0259] The present disclosure has been described above with reference to exemplary embodiments. However, those skilled in the art, having read this disclosure, will recognize that changes and modifications may be made to the exemplary embodiments without departing from the scope of the present disclosure. The changes or modifications are intended to be included within the scope of the present disclosure, as expressed in the following claims.

What is claimed is:

1. A method of treating cancer in an individual comprising administering to the individual:
 - a) an effective amount of a composition comprising a taxane, and
 - b) an effective amount of a composition comprising an agent that is an inhibitor of histone deacetylase romidepsin.
2. The method of claim 1, wherein said agent is romidepsin.
3. The method of claim 1, wherein taxane is paclitaxel.
4. The method of claim 1, wherein the cancer is a breast cancer.
5. The method of claim 4, wherein the breast cancer is an inflammatory breast cancer.
6. The method of claim 2 or 3, wherein the composition comprising paclitaxel and the composition comprising romidepsin are administered sequentially or concurrently.
7. The method of any one of claims 1-6, wherein the individual is a human.
8. A kit comprising: a) a composition comprising romidepsin and b) a composition comprising paclitaxel.
9. A medicine comprising: a) a composition comprising romidepsin and b) a composition comprising paclitaxel.

Cell Lines	Origin	Clinical Subtype	Molecular Subtype
MCF-7	Non-IBC	ER ⁺ /PR ⁺ /Her-2 ⁻	Luminal A
MDA-MB-3	IBC	ER ⁺ /PR ⁺ /Her-2 ⁺	Luminal B
AUS43	Non-IBC	ER, PR, Her-2 ⁻	Her-2 ⁻
KPL-4	IBC	ER, PR, Her-2 ⁺	Her-2 ⁺
SUM190	IBC	ER, PR, Her-2 ⁺	Her-2 ⁺
Mary-2	IBC	Triple Negative	Basal B
MDA-MB-231	Non-IBC	Triple Negative	Basal B
SUM149	IBC	Triple Negative	Basal B
SUM159	Non-IBC	Triple Negative	Basal B

Figure 1

	IC ₅₀	IC ₅₀	IC ₅₀	IC ₅₀
MCF-7	0.001200 µM	0.000000 µM		
MDA-MB-3	0.000000 µM	0.000011 µM		0.000100 µM
AUS43	0.000013 µM	0.000000 µM		0.000000 µM
SUM190	0.000000 µM	0.000000 µM	0.000000000 µM	0.000000 µM
SUM149	0.001000 µM	0.0001000 µM	0.000000000 µM	
MDA-MB-231	0.000010 µM	0.000000 µM	0.001100000 µM	
AUS43	0.000037 µM	0.0001000 µM	0.000000000 µM	
MARY-2 Spheroids			0.001000000 µM	
30 SUM190 Spheroids			0.000000000 µM	
30 SUM159 Spheroids			0.000000000 µM	

