(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2013 (22.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/123413 A2

(51) **International Patent Classification**:
A61K 31/506 (2006.01) *A61P 35/00* (2006.01)
A61K 31/517 (2006.01)

(21) **International Application Number**:
PCT/US2013/026462

(22) **International Filing Date**:
15 February 2013 (15.02.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
61/600,491 17 February 2012 (17.02.2012) US
61/602,544 23 February 2012 (23.02.2012) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with declaration under Article 17(2)(a); without abstract; title not checked by the International Searching Authority*

WO 2013/123413 A2

(54) **Title**: COMBINATIONS OF HISTONE DEACETYLASE INHIBITOR AND PAZOPANIB AND USES THEREOF

(57) **Abstract**:

COMBINATIONS OF HISTONE DEACETYLASE INHIBITOR AND PAZOPANIB AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application Serial No. 61/600,491, filed February 17, 2012, and U.S. Provisional Patent Application Serial No. 61/602,544, filed February 23, 2012, both of which are incorporated herein in their entirety by reference.

BACKGROUND OF THE INVENTION

[0002] The acetylation state of nucleosomal histones regulates gene expression. Deacetylation of nucleosomal histones is catalyzed by a group of enzymes known as histone deacetylases (HDACs), of which there are eleven known isoforms. Histone deacetylation leads to chromatin condensation resulting on transcriptional repression, whereas acetylation induces localized relaxation within specific chromosomal regions to allow better access to transcriptional machinery to facilitate transcription.

[0003] In tumor cells, use of selective inhibitors of HDAC enzymes has been reported to result in histone hyperacetylation. This alters the transcriptional regulation of a subset of genes, including many tumor suppressors, genes involved in cell cycle control, cell division and apoptosis. Further, HDAC inhibitors have been reported to inhibit tumor growth *in vivo*. The inhibition of tumor growth is accompanied by histone and tubulin hyperacetylation and may involve multiple mechanisms.

[0004] HDAC inhibitors block cancer cell proliferation both *in vitro* and *in vivo*. *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide (also known as PCI-24781 or abexinostat) is a hydroxamate-based HDAC inhibitor for use in the treatment of cancer in a human.

SUMMARY OF THE INVENTION

[0005] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat or a salt thereof, and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed,

resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof. In some embodiments, the salt of abexinostat is abexinostat HCl. In some embodiments, abexinostat, or a salt thereof, and the antiangiogenic agent are administered separately, concurrently or sequentially. In some embodiments, the subject is in an interdigestive state. In some embodiments, the abexinostat, or a salt thereof, and the antiangiogenic agent, are administered one hour before a meal or 2 hours after a meal. In some embodiments, the cycle of abexinostat, or a salt thereof, is 5 days. In some embodiments, at least one dose of abexinostat, or a salt thereof, is administered each day of the abexinostat cycle. In some embodiments, the dose of abexinostat, or a salt thereof, is sufficient to maintain an effective plasma concentration of abexinostat, or the salt thereof, in the individual for at least about 6 consecutive hours to about 8 consecutive hours. The method of claim 2, comprising administering a first dose of abexinostat, or a salt thereof, and a second dose of abexinostat, or a salt thereof, 4 to 8 hours apart. In some embodiments, the cancer is a hematological cancer, solid tumor or a sarcoma. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a metastatic solid tumor or an advanced solid tumor. In some embodiments, the cancer is a sarcoma. In some embodiments, the cancer is soft tissue sarcoma. In some embodiments, the cancer is renal cell carcinoma or ovarian cancer. In some embodiments, the method further comprises administering at least one additional therapy selected from anti-cancer agents, anti-emetic agents, radiation therapy, or combinations thereof.

[0006] Disclosed herein, in certain embodiments, are methods of treating a cancer in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat or a salt thereof, and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof. In some embodiments, the salt of abexinostat is abexinostat HCl. In some embodiments, abexinostat, or a salt thereof, and the antiangiogenic agent are administered separately, concurrently or sequentially. In some embodiments, the subject is in an interdigestive state. In some embodiments, the abexinostat, or a salt thereof, and the antiangiogenic agent, are administered one hour before a meal or 2 hours after a meal. In some embodiments, the cycle of

abexinostat, or a salt thereof, is 5 days. In some embodiments, at least one dose of abexinostat, or a salt thereof, is administered each day of the abexinostat cycle. In some embodiments, the dose of abexinostat, or a salt thereof, is sufficient to maintain an effective plasma concentration of abexinostat, or the salt thereof, in the individual for at least about 6 consecutive hours to about 8 consecutive hours. In some embodiments, the method further comprises a first dose of abexinostat, or a salt thereof, and a second dose of abexinostat, or a salt thereof, 4 to 8 hours apart. In some embodiments, the cancer is a hematological cancer, solid tumor or a sarcoma. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a metastatic solid tumor or an advanced solid tumor. In some embodiments, the cancer is a sarcoma. In some embodiments, the cancer is soft tissue sarcoma. In some embodiments, the cancer is renal cell carcinoma or ovarian cancer. In some embodiments, the cancer is resistant to the antiangiogenic agent; partially resistant to the antiangiogenic agent; or refractory to the antiangiogenic agent. In some embodiments, the method further comprises administering at least one additional therapy selected from anti-cancer agents, anti-emetic agents, radiation therapy, or combinations thereof.

[0007] Disclosed herein, in certain embodiments, are methods of treating a cancer in an individual in need thereof, comprising: administering (a) a cycle of abexinostat (or a salt thereof), and (b) pazopanib (or a salt thereof). In some embodiments, abexinostat (or a salt thereof) and pazopanib (or a salt thereof) are administered separately. In some embodiments, abexinostat (or a salt thereof) and pazopanib (or a salt thereof) are administered concurrently or sequentially. In some embodiments, the cycle of abexinostat (or a salt thereof) is 1 to 14 consecutive days, 2 to 14 consecutive days, 3 to 14 consecutive days, 4 to 14 consecutive days, 5 to 14 consecutive days, 6 to 14 consecutive days, 7 to 14 consecutive days, 8 to 14 consecutive days, 9 to 14 consecutive days, 10 to 14 consecutive days, 11 to 14 consecutive days, 12 to 14 consecutive days, or 13 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof) is 2 consecutive days, 3 consecutive days, 4 consecutive days, 5 consecutive days, 6 consecutive days, 7 consecutive days, 8 consecutive days, 9 consecutive days, 10 consecutive days, 11 consecutive days, 12 consecutive days, 13 consecutive days, or 14 consecutive days. In some embodiments, the methods further comprise an abexinostat (or a salt thereof) drug holiday following an abexinostat (or a salt thereof) cycle. In some embodiments, the abexinostat (or a salt thereof) drug holiday is 1 to 14 consecutive days, 2 to 14 consecutive days, 3 to 14 consecutive days, 4 to 14 consecutive days, 5 to 14 consecutive days, 6 to 14 consecutive days, 7 to 14 consecutive days, 8 to 14 consecutive days, 9 to 14 consecutive days, 10 to 14 consecutive days, 11 to 14 consecutive days, 12 to 14 consecutive days, or 13 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof) drug holiday is 2 consecutive days, 3 consecutive days, 4 consecutive days, 5 consecutive days, 6 consecutive

days, 7 consecutive days, 8 consecutive days, 9 consecutive days, 10 consecutive days, 11 consecutive days, 12 consecutive days, 13 consecutive days, or 14 consecutive days. In some embodiments, at least one dose of abexinostat (or a salt thereof) is administered each day of the abexinostat cycle. In some embodiments, the dose of abexinostate is sufficient to maintain an effective plasma concentration of abexinostat (or a salt thereof) in the individual for at least about 6 consecutive hours. In some embodiments, the dose of abexinostat (or a salt thereof) is sufficient to maintain an effective plasma concentration of abexinostat (or a salt thereof) in the individual for at least about 8 consecutive hours. In some embodiments, the dose of abexinostat (or a salt thereof) is sufficient to maintain an effective plasma concentrations of abexinostat (or a salt thereof) in the individual for about 6 consecutive hours to about 8 consecutive hours. In some embodiments, the methods comprise administering a first dose of abexinostat (or a salt thereof) and a second dose of abexinostat (or a salt thereof), wherein the first dose and the second dose are administered 4 to 8 hours apart. In some embodiments, the methods comprise administering a first dose of abexinostat (or a salt thereof), a second dose of abexinostat (or a salt thereof) and a third dose of abexinostat (or a salt thereof), wherein the first dose, the second dose and the third dose are administered 4 to 8 hours apart. In some embodiments, abexinostate (or a salt theorof) is formulated as an oral dosage form. In some embodiments, abexinostate (or a salt theorof) is formulated as an immediate release oral dosage form or a controlled release oral dosage form. In some embodiments, the methods comprise administering a first immediate release oral dosage form comprising abexinostat (or a salt thereof) and a second immediate release oral dosage form comprising abexinostat (or a salt thereof), wherein the second immediate release oral dosage form is administered about 4 to about 8 hours form the first immediate release oral dosage form. In some embodiments, the oral dosage form completely releases abexinostat (or a salt thereof) over a period of about 2 hours to about 10 hours after administration. In some embodiments, the methods comprise administering abexinostat (or a salt thereof) in fast mode. In some embodiments, the methods comprise administering pazopanib (or a salt thereof) in fast mode. In some embodiments, the methods comprise administering abexinostat (or a salt thereof) one hour before a meal or 2 hours after a meal. In some embodiments, the methods comprise administering pazopanib (or a salt thereof) one hour before a meal or 2 hours after a meal. In some embodiments, the methods comprise administering between about 30mg/m^2 and about 75mg/m^2 of abexinostat (or a salt thereof) BID. In some embodiments, a daily dose of abexinostat (or a salt thereof) is between about 60mg/m^2 and about 150 mg/m^2. In some embodiments, the methods comprise administering between about 400 mg and about 800 mg of pazopanib. In some embodiments, the salt of abexinostat is abexinostat HCl. In some embodiments, the salt of pazopanib is pazopanib HCl. In some embodiments, the

methods comprise administering between about 433.4 mg and about 866.8 mg of pazopanib HCl. In some embodiments, the cancer is a hematological cancer, solid tumor or a sarcoma. In some embodiments, the cancer is a sarcoma. In some embodiments, the cancer is soft tissue sarcoma. In some embodiments, the cancer is selected from a: breast cancer, colon cancer, colorectal cancer, non-small cell lung cancer, small-cell lung cancer, liver cancer, ovarian cancer, prostate cancer, uterine cervix cancer, urinary bladder cancer, gastric cancer, gastrointestinal stromal tumor, pancreatic cancer, germ cell tumor, mast cell tumor, neuroblastoma, mastocytosis, testicular cancer, glioblastoma, astrocytoma, B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, melanoma, myeloma, acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome, chronic myelogenous leukemia, and renal cell carcinoma. In some embodiments, the cancer is selected from: breast cancer, colon cancer, colorectal carcinomas, non-small cell lung cancer, liver cancer, ovarian cancer, uterine cervix cancer, gastric carcinoma, pancreatic cancer, glioblastomas, B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, myelodysplastic syndrome (MDS), and renal cell carcinoma. In some embodiments, the cancer is renal cell carcinoma or ovarian cancer. In some embodiments, the method further comprises administering at least one additional therapy selected from anti-cancer agents, anti-emetic agents, radiation therapy, or combinations thereof. In some embodiments, the method further comprises administering at least one additional therapeutic agent selected from among DNA-damaging agents; topoisomerase I or II inhibitors; alkylating agents; PARP inhibitors; proteasome inhibitors; RNA/DNA antimetabolites; antimitotics; immunomodulatory agents; antiangiogenics; aromatase inhibitors; hormone-modulating agents; apoptosis inducing agents; kinase inhibitors; monoclonal antibodies; abarelix; ABT-888; aldesleukin; aldesleukin; alemtuzumab; alitretinoin; allopurinol; altretamine; amifostine anastrozole; arsenic trioxide; asparaginase; azacitidine; AZD-2281; bendamustine; bevacizumab; bexarotene; bleomycin; bortezomib; BSI-201; busulfan; busulfan; calusterone; capecitabine; carboplatin; carfilozib; carmustine; carmustine; celecoxib; cetuximab; chlorambucil; cisplatin; cladribine; clofarabine; cyclophosphamide; cytarabine; cytarabine liposomal; dacarbazine; dactinomycin; darbepoetin alfa; dasatinib; daunorubicin liposomal; daunorubicin; decitabine; denileukin; dexrazoxane; docetaxel; doxorubicin; doxorubicin liposomal; dromostanolone propionate; epirubicin; epoetin alfa; erlotinib; estramustine; etoposide phosphate; etoposide; exemestane; filgrastim; floxuridine; fludarabine; fluorouracil; fulvestrant; gefitinib; gemcitabine; gemtuzumab ozogamicin; goserelin acetate; histrelin acetate; hydroxyurea; Ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; interferon alfa 2a; Interferon alfa-2b; irinotecan; lenalidomide; letrozole; leucovorin; leuprolide Acetate; levamisole; lomustine; meclorethamine; megestrol

acetate; melphalan; mercaptopurine; methotrexate; methoxsalen; mitomycin C; mitomycin C; mitotane; mitoxantrone; nandrolone phenpropionate; nelarabine; NPI-0052; nofetumomab; oprelvekin; oxaliplatin; paclitaxel; paclitaxel protein-bound particles; palifermin; pamidronate; panitumumab; pegademase; pegaspargase; pegfilgrastim; pemetrexed disodium; pentostatin; pipobroman; plicamycin, mithramycin; porfimer sodium; procarbazine; quinacrine; RAD001; rasburicase; rituximab; sargramostim; Sargramostim; sorafenib; streptozocin; sunitinib malate; tamoxifen; temozolomide; teniposide; testolactone; thalidomide; thioguanine; thiotepa; topotecan; toremifene; tositumomab; tositumomab/I-131 tositumomab; trastuzumab; tretinoin; uracil Mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zoledronate; and zoledronic acid.

FIGURES

[0008] FIG. 1 exemplifies effects of administering a combination of pazopanib + abexinostat (PCI-24781 to 786-O human kidney carcinoma cells. Effects of the combination were visualized by measuring alamarBlue.

[0009] FIG. 2 exemplifies effects of administering a combination of pazopanib + abexinostat (PCI-24781 to U2-OS osteosarcoma cells. Effects of the combination were visualized by measuring alamarBlue.

DETAILED DESCRIPTION

[0010] Antiangiogenic agents are commonly used in the treatment of various cancers. A common problem associated with antiangiogenic agents is increasing resistence to the agents by tumor cells during treatment. Pazopanib, an antiangiogenic agent, is a tyrosine kinase inhibitor. Resistance to pazopanib often develops during cancer treatment, decreasing the efficacy of pazopanib and ultimately denying patients use of a potentially life-saving medication. There exists a need for new treatment paradigms that decrease or reduce the effects of resistence to antiangiogenic agents such as pazopanib.

[0011] HDAC inhibitors produce various epigenetic modifications to the tumor cell genome. These modification may result in increased efficacy of any chemotherapeutic agents co-administered with an HDAC inhibitor. For example, HDAC inhibitors increase accessibility of DNA to various chemotherapeutic agents and therefore increase the cytotoxicity of the chemotherapeutics. *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide (also known as PCI-24781 or abexinostat) is a hydroxamate-based HDAC inhibitor for use in the treatment of cancer in a human.

[0012] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the

individual (a) a cycle of abexinostat, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[0013] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[0014] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[0015] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that

generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

Certain Terminology

[0016] The term "pharmaceutical composition" refers to a mixture of an active agent (or ingredient) with other inactive chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, coatings and/or excipients. The pharmaceutical composition facilitates administration of the compound to a human. In one aspect, the active agent is an HDAC inhibitor (e.g. abexinostat). In one aspect, the active agent is the HCl salt of abexinostat.

[0017] "Controlled release" as used herein refers to any release profile that is not entirely immediate release.

[0018] "Bioavailability" refers to the percentage of the weight of an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt, dosed that is delivered into the general circulation of the animal or human being studied. The total exposure ($AUC_{(0-\infty)}$) of a drug when administered intravenously is usually defined as 100% Bioavailable (F%). "Oral bioavailability" refers to the extent to which an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt, is absorbed into the general circulation when the pharmaceutical composition is taken orally as compared to intravenous injection.

[0019] "Blood plasma concentration" refers to the concentration an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt, in the plasma component of blood of a subject. It is understood that the plasma concentration of an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt, may vary significantly between subjects, due to variability with respect to metabolism and/or interactions with other therapeutic agents. In one aspect, the blood plasma concentration of an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt, varies from subject to subject. Likewise, values such as maximum plasma concentration (C_{max}) or time to reach maximum plasma concentration (T_{max}), or total area under the plasma concentration time curve ($AUC_{(0-\infty)}$) vary from subject to subject. Due to this variability, in one embodiment, the amount necessary to constitute "a therapeutically effective amount" of an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt, varies from subject to subject.

[0020] "Effective plasma concentrations" of an HDAC inhibitor refers to amounts of the HDAC inhibitor in the plasma that result in exposure levels that are effective for treating a cancer.

[0021] "Drug absorption" or "absorption" typically refers to the process of movement of drug from site of administration of a drug across a barrier into a blood vessel or the site of action, e.g., a drug moving from the gastrointestinal tract into the portal vein or lymphatic system.

[0022] A "measurable serum concentration" or "measurable plasma concentration" describes the blood serum or blood plasma concentration, typically measured in mg, μg, or ng of therapeutic agent per ml, dl, or l of blood serum, absorbed into the bloodstream after administration. As used herein, measurable plasma concentrations are typically measured in ng/ml or μg/ml.

[0023] "Pharmacodynamics" refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

[0024] "Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

[0025] "Drug holiday" means temporarily reducing or temporarily suspending administration of a drug for a certain length of time. The length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, and 365 days. In other embodiments, the dose reduction during a drug holiday is from about 10% to about 100%, including by way of example only about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, and about 100%.

[0026] "Fast mode" or "intergestive" is a physiological state where the stomach exhibits a cyclic activity called the interdigestive migrating motor complex (IMMC). The cyclic activity occurs in four phases: Phase I is the most quiescent, lasts 45 to 60 minutes, and develops few or no contractions; Phase II is marked by the incidence of irregular intermittent sweeping contractions that gradually increase in magnitude; Phase III, which lasts 5 to 15 minutes, is marked by the appearance of intense bursts of peristaltic waves involving both the stomach and the small bowel; and Phase IV is a transition period of decreasing activity which lasts until the next cycle begins. The total cycle time is approximately 90 minutes, and thus, powerful peristaltic waves sweep out the contents of the stomach every 90 minutes during the interdigestive mode. The IMMC may function as an intestinal housekeeper, sweeping swallowed saliva, gastric secretions, and debris to the small intestine and colon, preparing the upper tract for the next meal while preventing bacterial overgrowth. Pancreatic exocrine secretion of pancreatic peptide and motilin also cycle in synchrony with these motor patterns.

[0027] "Fed mode" or "postprandial" is a physiological state induced by food ingestion. It begins with changes to the motor pattern of the upper GI tract, the change occurring over a period of 30 seconds to one minute. The stomach generates 3-4 continuous and regular contractions per minute, similar to those of the interdigestive mode but of about half the amplitude. The change occurs almost simultaneously at all sites of the GI tract, before the stomach contents have reached the distal small intestine. Liquids and small particles flow continuously from the stomach into the intestine. Contractions of the stomach result in a sieving process that allows liquids and small particles to pass through a partially open pylorus. Indigestible particles greater than the size of the pylorus are retropelled and retained in the stomach. Particles exceeding about 1 cm in size are thus retained in the stomach for approximately 4 to 6 hours.

[0028] As used herein, increasing the effectiveness of an active agent (for example, an antiangiogenic agent, more specifically, pazopanib) includes reducing resistance to the active agent, delaying the development of resistance to the active agent, delaying the onset of the cancer becoming refractory to the active agent, prolonging the usefulness of the active agent, allowing use of the active agent in the treatment of cancers that generally develop, or have developed, resistance to the active agent, increasing patient response to the active agent, increasing cellular response to the active agent, decreasing the effective dosage of the active agent, or any combination thereof.

Abexinostat

[0029] Abexinostat (or, PCI-24781) is a hydroxamate-based HDAC inhibitor. Abexinostat has the chemical name 3-[(dimethylamino)methyl]-N-{2-[4-(hydroxycarbamoyl)phenoxy]ethyl}-1-benzofuran-2- carboxamide.

[0030] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[0031] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[0032] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[0033] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[0034] Cancers may result fromgenetic defects, such as a gene mutations and deletions and chromosomal abnormalities, that result in the loss of function of tumor suppressor genes and/or gain of function or hyperactivation of oncogenes.

[0035] Cancers are often characterized by genome-wide changes in gene expression within the tumor. These changes enhance the ability of a tumor to progress through the cell cycle, avoid

apoptosis, or become resistant to chemotherapy. HDAC inhibitors have been shown to reverse several of these changes, and restore a pattern more like that of a normal cell.

[0036] The human genome consists of a complex network of genes which are turned on or off depending on the needs of the cell. One of the ways in which genes are turned on or off is by means of chemical modification of histone proteins. Histone proteins are structural components of chromosomes, and form a scaffold upon which DNA, the genetic material, is arranged. A well studied histone modification is acetylation and deacetylation, modifications that are catalyzed by a family of enzymes known as histone acetyl transferases and histone deacetylases.

[0037] Inhibition of HDAC enzymes by abexinostat tips the balance in favor of the acetylated state, a state that allows transcription to occur, which can be thought of as turning a gene "on". When a cell is treated with abexinostat, waves of previously silenced genes are initially turned on. Some of these genes are regulators themselves, and will activate or repress the expression of still other genes. The result is an orchestra of changes to gene expression: some genes being turned on, while others are kept in the off state.

[0038] Following chemotherapy and/or radiation treatment, some patient's tumors may turn on certain genes as a strategy by the tumor to adapt to the therapy and become resistant to cell death. One example of a genetic change that occurs in many cancers is the activation of the DNA repair gene RAD51. In response to treatment with DNA-damaging chemotherapy or radiation, tumors will often turn on DNA repair genes (including RAD51) as an adaptive strategy to help the tumor repair the DNA damage done by these agents. In pre-clinical models, abexinostat was able to turn off RAD51 (and other DNA repair genes), effectively blocking the ability of the tumor to repair its damaged DNA, sensitizing the tumor to chemotherapy and radiation.

[0039] In preclinical studies abexinostat and salts thereof (e.g., abexinostat HCl) have been found to have anticancer activities with remarkable tumor specificity. These early studies provided important information about the *in vitro* and *in vivo* activities of abexinostat and salts thereof (e.g., abexinostat HCl) and determined the molecular mechanism underlying the anticancer effects.