Figure 2

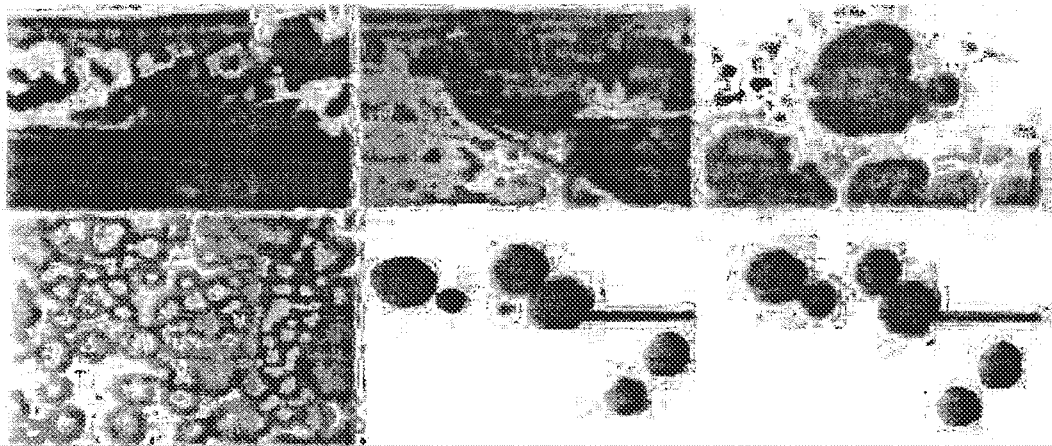


Figure 3



Figure 4A

Figure 4B

Figure 4C

Figure 4D

Figure 4E

Figure 4F

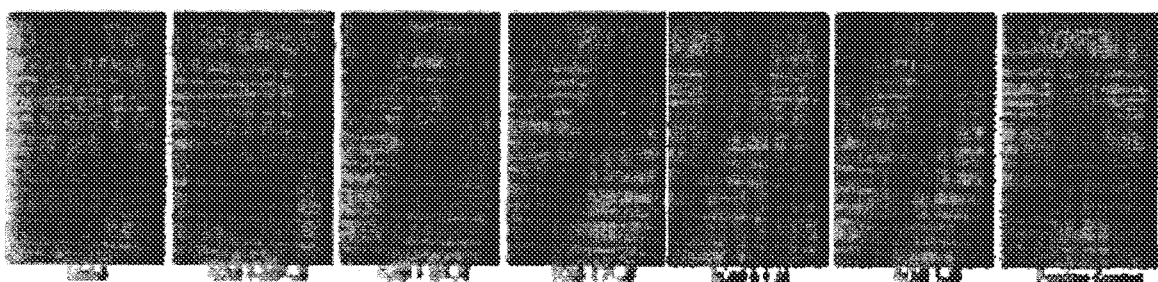


Figure 5A

Figure 5B

Figure 5C

Figure 5D

Figure 5E

Figure 5F

Figure 5G

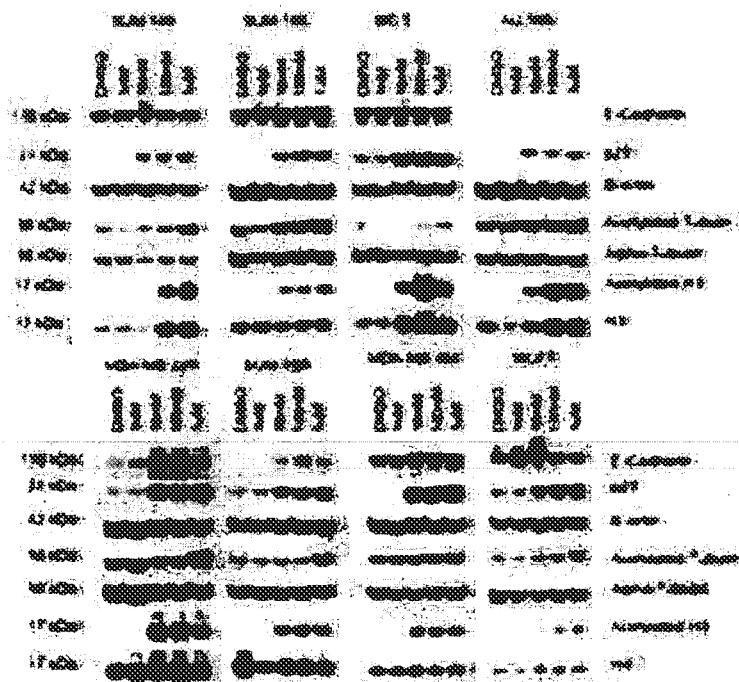


Figure 6

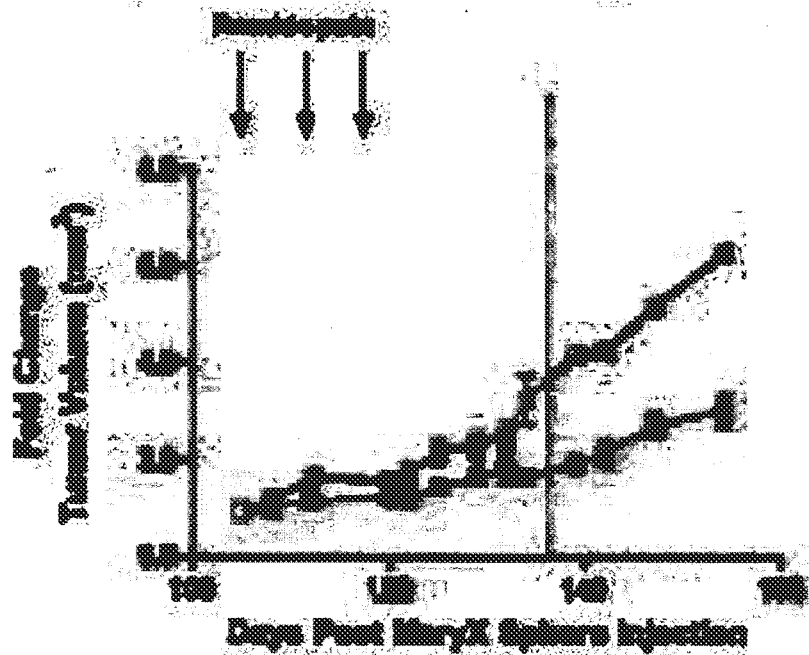


Figure 7

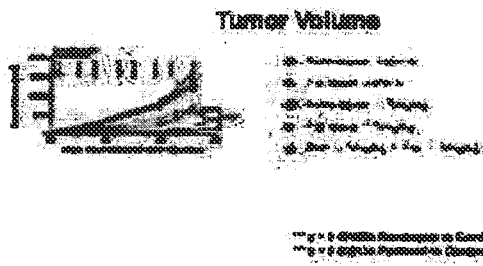


Figure 8A

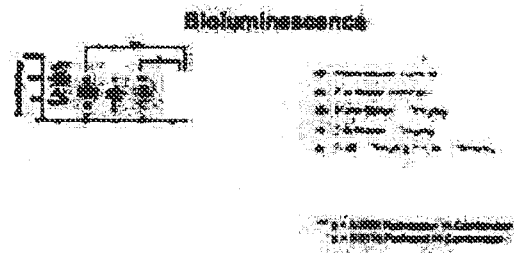


Figure 8B

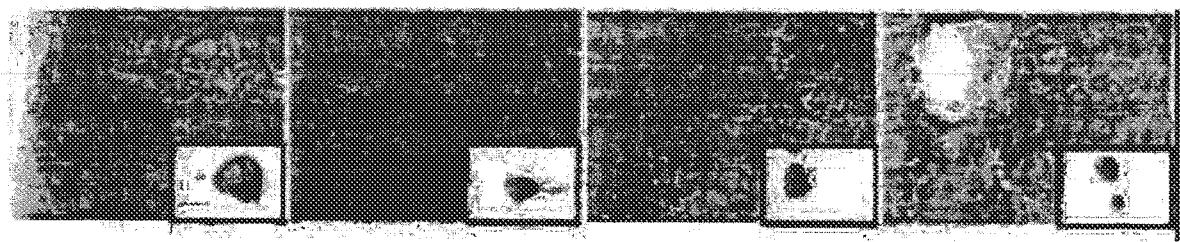


Figure 9A

Figure 9B

Figure 9C

Figure 9D

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/067759

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/337 A61K38/15 A61K45/06 A61P35/00
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 practicable, search terms used)

EPO-Internal , WPI Data, PAJ, EMBASE, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	page 9; claims 11-15 , 27-29 -----	5
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Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

19 February 2013

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27/02/2013

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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