[0040] *In vitro*: abexinostat and salts thereof (e.g., abexinostat (or a salt thereof; e.g., abexinostat HCl) HCl) are active against many tumor cell lines and is efficacious in mouse models of lung, colon, prostate, pancreatic and brain tumors.

[0041] *Ex vivo*: abexinostat and salts thereof (e.g., abexinostat HCl) are active in primary human tumors from patients with colon, ovarian, lung and many hematological cancers.

[0042] Extensive safety and toxicology studies have been completed in multiple animal species. The mechanism of action of abexinostat and salts thereof (e.g., abexinostat HCl) have

been studied, and involves a multi-pronged attack on tumor cells: upregulation of p21 and other tumor suppressors and cell cycle genes; induction of reactive oxygen species and attenuation of anti-oxidant pathways; alterations in calcium homeostasis and increased ER stress; downregulation of DNA repair pathways and increased DNA damage; direct induction of apoptosis via death receptors and activation of caspases.

[0043] In clinical trials involving humans with cancer, abexinostat in solution form was administered at 2 mg/kg as a single oral dose and as multiple 2-hour IV infusion doses. Systemic exposure measured as $AUC_{0-\infty}$ for IV and oral dosing was 5.9 μM*hr and 1.45 μM*hr, respectively, indicating an oral bioavailability of about 27% in humans.

Treatment Regimen

[0044] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[0045] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[0046] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the

development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[0047] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[0048] In some embodiments, the cancer is a hematological cancer, solid tumor or a sarcoma.

[0049] In some embodiments, the cancer is a sarcoma. In some embodiments, the cancer is soft tissue sarcoma.

[0050] In some embodiments, the cancer is selected from a: breast cancer, colon cancer, colorectal cancer, non-small cell lung cancer, small-cell lung cancer, liver cancer, ovarian cancer, prostate cancer, uterine cervix cancer, urinary bladder cancer, gastric cancer, gastrointestinal stromal tumor, pancreatic cancer, germ cell tumor, mast cell tumor, neuroblastoma, mastocytosis, testicular cancer, glioblastoma, astrocytoma, B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, melanoma, myeloma, acute myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome, chronic myelogenous leukemia, and renal cell carcinoma.

[0051] In some embodiments, the cancer is selected from: breast cancer, colon cancer, colorectal carcinomas, non-small cell lung cancer, liver cancer, ovarian cancer, uterine cervix cancer, gastric carcinoma, pancreatic cancer, glioblastomas, B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, myeloma, myelodysplastic syndrome (MDS), and renal cell carcinoma. In some embodiments, the cancer is renal cell carcinoma or ovarian cancer.

[0052] In some embodiments of the methods disclosed herein, an HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof; e.g.,

pazopanib HCl) are administered in one dosage form (e.g., one oral dosage form). In some embodiments of the methods disclosed herein, an HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered separately (i.e., in separate oral dosage forms). Where an HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered separately, they are administered concurrently or sequentially. In some embodiments, an HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof; e.g., pazopanib HCl), are administered separately and sequentially. In some embodiments, an HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered separately and concurrently.

[0053] In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof; e.g., abexinostat HCl), and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered in one dosage form (e.g., one oral dosage form). In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof; e.g., abexinostat HCl), and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered separately (i.e., in separate oral dosage forms). Where abexinostat (or a salt thereof; e.g., abexinostat HCl), and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered separately, they are administered concurrently or sequentially. In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl), and pazopanib (or a salt thereof; e.g., pazopanib HCl), are administered separately and sequentially. In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl), and pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered separately and concurrently.

[0054] In some embodiments of the methods disclosed herein, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and/or pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered by immediate release dosage forms. In some embodiments of the methods disclosed herein, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and/or pazopanib (or a salt thereof; e.g., pazopanib HCl), are administered by controlled release dosage forms. In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) is administered by a controlled release dosage form and pazopanib, or a salt of pazopanib (e.g., pazopanib HCl), is administered by an immediate release dosage form.

[0055] In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof; e.g., abexinostat HCl), and/or pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered by immediate release dosage forms. In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof; e.g., abexinostat HCl), and/or pazopanib (or a salt thereof; e.g.,

pazopanib HCl), are administered by controlled release dosage forms. In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered by a controlled release dosage form and pazopanib, or a salt of pazopanib (e.g., pazopanib HCl), is administered by an immediate release dosage form.

[0056] In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and/or pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered orally (e.g., by capsules or tablets). In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) is administered orally (e.g., by capsules or tablets). In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered orally (e.g., by capsules or tablets).

[0057] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl), and/or pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered orally (e.g., by capsules or tablets). In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered orally (e.g., by capsules or tablets). In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered orally (e.g., by capsules or tablets).

[0058] In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and/or pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered intravenously. In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) is administered intravenously. In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered intravenously

[0059] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl), and/or pazopanib (or a salt thereof; e.g., pazopanib HCl) are administered intravenously. In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered intravenously. In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered intravenously.

[0060] In some embodiments of the methods disclosed herein, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) in fast mode. In some embodiments of the methods disclosed herein, pazopanib (or a salt thereof) is administered in fast mode. In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof) are administered in fast mode.

[0061] In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof) is administered in fast mode. In some embodiments of the methods disclosed herein, pazopanib (or a salt thereof) is administered in fast mode. In some embodiments, abexinostat (or a salt thereof), and pazopanib (or a salt thereof) are administered in fast mode.

[0062] In some embodiments of the methods disclosed herein, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) is administered at least about one hour before a meal or at least about 2 hours after a meal. In some embodiments of the methods disclosed herein, pazopanib (or a salt thereof) is administered at least about one hour before a meal or at least about 2 hours after a meal. In some embodiments, the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) and pazopanib (or a salt thereof) are administered at least about one hour before a meal or at least about 2 hours after a meal

[0063] In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof) is administered at least about one hour before a meal or at least about 2 hours after a meal. In some embodiments of the methods disclosed herein, pazopanib (or a salt thereof) is administered at least about one hour before a meal or at least about 2 hours after a meal. In some embodiments, abexinostat (or a salt thereof), and pazopanib (or a salt thereof) are administered at least about one hour before a meal or at least about 2 hours after a meal

[0064] In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) BID. In some embodiments, the methods disclosed herein comprise administering between about 400 mg and about 800 mg of pazopanib (or a salt thereof). In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) BID, and about 200 mg to about 800 mg of pazopanib (or a salt thereof). In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of the HDAC inhibitor (e.g., abexinostat or a salt thereof such as abexinostat HCl) BID, and about 216.7 mg to about 866.8 mg of pazopanib HCl.

[0065] In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of abexinostat (or a salt thereof) BID. In some embodiments, the methods disclosed herein comprise administering between about 400 mg and about 800 mg of pazopanib (or a salt thereof). In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of abexinostat (or a salt thereof) BID, and about 200 mg to about 800 mg of pazopanib (or a salt thereof). In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of abexinostat (or a salt thereof) BID, and about 216.7 mg to about 866.8 mg of pazopanib HCl.

[0066] In some embodiments, the methods disclosed herein comprise administering between about 30mg/m2 and about 75mg/m2 of abexinostat (or a salt thereof) BID for 5 days, followed by 2 days without administration of abexinostat (or a salt thereof). In some embodiments, the

methods disclosed herein comprise administering between about 400 mg and about 800 mg of pazopanib (or a salt thereof). In some embodiments, the methods disclosed herein comprise administering (a) between about 30mg/m2 and about 75mg/m2 of abexinostat (or a salt thereof) BID for 5 days, followed by 2 days without administration of abexinostat (or a salt thereof), and (b) about 200 mg to about 800 mg of pazopanib (or a salt thereof). In some embodiments, the methods disclosed herein comprise administering (a) between about 30mg/m2 and about 75mg/m2 of abexinostat (or a salt thereof) BID for 5 days, followed by 2 days without administration of abexinostat (or a salt thereof), and (b) about 216.7 mg to about 866.8 mg of pazopanib HCl.

[0067] In some embodiments, the methods disclosed herein are continued until the cancer is in remission. In some embodiments, the methods disclosed herein are continued until disease progression, unacceptable toxicity, or individual choice. In some embodiments, the methods disclosed herein are continued chronically.

Abexinostat

[0068] In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 1 to 14 consecutive days, 2 to 14 consecutive days, 3 to 14 consecutive days, 4 to 14 consecutive days, 5 to 14 consecutive days, 6 to 14 consecutive days, 7 to 14 consecutive days, 8 to 14 consecutive days, 9 to 14 consecutive days, 10 to 14 consecutive days, 11 to 14 consecutive days, 12 to 14 consecutive days, or 13 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 1 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 2 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 3 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 4 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 5 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 6 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 7 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 8 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 9 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 10 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 11 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 12 to 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 13 to 14

consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 5 to 9 days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 6 to 8 days.

[0069] In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 2 consecutive days, 3 consecutive days, 4 consecutive days, 5 consecutive days, 6 consecutive days, 7 consecutive days, 8 consecutive days, 9 consecutive days, 10 consecutive days, 11 consecutive days, 12 consecutive days, 13 consecutive days, or 14 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 2 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 3 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 4 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 5 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 6 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 7 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 8 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 9 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 10 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 11 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 12 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 13 consecutive days. In some embodiments, the cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl) is 14 consecutive days.

[0070] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered once per day during a cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered twice per day during a cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered three times per day during a cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl). In certain instances, twice a day dosing reduces the incidences of thrombocytopenia as compared to three times a day dosing.

[0071] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered twice per day during a cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, each dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered 4 to 8 hours apart. In some embodiments, any of the methods disclosed herein

comprise administering a first dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) and a second dose of abexinostat (or a salt thereof; e.g., abexinostat HCl), wherein the first dose and the second dose are administered 4 to 8 hours apart.

[0072] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered three times per day during a cycle of abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, each dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered 4 to 8 hours apart. In some embodiments, any of the methods disclosed herein comprise administering a first dose of abexinostat (or a salt thereof; e.g., abexinostat HCl), a second dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) and a third dose of abexinostat (or a salt thereof; e.g., abexinostat HCl), wherein the first dose, the second dose and the third dose are administered 4 to 8 hours apart.

[0073] For therapeutic effect, the effective plasma concentration of abexinostat in humans should be maintained for at least 6 consecutive hours, at least 7 consecutive hours, or at least 8 consecutive hours each day on days of dosing. Maintaining the effective plasma concentrations for about 6 consecutive hours to about 8 consecutive hours of abexinostat on days of dosing increases the efficacy of tumor cell growth inhibition and minimizes the incidences of thrombocytopenia.

[0074] In some embodiments, the effective plasma concentration of abexinostat in humans is maintained for at least 6 consecutive hours each day on days of dosing. In some embodiments, a dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) is sufficient to maintain an effective plasma concentration of the HDAC inhibitor in the individual for at least about 6 consecutive hours.

[0075] In some embodiments, the effective plasma concentration of abexinostat in humans is maintained for at least 7 consecutive hours each day on days of dosing. In some embodiments, a dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) is sufficient to maintain an effective plasma concentration of the HDAC inhibitor in the individual for at least about 7 consecutive hours.

[0076] In some embodiments, the effective plasma concentration of abexinostat in humans is maintained for at least 8 consecutive hours each day on days of dosing. In some embodiments, a dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) is sufficient to maintain an effective plasma concentration of the HDAC inhibitor in the individual for at least about 8 consecutive hours.

[0077] In some embodiments, the effective plasma concentration of abexinostat in humans is maintained for at least 6 consecutive hours but not exceeding 12, 13, or 14 consecutive hours on days of dosing. Maintaining the effective plasma concentrations for at least 6 consecutive hours

but not exceeding 14 consecutive hours of abexinostat on days of dosing increases the efficacy of tumor cell growth inhibition and minimizes the incidences of thrombocytopenia.

[0078] The oral bioavailability of abexinostat in humans, administered as immediate release capsules or an oral solution, was determined to be about 27 %. A difference in pharmacokinetics was observed in laboratory animals between the fasted state the fed state. Abexinostat appears to be preferentially absorbed in the intestines.

[0079] Daily amounts of abexinostat which are administered to humans range from about 10 mg/mm^2 to about 200 mg/mm^2. In some embodiments, the daily dose of abexinostat is between about 30 mg/mm^2 to about 90 mg/mm^2. In some embodiments, the daily dose of abexinostat is between about 60 mg/mm^2 to about 150 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 20 mg/mm^2, about 30 mg/mm^2, about 40 mg/mm^2, about 50 mg/mm^2, about 60 mg/mm^2, about 70 mg/mm^2, about 80 mg/mm^2, about 90 mg/mm^2, about 100 mg/mm^2, about 110 mg/mm^2, about 120 mg/mm^2, about 130 mg/mm^2, about 140 mg/mm^2, or about 150 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 20 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 30 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 40 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 50 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 60 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 70 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 80 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 90 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 100 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 110 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 120 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 130 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 140 mg/mm^2. In some embodiments, the daily dose of abexinostat is about 150 mg/mm^2.

[0080] In some embodiments, the daily dose of abexinostat is between about 40 mg to about 600 mg of abexinostat.

[0081] The daily dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) that is administered varies depending upon factors including, by way of non-limiting example, the type of formulation utilized, the type of cancer and its severity, the identity (*e.g.*, weight, age) of the human, and/or the route of administration.

[0082] In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered by immediate release dosage forms. In some embodiments of the methods disclosed herein, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered by controlled release dosage forms.

[0083] In some embodiments, the dosage form completely releases abexinostat (or a salt thereof) over a period of about 2 hours to about 10 hours after administration.

[0084] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered orally (e.g., by capsules or tablets). In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered by an immediate release oral dosage form (e.g., by capsules or tablets). In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered by a controlled release oral dosage form (e.g., by capsules or tablets).

[0085] In some embodiments of the methods disclosed herein, the methods comprise administering a first immediate release oral dosage form comprising abexinostat (or a salt thereof) and a second immediate release oral dosage form comprising abexinostat (or a salt thereof) , wherein the second immediate release oral dosage form is administered about 4 to about 8 hours form the first immediate release oral dosage form.

[0086] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered intravenously.

[0087] In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered when the individual is in fast mode. In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered at least about 1 hour before a meal. In some embodiments, abexinostat (or a salt thereof; e.g., abexinostat HCl) is administered at least about 2 hours after a meal.

[0088] In some embodiments, abexinostat (or a salt thereof) is administered until the cancer is in remission. In some embodiments, abexinostat (or a salt thereof) is administered until disease progression, unacceptable toxicity, or individual choice. In some embodiments, abexinostat (or a salt thereof) is administered chronically.

Abexinostat Drug Holiday

[0089] In certain instances, thrombocytopenia is a side effect observed in humans that receive treatment with HDAC inhibitor compounds. Grade 4 thrombocytopenia typically includes instances when the human has a platelet count less than 25,000 per mm^2. Thrombocytopenia may be ameliorated or avoided by lowering the daily dose of abexinostat. In some embodiment, a method disclosed herein further comprises an abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday following an abexinostat (or a salt thereof; e.g., abexinostat HCl) cycle. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday does not compromise the efficacy of an abexinostat (or a salt thereof; e.g., abexinostat HCl) treatment regimen.

[0090] In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 1 to 14 consecutive days, 2

to 14 consecutive days, 3 to 14 consecutive days, 4 to 14 consecutive days, 5 to 14 consecutive days, 6 to 14 consecutive days, 7 to 14 consecutive days, 8 to 14 consecutive days, 9 to 14 consecutive days, 10 to 14 consecutive days, 11 to 14 consecutive days, 12 to 14 consecutive days, or 13 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 1 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 2 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 3 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 4 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 5 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 6 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 7 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 8 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 9 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 10 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 11 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 12 to 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday 13 to 14 consecutive days.

[0091] In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 2 consecutive days, 3 consecutive days, 4 consecutive days, 5 consecutive days, 6 consecutive days, 7 consecutive days, 8 consecutive days, 9 consecutive days, 10 consecutive days, 11 consecutive days, 12 consecutive days, 13 consecutive days, or 14 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 2 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug

holiday is 3 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 4 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 5 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 6 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 7 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 8 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 9 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 10 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 11 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 12 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 13 consecutive days. In some embodiments, the abexinostat (or a salt thereof; e.g., abexinostat HCl) abexinostat (or a salt thereof; e.g., abexinostat HCl) drug holiday is 14 consecutive days.

[0092] In some embodiments, the methods disclosed herein comprise 5-9 consecutive days of daily dosing of abexinostat (or a salt thereof; e.g., abexinostat HCl), followed by 5-9 consecutive days without dosing abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, the methods disclosed herein comprise 5-9 consecutive days of daily dosing of abexinostat (or a salt thereof; e.g., abexinostat HCl), followed by 2-9 consecutive days without dosing abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, the methods disclosed herein comprise 6-8 consecutive days of daily dosing of abexinostat (or a salt thereof; e.g., abexinostat HCl), followed by 6-8 consecutive days without dosing abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, the methods disclosed herein comprise 6-8 consecutive days of daily dosing of abexinostat (or a salt thereof; e.g., abexinostat HCl), followed by 2-8 consecutive days without dosing abexinostat (or a salt thereof; e.g., abexinostat HCl).

[0093] In some embodiments, the methods disclosed herein comprise 7 consecutive days of daily dosing of abexinostat (or a salt thereof; e.g., abexinostat HCl), followed by 7 consecutive days without dosing abexinostat (or a salt thereof; e.g., abexinostat HCl).

[0094] In some embodiments, the methods disclosed herein comprise 5 consecutive days of daily dosing of abexinostat (or a salt thereof; e.g., abexinostat HCl), followed by 2 consecutive days without dosing abexinostat (or a salt thereof; e.g., abexinostat HCl).

Pazopanib

[0095] Pazopanib, 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)(methyl)amino]pyrimidin-2-yl]amino]-2-methylbenzenesulfonamide monohydrochloride, is an oral angiogenesis inhibitor targeting the tyrosine kinase activity associated with vascular endothelial growth factor receptor (VEGFR)-1, -2 and -3, platelet-derived growth factor receptor (PDGFR)-α, and PDGFR–β, and stem cell factor receptor (c-KIT).

[0096] In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl), is administered to an individual in combination with abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, pazopanib is administered to an individual in combination with abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, pazopanib HCl is administered to an individual in combination with abexinostat (or a salt thereof; e.g., abexinostat HCl). In some embodiments, pazopanib HCl is administered to an individual in combination with a salt of abexinostat (e.g., abexinostat HCl).

[0097] In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered to the individual continuously, e.g., without drug holidays. In some embodiments, administration of pazopanib (or a salt thereof; e.g., pazopanib HCl), is not halted on the days that abexinostat is not administered (i.e., during an abexinostat drug holiday). In some embodiments, administration of pazopanib (or a salt thereof; e.g., pazopanib HCl) is halted on the days that abexinostat is not administered (i.e., during an abexinostat drug holiday).

[0098] In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered by an immediate release dosage form. In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered by a controlled release dosage form.

[0099] In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered orally (e.g., by capsules or tablets). In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered by an immediate release oral dosage form (e.g., by capsules or tablets). In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered by a controlled release oral dosage form (e.g., by capsules or tablets).

[00100] In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered intravenously.

[00101] In some embodiments, abexinostat (or a salt thereof) is administered until the cancer is in remission. In some embodiments, abexinostat (or a salt thereof) is administered until disease

progression, unacceptable toxicity, or individual choice. In some embodiments, abexinostat (or a salt thereof) is administered chronically.

[00102] In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered when the individual is in fast mode. In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered at least about 1 hour before a meal. In some embodiments, pazopanib (or a salt thereof; e.g., pazopanib HCl) is administered at least about 2 hours after a meal.

[00103] In some embodiments, pazopanib (or a salt thereof) is administered once per day, twice per day, three times per day, or four times per day. In some embodiments, pazopanib (or a salt thereof) is administered once per day. In some embodiments, pazopanib (or a salt thereof) is administered twice per day. In some embodiments, pazopanib (or a salt thereof) is administered three times per day. In some embodiments, pazopanib (or a salt thereof) is administered four times per day.

[00104] In some embodiments, pazopanib (or a salt thereof) is administered twice per day. In some embodiments, each dose of pazopanib (or a salt thereof) is administered 4 to 8 hours apart. In some embodiments, any of the methods disclosed herein comprise administering a first dose of pazopanib (or a salt thereof) and a second dose of pazopanib (or a salt thereof), wherein the first dose and the second dose are administered 4 to 8 hours apart.

[00105] In some embodiments, pazopanib (or a salt thereof) is administered three times per day. In some embodiments, each dose of pazopanib (or a salt thereof) is administered 4 to 8 hours apart. In some embodiments, any of the methods disclosed herein comprise administering a first dose of pazopanib (or a salt thereof), a second dose of pazopanib (or a salt thereof) and a third dose of pazopanib (or a salt thereof), wherein the first dose, the second dose and the third dose are administered 4 to 8 hours apart.

[00106] In some embodiments, pazopanib (or a salt thereof) is administered four times per day. In some embodiments, each dose of pazopanib (or a salt thereof) is administered 4 to 8 hours apart. In some embodiments, any of the methods disclosed herein comprise administering a first dose of pazopanib (or a salt thereof), a second dose of pazopanib (or a salt thereof), a third dose of pazopanib (or a salt thereof), and a fourth dose of pazopanib (or a salt thereof), wherein the first dose, the second dose, the third dose and the fourth dose are administered 4 to 8 hours apart.

[00107] In some embodiments, the daily dose of pazopanib is about 200 mg to about 800 mg, about 400 mg to about 800 mg, or about 600 mg to about 800 mg. In some embodiments, the daily dose of pazopanib is about 200 mg to about 800 mg. In some embodiments, the daily dose of pazopanib is about 400 mg to about 800 mg. In some embodiments, the daily dose of pazopanib is about 600 mg to about 800 mg.

[00108] In some embodiments, the daily dose of pazopanib is about 200 mg, about 400 mg, about 600 mg or about 800 mg. In some embodiments, the daily dose of pazopanib is about 200 mg. In some embodiments, the daily dose of pazopanib is about 400 mg. In some embodiments, the daily dose of pazopanib is about 600 mg. In some embodiments, the daily dose of pazopanib is about 800 mg.

[00109] In some embodiments, the daily dose of pazopanib HCl is about 216.7 mg to about 866.8 mg, about 433.4 mg to about 866.8 mg, or about 650.1 mg to about 866.8 mg. In some embodiments, the daily dose of pazopanib HCl is about 216.7 mg to about 866.8 mg. In some embodiments, the daily dose of pazopanib HCl is about 433.4 mg to about 866.8 mg. In some embodiments, the daily dose of pazopanib HCl is about 650.1 mg to about 866.8 mg.

[00110] In some embodiments, the daily dose of pazopanib HCl is about 216.7 mg, about 433.4 mg, about 650.1 mg or about 866.8 mg. In some embodiments, the daily dose of pazopanib HCl is about 216.7 mg. In some embodiments, the daily dose of pazopanib HCl is about 433.4 mg. In some embodiments, the daily dose of pazopanib HCl is about 650.1 mg. In some embodiments, the daily dose of pazopanib HCl is about 866.8 mg.

[00111] The daily dose of abexinostat (or a salt thereof; e.g., abexinostat HCl) that is administered varies depending upon factors including, by way of non-limiting example, the type of formulation utilized, the type of cancer and its severity, the identity (*e.g.*, weight, age) of the human, and/or the route of administration.

HDAC Inhibitor Compounds

[00112] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of an HDAC inhibitor, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the HDAC inhibitor is abexinostat. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

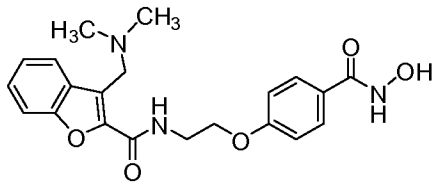
[00113] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of an HDAC inhibitor, or a salt thereof; and (b) pazopanib, or a salt

thereof. In some embodiments, the HDAC inhibitor is abexinostat. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00114] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of an HDAC inhibitor, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the HDAC inhibitor is abexinostat. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00115] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of an HDAC inhibitor, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the HDAC inhibitor is abexinostat. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00116] *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide (abexinostat) has the following structure:



Abexinostat.

[00117] In one aspect, abexinostat is used in the methods disclosed herein as a pharmaceutically acceptable salt. In one aspect, abexinostat is used as the hydrochloride salt.

[00118] Additional pharmaceutically acceptable salts of abexinostat include: (a) salts formed when the acidic proton of abexinostat is replaced by a metal ion, such as for example, an alkali metal ion (e.g. lithium, sodium, potassium), an alkaline earth ion (e.g. magnesium, or calcium), or an aluminum ion, or is replaced by an ammonium cation (NH_4^+); (b) salts formed by reacting abexinostat with a pharmaceutically acceptable organic base, which includes alkylamines, such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, dicyclohexylamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like; (c) salts formed by reacting abexinostat with a pharmaceutically acceptable acid, which provides acid addition salts. Pharmaceutically acceptable acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, metaphosphoric acid, and the like; or with an organic acid, such as, for example, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, trifluoroacetic acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1 -carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

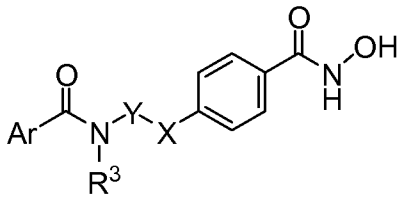
[00119] Additional pharmaceutically acceptable salts include those described in Berge *et al.*, *J. Pharm. Sci.* 1977, 66, 1-19; and "Handbook of Pharmaceutical Salts, Properties, and Use," Stah and Wermuth, Ed.; Wiley-VCH and VHCA, Zurich, 2002.

[00120] In some embodiments, sites on the aromatic ring portion of compounds described herein that are susceptible to various metabolic reactions are modified such that the various metabolic reactions are reduced, minimized or eliminated. Such modifications include incorporation of appropriate substituents on the aromatic ring structures, such as, by way of

example only, halogens, deuterium, and the like. In one aspect, HDAC inhibitor compounds described herein are deuterated at sites susceptible to metabolic reactions.

[00121] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, respectively. Certain isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Further, substitution with isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements.

[00122] Other HDAC inhibitor compounds that are contemplated for use in the pharmaceutical compositions, pharmacokinetic strategies, dosing regimens, methods of treatments, and combination therapies include those compounds with the structure of Formula (I):



Formula (I)

wherein:

X is –O-, -NR^2-, or –$S(O)_n$ where n is 0, 1, or 2 and R^2 is hydrogen, –CH_3, -CH_2CH_3;

Y is ethylene, propylene, 1-methylpropylene, 2-methylpropylene, -$CH(C_2H_5)CH_2$-, -$CH(CH(CH_3)_2)CH_2$-, and -$CH(CH_3)CH_2$-;

R^3 is hydrogen, -CH_3, or -CH_2CH_3;

Ar is phenyl, naphthyl, quinolinyl, benzofuranyl, benzothienyl, *trans* phenylCH=CH- or *trans* (benzofuran-2-yl)CH=CH-, wherein Ar is optionally substituted with one or two substituents independently selected from chloro, fluoro, trifluoromethyl, methyl, ethyl, methoxy, ethoxy, methylenedioxy, -OH, 1-cyclopropylpiperidin-4-yloxy, 1-(2,2,2-trifluoroethyl)piperidin-4-yloxy, *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, 2-methoxyethoxymethyl, phenoxymethyl, 2-methoxyethoxy, 2-morpholin-4-ylethoxy, pyridin-3-ylmethoxy, 2-hydroxyethoxy, 2-*N,N*-dimethylaminoethoxy, methoxymethyl, 3-*i*-propoxymethyl, morpholin-4-ylmethyl, 3-hydroxypropyloxymethyl, 2-fluorophenoxymethyl, 3-fluorophenoxymethyl, 4-

fluorophenoxy-methyl, 3-methoxypropyloxymethyl, pyridin-4-yloxymethyl, 2,4,6-trifluorophenoxymethyl, 2-oxopyridin-1-ylmethyl, 2,2,2-trifluoroethoxymethyl, 4-imidazol-1-ylphenoxymethyl, 4-[1.2.4-triazin-1-yl-phenoxymethyl, 2-phenylethyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, 4-trifluoromethylpiperidin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 3,3,3-trifluoropropyloxymethyl, 4-fluorophenylthiomethyl, 4-fluorophenylsulfinylmethyl, 4-fluorophenylsulfonylmethyl, pyridin-3-ylmethyloxymethyl, tetrahydropyran-4-yloxy, 2,2,2-trifluoroethyloxy, 2-pyrrolidin-1-ylethyloxy, piperidin-4-yloxy, *N*-methyl-*N*-benzylaminomethyl, *N*-methyl-*N*-2-phenylethylaminomethyl, 3-hydroxypropylthiomethyl, 3-hydroxypropylsulfinylmethyl, 3-hydroxypropylsulfonyl-methyl, *N*-methyl-*N*-2-indol-3-ylethylaminomethyl, 2-(4-trifluoromethylphenyl)ethyl, 2-(3-trifluoromethoxyphenyl)ethyl, *N*-hydroxyaminocarbonyl-methylaminomethyl, or 3-(2-carboxyethylamino-methyl); or

a pharmaceutically acceptable salt thereof.

[00123] In some embodiments, Ar is benzofuran-2-yl and is monosubstituted at the 3-position of the benzofuran-2-yl ring with *N*,*N*-dimethylaminomethyl, *N*,*N*-diethylaminomethyl, 2-fluorophenoxymethyl, 3-fluorophenoxymethyl, 4-fluorophenoxy-methyl, hydroxyl-4-yloxymethyl, 2,4,6-trifluorophenoxy-methyl, 2-oxopyridin-1-ylmethyl, 2,2,2-trifluoroethoxy-methyl, 4-imidazol-1-ylphenoxy-methyl, 4-[1.2.4-triazin-1-yl-phenoxymethyl, 2-phenylethyl, 3-hydroxypropyloxymethyl, 2-methoxyethyloxymethyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, 4-trifluoromethylpiperidin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 3,3,3-trifluoropropyloxymethyl, 4-fluorophenylthiomethyl, 4-fluorophenylsulfinylmethyl, 4-fluorophenylsulfonylmethyl, 2-(3-trifluoromethoxyphenylethyl), *N*-methyl-*N*-benzylaminomethyl, *N*-methyl-*N*-2-phenylethylaminomethyl, 3-hydroxypropyl-thiomethyl, 3-hydroxypropylsulfinyl-methyl, 3-hydroxypropylsulfonylmethyl, *N*-methyl-*N*-2-indol-3-ylethylaminomethyl, 2-(4-trifluoromethylphenyl)ethyl, *N*-hydroxyaminocarbonyl-methylaminomethyl, or 2-carboxyethylaminomethyl.

[00124] In some embodiments, Ar is benzofuran-2-yl and is monosubstituted at the 3-position of the benzofuran-2-yl ring with *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, 2-methoxyethoxymethyl, methoxymethyl, 3-*i*-propoxymethyl, morpholin-4-ylmethyl, 3-hydroxypropyloxymethyl, 3-methoxypropyloxymethyl, pyrrolidin-1-ylmethyl, or piperidin-1-ylmethyl.

[00125] In some embodiments, Ar is benzofuran-2-yl and is substituted at the 5-position of the benzofuran-2-yl ring with 1-cyclopropylpiperidin-4-yloxy, piperidin-4-yloxy, tetrahydropyran-

4-yloxy, 2,2,2-trifluoroethoxy, 2-pyrrolidin-1-ylethyloxy, or 1-(2,2,2-trifluoroethyl)piperidin-4-yloxy.

[00126] In some embodiments, Ar is *trans* phenylCH=CH- wherein the phenyl is optionally substituted with one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, methylenedioxy, or –OH. In some embodiments, Ar is *trans* phenylCH=CH-.

[00127] In some embodiments, Ar is naphthyl wherein the naphthyl is optionally substituted with one or two substituents.

[00128] In some embodiments, Ar is quinolinyl wherein the quinolinyl is optionally substituted with one or two substituents.

[00129] In some embodiments, Ar is quinolinyl wherein the quinolinyl is optionally substituted with one or two substituents independently selected from chloro, fluoro, trifluoromethyl, methyl, ethyl, methoxy, ethoxy, methylenedioxy, -OH, 2-methoxyethoxy, 2-hydroxyethoxy, methoxymethyl, 3-*i*-propoxymethyl, 3-hydroxypropyloxymethyl, 3-methoxypropyloxymethyl, or 3,3,3-trifluoropropyloxymethyl.

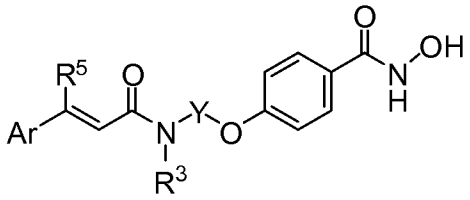
[00130] In some embodiments, X is –O- and R^3 is hydrogen.

[00131] In some embodiments, X is $–S(O)_n$ and R^3 is hydrogen.

[00132] In some embodiments, Y is ethylene. In some embodiments, Y is ethylene or -$CH(C_2H_5)CH_2$-. In some embodiments, Y is -$CH(C_2H_5)CH_2$-.

[00133] In some embodiments, X is –O-; R^3 is hydrogen; and Y is ethylene or -$CH(C_2H_5)CH_2$-.

[00134] Yet other HDAC inhibitor compounds that are contemplated for use in the pharmaceutical compositions, pharmacokinetic strategies, dosing regimens, methods of treatments, and combination therapies include those compounds with the structure of Formula (II):



Formula (II)

wherein:

X is –O-, -NR^2-, or $–S(O)_n$ where n is 0, 1, or 2 and R^2 is hydrogen, $–CH_3$, -CH_2CH_3;

Y is ethylene, propylene, 1-methylpropylene, 2-methylpropylene, -$CH(C_2H_5)CH_2$-, -$CH(CH(CH_3)_2)CH_2$-, and -$CH(CH_3)CH_2$-;

R^3 is hydrogen, -CH_3, or -CH_2CH_3;

Ar is phenyl, naphthyl, quinolinyl, benzofuranyl, or benzothienyl, wherein Ar is optionally substituted with one or two substituents independently selected from

chloro, fluoro, trifluoromethyl, methyl, ethyl, methoxy, ethoxy, methylenedioxy, -OH;

R^5 is trifluoromethyl, methyl, ethyl, *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, 2-methoxyethoxymethyl, phenoxymethyl, methoxymethyl, 3-*i*-propoxymethyl, morpholin-4-ylmethyl, 3-hydroxypropyloxymethyl, 2-fluorophenoxymethyl, 3-fluorophenoxymethyl, 4-fluorophenoxy-methyl, 3-methoxypropyloxymethyl, pyridin-4-yloxymethyl, 2,4,6-trifluorophenoxymethyl, 2-oxopyridin-1-ylmethyl, 2,2,2-trifluoroethoxymethyl, 4-imidazol-1-ylphenoxymethyl, 2-phenylethyl, pyrrolidin-1-ylmethyl, piperidin-1-ylmethyl, 4-trifluoromethylpiperidin-1-ylmethyl, 4-methylpiperazin-1-ylmethyl, 3,3,3-trifluoropropyloxymethyl, 4-fluorophenylthiomethyl, 4-fluorophenylsulfinylmethyl, 4-fluorophenylsulfonylmethyl, pyridin-3-ylmethyloxymethyl, *N*-methyl-*N*-benzylaminomethyl, *N*-methyl-*N*-2-phenylethylaminomethyl, 3-hydroxypropylthiomethyl, 3-hydroxypropylsulfinylmethyl, 3-hydroxypropylsulfonyl-methyl, *N*-methyl-*N*-2-indol-3-ylethylaminomethyl, 2-(4-trifluoromethylphenyl)ethyl, 2-(3-trifluoromethoxyphenyl)ethyl, *N*-hydroxyaminocarbonyl-methylaminomethyl, or 3-(2-carboxyethylamino-methyl); or a pharmaceutically acceptable salt thereof.

[00135] In some embodiments, Ar is benzofuranyl.

[00136] In some embodiments, R^5 is *N,N*-dimethylaminomethyl, *N,N*-diethylaminomethyl, pyrrolidin-1-ylmethyl, or piperidin-1-ylmethyl.

[00137] In some embodiments, the HDAC inhibitor is selected from: *N*-hydroxy-4-[2-(4-methoxyquinolin-2-ylcarbonylamino)ethoxy]benzamide; *N*-hydroxy-4-[2*S*-(*trans*-cinnamoylamino)butoxy]benzamide; *N*-hydroxy-4-[2*R*-(*trans*-cinnamoylamino)butoxy]benzamide; *N*-hydroxy-4-{2-[4-(2-methoxyethoxy)quinolin-2-ylcarbonylamino]ethoxy}benzamide; *N*-hydroxy-4-[2*S*-(benzothiophen-2-ylcarbonylamino)butoxy]-benzamide; *N*-hydroxy-4-{2S-[benzofuran-2-ylcarbonylamino]butoxy}benzamide; *N*-hydroxy-4-{2-[3-(methoxymethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide; *N*-hydroxy-4-{2-[3-(*N,N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide (abexinostat); *N*-hydroxy-4-{2-[3-(*i*-propoxymethyl)benzofuran-2-ylcarbonylamino]ethoxy}benzamide; *N*-hydroxy-4-{2-[3-(3-hydroxypropoxymethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide; *N*-hydroxy-4-{2-[3-(2-methoxyethyloxymethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide; *N*-hydroxy-4-{2-[3-(pyrrolidin-1-ylmethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide; *N*-hydroxy-4-{2-[3-(piperidin-1-ylmethyl)benzofuran-2-

ylcarbonylamino]ethoxy}-benzamide; *N*-hydroxy-4-{2-[3-(4-methylpiperazin-1-ylmethyl)benzofuran-2-ylcarbonylamino]-ethoxy}benzamide; *N*-hydroxy-4-{2-[5-(tetrahydropyran-4-yloxy)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide; *N*-hydroxy-4-{2-[5-(2-pyrrolidin-1-ylethyloxy)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide; *N*-hydroxy-4-{2*S*-[5-(2-pyrrolidin-1-ylethyloxy)benzofuran-2-ylcarbonylamino]butoxy}-benzamide; *N*-hydroxy-4-{2-[5-(2-pyrrolidin-1-ylethyloxy)benzofuran-2-ylcarbonylamino]-1*R*-methyl-ethoxy}benzamide; and *N*-hydroxy-4-{2-[(3-(benzofuran-2-yl)-4-(dimethylamino)-but-2-enoyl)amino]-ethoxy}benzamide; or a pharmaceutically acceptable salt thereof.

[00138] In some embodiments, the HDAC inhibitor is *N*-hydroxy-4-{2-[3-(*N*,*N*-dimethylaminomethyl)benzofuran-2-ylcarbonylamino]ethoxy}-benzamide (abexinostat).

[00139] In some embodiments, the HDAC inhibitor is selected from HDAC inhibitors disclosed in WO 2004/092115 or WO 2005/097770, both of which are herein incorporated by reference.

Forms and Phases

[00140] HDAC inhibitors (e.g. abexinostat), including pharmaceutically acceptable salts thereof, and pharmaceutically acceptable solvates thereof, are in various forms, including but not limited to, amorphous phase, partially crystalline forms, crystalline forms, milled forms, and nano-particulate forms. The crystalline forms are known as polymorphs. Polymorphs include the different crystal packing arrangements of the same elemental composition of a compound. This arrangement can significantly affect the physiochemical, formulation and processing parameters as well as the shelf life or stability of the substance and excipients. Polymorphs usually have different X-ray diffraction patterns, infrared spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Various factors such as the recrystallization solvent, rate of crystallization, and storage temperature cause a single crystal form to dominate. In one aspect, a crystalline form of an HDAC inhibitor (e.g. abexinostat) is used in the pharmaceutical compositions disclosed herein. In one aspect, a crystalline form of the HCl salt of abexinostat is used in the pharmaceutical compositions disclosed herein. In one aspect, amorphous abexinostat is used in the pharmaceutical compositions disclosed herein. In one aspect, amorphous HCl salt of abexinostat is used in the pharmaceutical composition disclosed herein.

Pharmaceutical Compositions

[00141] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to

the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00142] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00143] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00144] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt

thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00145] Compositions for use with the methods disclosed herein are formulated in a conventional manner using one or more physiologically acceptable carriers (i.e. inactive ingredients) comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which are used pharmaceutically. Suitable techniques, carriers, and excipients include those found within, for example, Remington*: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins1999), herein incorporated by reference in their entirety.

[00146] Compositions for use with the methods disclosed herein comprise abexinostat (or a salt thereof), and/or pazopanib (or a salt thereof), and one or more of the following: (a) binders; (b) coatings; (c) disintegrants; (d) fillers (diluents); (e) lubricants; (f) glidants (flow enhancers); (g) compression aids; (h) colors; (i) sweeteners; (j) preservatives; (k) suspensing/dispersing agents; (l) film formers/coatings; (m) flavors; (n) printing inks; (o) gelling agents; (p) a second therapeutically active agent.

[00147] In one aspect, pharmaceutical compositions for use with the methods disclosed herein include one or more of the following in addition to the active agent(s) (e.g. abexinostat, a salt of abexinostat, pazopanib, and/or a salt of pazopanib): (a) magnesium stearate; (b) lactose; (c) microcrystalline Cellulose; (d) silicified microcrystalline cellulose; (e) mannitol; (f) starch (corn); (g) silicon dioxide; (h) titanium dioxide; (i) stearic acid; (j)s Starch glycolate; (k) gelatin; (l) talc; (m) sucrose; (n) aspartame; (o) calcium stearate; (p) povidone; (q) pregelatinized starch; (r) hydroxy propyl methylcellulose; (s) OPA products (coatings & inks); (t) croscarmellose; (u) hydroxy propyl cellulose; (v) ethylcellulose; (w) calcium phosphate (dibasic); (x) crospovidone; (y) shellac (and glaze); (z) sodium carbonate.

[00148] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein comprise an active ingredient (e.g., abexinostat, a salt of abexinostat, pazopanib, and/or a salt of pazopanib) in a pharmaceutically acceptable vehicle, carrier, diluent, or excipient, or a mixture thereof; and one or more release controlling excipients as described herein. Suitable modified release dosage vehicles include, but are not limited to, hydrophilic or hydrophobic matrix devices, water-soluble separating layer coatings, enteric coatings, osmotic devices, multi-particulate devices, and combinations thereof. The pharmaceutical compositions may also comprise non-release controlling excipients.

[00149] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are film-coated dosage forms, which comprise a combination of an active ingredient and one or more tabletting excipients to form a tablet core using conventional tabletting processes and subsequently coating the core. The tablet cores can be produced using conventional granulation methods, for example wet or dry granulation, with optional comminution of the granules and with subsequent compression and coating. Granulation methods are described, for example, in Voigt, pages 156-69.

[00150] Suitable excipients for the production of granules are, for example pulverulent fillers optionally having flow-conditioning properties, for example talcum, silicon dioxide, for example synthetic amorphous anhydrous silicic acid of the Syloid® type (Grace), for example SYLOID 244 FP, microcrystalline cellulose, for example of the Avicel® type (FMC Corp.), for example of the types AVICEL PH101, 102, 105, RC581 or RC 591, Emcocel® type (Mendell Corp.) or Elcema® type (Degussa); carbohydrates, such as sugars, sugar alcohols, starches or starch derivatives, for example lactose, dextrose, saccharose, glucose, sorbitol, mannitol, xylitol, potato starch, maize starch, rice starch, wheat starch or amylopectin, tricalcium phosphate, calcium hydrogen phosphate or magnesium trisilicate; binders, such as gelatin, tragacanth, agar, alginic acid, cellulose ethers, for example methylcellulose, carboxymethylcellulose or hydroxypropylmethylcellulose, polyethylene glycols or ethylene oxide homopolymers, especially having a degree of polymerization of approximately from $2.0x10^3$ to $1.0x10^5$ and an approximate molecular weight of about from $1.0x10^5$ to $5.0x10^6$, for example excipients known by the name Polyox® (Union Carbide), polyvinylpyrrolidone or povidones, especially having a mean molecular weight of approximately 1000 and a degree of polymerization of approximately from about 500 to about 2500, and also agar or gelatin; surface-active substances, for example anionic surfactants of the alkyl sulfate type, for example sodium, potassium or magnesium n-dodecyl sulfate, n-tetradecyl sulfate, n-hexadecyl sulfate or n-octadecyl sulfate, of the alkyl ether sulfate type, for example sodium, potassium or magnesium n-dodecyloxyethyl sulfate, n-tetradecyloxyethyl sulfate, n-hexadecyloxyethyl sulfate or n-octadecyloxyethyl sulfate, or of the alkanesulfonate type, for example sodium, potassium or magnesium n-dodecanesulfonate, n-tetradecanesulfonate, n-hexadecanesulfonate or n-octadecanesulfonate, or non-ionic surfactants of the fatty acid polyhydroxy alcohol ester type, such as sorbitan monolaurate, monooleate, monostearate or monopalmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxy alcohol esters, such as polyoxyethylene sorbitan monolaurate, monooleate, monostearate, monopalmitate, tristearate or trioleate, polyethylene glycol fatty acid esters, such as polyoxyethyl stearate, polyethylene glycol 400 stearate, polyethylene glycol 2000

stearate, especially ethylene oxide/propylene oxide block polymers of the Pluronics® (BWC) or Synperonic® (ICI) type

[00151] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated in enteric coated dosage forms, which comprise a combination of an active ingredient, or a pharmaceutically acceptable salt, solvate, or prodrug thereof; and one or more release controlling excipients for use in an enteric coated dosage form. The pharmaceutical compositions may also comprise non-release controlling excipients.

[00152] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated as a dosage form that has an instant releasing component and at least one delayed releasing component, and is capable of giving a discontinuous release of the compound in the form of at least two consecutive pulses separated in time from 0.5 hour up to 8 hours. The pharmaceutical compositions comprise a combination of an active ingredient, and one or more release controlling and non-release controlling excipients, such as those excipients suitable for a disruptable semi-permeable membrane and as swellable substances.

[00153] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated as a dosage form for oral administration to a subject, which comprises a combination of an active ingredient; and one or more pharmaceutically acceptable excipients or carriers, enclosed in an intermediate reactive layer comprising a gastric juice-resistant polymeric layered material partially neutralized with alkali and having cation exchange capacity and a gastric juice-resistant outer layer.

[00154] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein comprise an active ingredient, in the form of enteric-coated granules, as delayed-release capsules for oral administration.

[00155] The pharmaceutical compositions provided herein may be provided in unit-dosage forms or multiple-dosage forms. Unit-dosage forms, as used herein, refer to physically discrete units suitable for administration to human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the active ingredient(s) sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carriers or excipients. Examples of unit-dosage forms include individually packaged tablets and capsules. Unit-dosage forms 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 multiple-dosage forms include bottles of tablets or capsules.

[00156] Pharmaceutical dosage forms can be formulated in a variety of methods and can provide a variety of drug release profiles, including immediate release, sustained release, and

delayed release. In some cases it may be desirable to prevent drug release after drug administration until a certain amount of time has passed (i.e. timed release), to provide substantially continuous release over a predetermined time period (i.e. sustained release) or to provide release immediately following drug administration (i.e., immediate release).

[00157] Oral formulations are presented in the form of: tablets, capsules, pills, pellets, beads, granules, bulk powders. Capsules include mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Tablet formulations are made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. In some embodiments are surface modifying agents which include nonionic and anionic surface modifying agents. For example, surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine.

[00158] In one aspect, oral formulations described herein utilize standard delay or time release formulations to alter the absorption of the active compound(s).

[00159] 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. Binder levels are from about 50% to about 99% by weight in the pharmaceutical compositions provided herein.

[00160] 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.

[00161] Suitable disintegrants include, but are not limited to, agar; bentonite; celluloses, such as methylcellulose and carboxymethylcellulose; wood products; natural sponge; cation-exchange resins; alginic acid; gums, such as guar gum and Veegum HV; citrus pulp; cross-linked celluloses, such as croscarmellose; cross-linked polymers, such as crospovidone; cross-linked starches; calcium carbonate; microcrystalline cellulose, such as sodium starch glycolate; polacrilin potassium; starches, such as corn starch, potato starch, tapioca starch, and pre-gelatinized starch; clays; aligns; and mixtures thereof. The amount of 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. In one aspect, the pharmaceutical compositions provided herein include from about 0.5 to about 15% or from about 1 to about 5% by weight of a disintegrant.

[00162] 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. In one aspect, the pharmaceutical compositions provided herein include from about 0.1 to about 5% by weight of a lubricant.

[00163] Suitable glidants include colloidal silicon dioxide, CAB-O-SIL® (Cabot Co. of Boston, MA), and asbestos-free talc. Coloring agents include 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.

[00164] It should be understood that many carriers and excipients may serve several functions, even within the same formulation.

[00165] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated as compressed tablets, tablet triturates, rapidly dissolving

tablets, multiple compressed tablets, or enteric-coating tablets, sugar-coated, or film-coated tablets.

[00166] Enteric-coatings are coatings that resist the action of stomach acid but dissolve or disintegrate in the intestine.

[00167] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein include an enteric coating(s). Enteric coatings include one or more of the following: cellulose acetate phthalate; methyl acrylate-methacrylic acid copolymers; cellulose acetate succinate; hydroxy propyl methyl cellulose phthalate; hydroxy propyl methyl cellulose acetate succinate (hypromellose acetate succinate); polyvinyl acetate phthalate (PVAP); methyl methacrylate-methacrylic acid copolymers; methacrylic acid copolymers, cellulose acetate (and its succinate and phthalate version); styrol maleic acid co-polymers; polymethacrylic acid/acrylic acid copolymer; hydroxyethyl ethyl cellulose phthalate; hydroxypropyl methyl cellulose acetate succinate; cellulose acetate tetrahydrophtalate; acrylic resin; shellac.

[00168] An enteric coating is a coating put on a tablet, pill, capsule, pellet, bead, granule, particle, etc. so that it doesn't dissolve until it reaches the small intestine.

[00169] 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.

[00170] 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.

[00171] The tablet dosage forms may 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.

[00172] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are 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 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.

[00173] Coloring and flavoring agents can be used in all of the above dosage forms.

[00174] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated as immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

[00175] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are in the form of immediate or modified release dosage forms, including delayed-, sustained, pulsed-, controlled, targeted-, and programmed-release forms.

Controlled Release

[00176] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are in the form of a controlled release dosage form. As used herein, the term "controlled release" refers to a dosage form in which the rate or place of release of the active ingredient(s) is different from that of an immediate dosage form when orally administered. Controlled release dosage forms include delayed-, extended-, prolonged-, sustained-, pulsatile-, modified -, targeted-, programmed-release. The pharmaceutical compositions in controlled release dosage forms are prepared using a variety of modified release devices and methods known to those skilled in the art, including, but not limited to, matrix controlled release devices, osmotic controlled release devices, multiparticulate controlled release devices, ion-exchange resins, enteric coatings, multilayered coatings, and combinations thereof. The release rate of the active ingredient(s) can also be modified by varying the particle sizes.

[00177] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated to provide a controlled release of an active agent (e.g. abexinostat, a salt of abexinostat, pazopanib, and/or a salt of pazopanib), or a pharmaceutically acceptable salt thereof.

[00178] In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a human over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations. In some embodiments, controlled release compositions provide therapeutically effective levels of the HDAC inhibitor (e.g. abexinostat) for an extended period of time and thereby provide a longer period of pharmacologic response.

[00179] In some embodiments, the solid dosage forms described herein can be formulated as enteric coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical composition as described herein which utilizes an enteric coating to affect release in the small intestine of the gastrointestinal tract. The enteric coated dosage form is a compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder, pellets, beads or particles of the active ingredient and/or other composition components, which are themselves coated or uncoated. In one aspect, the enteric coated oral dosage form may is a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or the composition, which are themselves coated or uncoated.

[00180] The term "delayed release" as used herein refers to the delivery so that the release can be accomplished at some generally predictable location in the intestinal tract more distal to that which would have been accomplished if there had been no delayed release alterations. In some embodiments the method for delay of release is coating. Any coatings should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention to achieve delivery to the lower gastrointestinal tract. In some embodiments the polymers for use in the present invention are anionic carboxylic polymers. In other embodiments, the polymers and compatible mixtures thereof, and some of their properties, include, but are not limited to:

[00181] Shellac, also called purified lac. This coating dissolves in media of pH >7;

[00182] Acrylic polymers. The performance of acrylic polymers (primarily their solubility in biological fluids) can vary based on the degree and type of substitution. Examples of suitable acrylic polymers include methacrylic acid copolymers and ammonio methacrylate copolymers. The Eudragit series E, L, R, S, RL, RS and NE (Rohm Pharma) are available as solubilized in organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine;

[00183] Cellulose Derivatives. Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH >6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP psuedolatex with particles <1 μm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose

acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethylcellulose acetate succinate include, but are not limited to, AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (HF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions;

[00184] Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH >5, and it is much less permeable to water vapor and gastric fluids.

[00185] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflec A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00186] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[00187] A particularly suitable methacrylic copolymer is Eudragit L®, particularly L-30D® and Eudragit 100-55®, manufactured by Rohm Pharma, Germany. In Eudragit L-30D®, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH values present in the small intestine.

[00188] In some embodiments, materials include shellac, acrylic polymers, cellulosic derivatives, polyvinyl acetate phthalate, and mixtures thereof. In other embodiments, materials include Eudragit® series E, L, RL, RS, NE, L, L300, S, 100-55, cellulose acetate phthalate, Aquateric, cellulose acetate trimellitate, ethyl cellulose, hydroxypropyl methyl cellulose

phthalate, hydroxypropyl methyl cellulose acetate succinate, poly vinyl acetate phthalate, and Cotteric.

[00189] For some types of drugs, it is preferred to release the drug in "pulses," wherein a single dosage form provides for an initial dose of drug followed by a release-free interval, after which a second dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses." Alternatively, no drug is released for a period of time after administration of the dosage form, after which a dose of drug is released, followed by one or more additional release-free intervals and drug release "pulses."

[00190] Pulsatile drug delivery is useful, for example, with active agents that have short half-lives are administered two or three times daily, with active agents that are extensively metabolized presystemically, and with active agents that should maintain certain plasma levels in order have optimized pharmacodynamic effects.

[00191] A pulsatile dosage form is capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Pulsatile dosage forms including the formulations described herein, which include an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt thereof, is administered using a variety of pulsatile formulations that have been described. For example, such formulations include, but are not limited to, those described in U.S. Pat. Nos. 5,011,692, 5,017,381, 5,229,135, 5,840,329, 4,871,549, 5,260,068, 5,260,069, 5,508,040, 5,567,441 and 5,837,284. In one embodiment, the controlled release dosage form is pulsatile release solid oral dosage form including at least two groups of particles, (*i.e.* multiparticulate) each containing the formulation described herein. The first group of particles provides a substantially immediate dose of an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt thereof, upon ingestion by a mammal. The first group of particles can be either uncoated or include a coating and/or sealant. The second group of particles includes coated particles, which includes from about 2% to about 75%, preferably from about 2.5% to about 70%, and more preferably from about 40% to about 70%, by weight of the total dose of an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt thereof, in said formulation, in admixture with one or more binders. The coating includes a pharmaceutically acceptable ingredient in an amount sufficient to provide a delay of from about 2 hours to about 7 hours following ingestion before release of the second dose. Suitable coatings include one or more differentially degradable coatings such as, by way of example only, pH sensitive coatings (enteric coatings) such as acrylic resins (e.g., Eudragit® EPO, Eudragit® L30D-55, Eudragit® FS 30D Eudragit® L100-55, Eudragit® L100, Eudragit® S100, Eudragit® RD100, Eudragit® E100, Eudragit® L12.5, Eudragit® S12.5, and Eudragit® NE30D, Eudragit® NE 40D) either alone or blended with cellulose derivatives, e.g.,

ethylcellulose, or non-enteric coatings having variable thickness to provide differential release of the formulation that includes an HDAC inhibitor (e.g. abexinostat), or a pharmaceutically acceptable salt thereof.

Multiparticulate Controlled Release Devices

[00192] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are multiparticulate controlled release devices, which include a multiplicity of particles, granules, or pellets, ranging from about 10 μm to about 3 mm, about 50 μm to about 2.5 mm, or from about 100 μm to about 1 mm in diameter. Such multiparticulates are made by wet-granulation, dry-granulation, extrusion/spheronization, roller-compaction, melt-congealing, by spray-coating seed cores, and combinations thereof. *See,* for example, *Multiparticulate Oral Drug Delivery*; Marcel Dekker: 1994; and *Pharmaceutical Pelletization Technology*; Marcel Dekker: 1989.

[00193] Other excipients or carriers as described herein are blended with the pharmaceutical compositions to aid in processing and forming the multiparticulates. The resulting particles may themselves constitute the multiparticulate device or may be coated by various film-forming materials, such as enteric polymers, water-swellable, and water-soluble polymers. The multiparticulates can be further processed as a capsule or a tablet.

[00194] Intestinal protective drug absorption system (IPDAS) is a multiparticulate tablet technology that consists of high density controlled release beads that are compressed into a tablet form. The beads may be manufactured by techniques such as extrusion spheronization and controlled release can be achieved with the use of different polymer systems to coat the resultant beads. Alternatively, the drug can also be coated onto an inert carrier such as non-pareil seeds to produce instant release multiparticulates. Controlled release can be achieved by the formation of a polymeric membrane onto these instant release multparticulates. Once an IPDAS tablet is ingested, it rapidly disintegrates and disperses beads containing the drug in the stomach which subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and /or the micro matrix of the polymer/active ingredient formed in the extruded/spheronized multiparticulates. The intestinal protection of IPDAS is by virtue of the multiparticulate nature of the formulation which ensures wide dispersion of drug throughout the gastrointestinal tract.

[00195] Spheroidal oral drug absorption system (SODAS) is a multiparticulate technology that enables the production of customized dosage forms and responds directly to individual drug candidate needs. It can provide a number of tailored drugs release profiles including immediate release of drug followed by sustained release to give rise to a fast onset of action which is

maintained for at least 12 hours. Alternatively, the opposite scenario can be achieved where drug release is delayed for a number of hours.

[00196] Programmable oral drug absorption system (PRODAS) is presented as a number of mini tablets contained in hard gelatin capsule. It thus combines the benefits of tableting technology within a capsule. It is possible to incorporate many different minitablets, each one formulated individually and programmed to release drug at different sites within the gastrointestinal tract. These combinations may include immediate release, delayed release, and/or controlled release mini tablets. It is also possible to incorporate mini tablets of different sizes so that high drug loading is possible. Their size ranges usually from 1.5-4 mm in diameter.

[00197] Many other types of controlled release systems known to those of ordinary skill in the art and are suitable for use with the formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, plyanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman et al., *Pharmaceutical Dosage Forms*, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh *et al.*, *Encyclopedia of Pharmaceutical Technology*, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725, 4,624,848, 4,968,509, 5,461,140, 5,456,923, 5,516,527, 5,622,721, 5,686,105, 5,700,410, 5,977,175, 6,465,014 and 6,932,983.

Matrix Controlled Release Devices

[00198] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are in a modified release dosage form that is fabricated using a matrix controlled release device known to those skilled in the art (*see*, Takada *et al* in "Encyclopedia of Controlled Drug Delivery," Vol. 2, Mathiowitz ed., Wiley, 1999).

[00199] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated using an erodible matrix device, which is water-swellable, erodible, or soluble polymers, including synthetic polymers, and naturally occurring polymers and derivatives, such as polysaccharides and proteins.

[00200] Materials useful in forming an erodible matrix include, but are not limited to, chitin, chitosan, dextran, and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum, and scleroglucan; starches, such as dextrin and maltodextrin; hydrophilic colloids, such as pectin; phosphatides, such as lecithin; alginates; propylene glycol alginate; gelatin; collagen; and cellulosics, such as ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl

cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate (HPMCAT), and ethylhydroxy ethylcellulose (EHEC); polyvinyl pyrrolidone; polyvinyl alcohol; polyvinyl acetate; glycerol fatty acid esters; polyacrylamide; polyacrylic acid; copolymers of ethacrylic acid or methacrylic acid (EUDRAGIT®, Rohm America, Inc., Piscataway, NJ); poly(2-hydroxyethyl-methacrylate); polylactides; copolymers of L-glutamic acid and ethyl-L-glutamate; degradable lactic acid-glycolic acid copolymers; poly-D-(-)-3-hydroxybutyric acid; and other acrylic acid derivatives, such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl)methacrylate, and (trimethylaminoethyl)methacrylate chloride.

[00201] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated with a non-erodible matrix device. The active ingredient(s) is dissolved or dispersed in an inert matrix and is released primarily by diffusion through the inert matrix once administered. Materials suitable for use as a non-erodible matrix device included, but are not limited to, insoluble plastics, such as polyethylene, polypropylene, polyisoprene, polyisobutylene, polybutadiene, polymethylmethacrylate, polybutylmethacrylate, chlorinated polyethylene, polyvinylchloride, methyl acrylate-methyl methacrylate copolymers, ethylene-vinylacetate copolymers, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, vinylchloride 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, polyvinyl chloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, and ; hydrophilic polymers, such as ethyl cellulose, cellulose acetate, crospovidone, and cross-linked partially hydrolyzed polyvinyl acetate,; and fatty compounds, such as carnauba wax, microcrystalline wax, and triglycerides.

[00202] In a matrix controlled release system, the desired release kinetics can be controlled, for example, via the polymer type employed, the polymer viscosity, the particle sizes of the polymer and/or the active ingredient(s), the ratio of the active ingredient(s) versus the polymer, and other excipients or carriers in the compositions.

[00203] In one aspect, modified release dosage forms are prepared by methods known to those skilled in the art, including direct compression, dry or wet granulation followed by compression, melt-granulation followed by compression.

[00204] In some embodiments, a matrix controlled release system includes an enteric coating so that no drug is released in the stomach.

Osmotic Controlled Release Devices

[00205] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are fabricated using an osmotic controlled release device, including one-chamber system, two-chamber system, asymmetric membrane technology (AMT), and extruding core system (ECS). In general, such devices have at least two components: (a) the core which contains the active ingredient(s); and (b) a semipermeable membrane with at least one delivery port, which encapsulates the core. The semipermeable membrane controls the influx of water to the core from an aqueous environment of use so as to cause drug release by extrusion through the delivery port(s).

[00206] In addition to the active ingredient(s), the core of the osmotic device optionally includes an osmotic agent, which creates a driving force for transport of water from the environment of use into the core of the device. One class of osmotic agents water-swellable hydrophilic polymers, which are also referred to as "osmopolymers" and "hydrogels," including, but not limited to, hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly(2-hydroxyethyl methacrylate), poly(acrylic) acid, poly(methacrylic) acid, polyvinylpyrrolidone (PVP), crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers, PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate and vinyl acetate, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl, cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium starch glycolate.

[00207] The other class of osmotic agents are osmogens, which are capable of imbibing water to affect an osmotic pressure gradient across the barrier of the surrounding coating. Suitable osmogens include, but are not limited to, inorganic salts, such as magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, potassium phosphates, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, and sodium sulfate; sugars, such as dextrose, fructose, glucose, inositol, lactose, maltose, mannitol, raffinose, sorbitol, sucrose, trehalose, and xylitol,; organic acids, such as ascorbic acid, benzoic acid, fumaric acid, citric acid, maleic acid, sebacic acid, sorbic acid, adipic acid, edetic acid, glutamic acid, p-tolunesulfonic acid, succinic acid, and tartaric acid; urea; and mixtures thereof.

[00208] Osmotic agents of different dissolution rates may be employed to influence how rapidly the active ingredient(s) is initially delivered from the dosage form. For example,

amorphous sugars, such as Mannogeme EZ (SPI Pharma, Lewes, DE) can be used to provide faster delivery during the first couple of hours to promptly produce the desired therapeutic effect, and gradually and continually release of the remaining amount to maintain the desired level of therapeutic or prophylactic effect over an extended period of time. In this case, the active ingredient(s) is released at such a rate to replace the amount of the active ingredient metabolized and excreted.

[00209] The core may also include a wide variety of other excipients and carriers as described herein to enhance the performance of the dosage form or to promote stability or processing.

[00210] Materials useful in forming the semi-permeable membrane include various grades of acrylics, vinyls, ethers, polyamides, polyesters, and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration, such as crosslinking. Examples of suitable polymers useful in forming the coating, include plasticized, unplasticized, and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxylated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly(acrylic) acids and esters and poly-(methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00211] Semi-permeable membrane may also be a hydrophobic microporous membrane, wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed in U.S. Pat. No. 5,798,119. Such hydrophobic but water-vapor permeable membrane are typically composed of hydrophobic polymers such as polyalkenes, polyethylene, polypropylene, polytetrafluoroethylene, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinylidene fluoride, polyvinyl esters and ethers, natural waxes, and synthetic waxes.

[00212] The delivery port(s) on the semi-permeable membrane may be formed post-coating by mechanical or laser drilling. Delivery port(s) may also be formed in situ by erosion of a plug of water-soluble material or by rupture of a thinner portion of the membrane over an indentation in

the core. In addition, delivery ports may be formed during coating process, as in the case of asymmetric membrane coatings of the type disclosed in U.S. Pat. Nos. 5,612,059 and 5,698,220.

[00213] The total amount of the active ingredient(s) released and the release rate can substantially by modulated via the thickness and porosity of the semi-permeable membrane, the composition of the core, and the number, size, and position of the delivery ports.

[00214] The pharmaceutical compositions in an osmotic controlled-release dosage form may further comprise additional conventional excipients or carriers as described herein to promote performance or processing of the formulation.

[00215] The osmotic controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art (*see, Remington: The Science and Practice of Pharmacy*, supra; Santus and Baker, *J. Controlled Release* 1995, *35*, 1-21; Verma *et al.*, *Drug Development and Industrial Pharmacy* 2000, *26*, 695-708; Verma et al., *J. Controlled Release* 2002, *79*, 7-27).

[00216] In other embodiments, pharmaceutical compositions provided herein are formulated as AMT controlled-release dosage form, which comprises an asymmetric osmotic membrane that coats a core comprising the active ingredient(s) and other pharmaceutically acceptable excipients or carriers. *See* U.S. Pat. No. 5,612,059 and WO 2002/17918. The AMT controlled-release dosage forms can be prepared according to conventional methods and techniques known to those skilled in the art, including direct compression, dry granulation, wet granulation, and a dip-coating method.

[00217] In certain embodiments, the pharmaceutical compositions provided herein are formulated as ESC controlled-release dosage form, which comprises an osmotic membrane that coats a core comprising the active ingredient(s), a hydroxylethyl cellulose, and other pharmaceutically acceptable excipients or carriers.

Multilayered tablets

[00218] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are in the form of a multilayered tablet. Multilayered tablets include an inert core, onto which is applied a layered of drug (plus optional excipients), followed by an enteric coating. A second layer of drug is applied onto the first enteric coating followed by a second enteric coating on the second layer of drug. The enteric coatings should ensure that the release of drug from each layer is separated in time by at least 3-6 hours.

Immediate Release

[00219] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are immediate release dosage form capable of releasing not less than 75 % of the therapeutically active ingredient or combination and/or meet the disintegration or dissolution

requirements for immediate release tablets of the particular therapeutic agents or combination included in the tablet core, as set forth in USP XXII, 1990 (The United States Pharmacopeia.). Immediate release pharmaceutical compositions include capsules, tablets, oral solutions, powders, beads, pellets, particles, and the like.

Parenteral Administration

[00220] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are 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, and subcutaneous administration.

[00221] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are 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).

[00222] The pharmaceutical compositions intended for parenteral administration may 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.

[00223] 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. 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. 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, dimethylacetamide, and dimethylsulfoxide.

[00224] Suitable antimicrobial agents or preservatives include, but are not limited to, phenols, cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzates, thimerosal, benzalkonium chloride, benzethonium chloride, methyl- and propyl-parabens, and sorbic acid. Suitable isotonic agents include, but are not limited to, sodium chloride, glycerin, and dextrose. Suitable buffering agents include, but are not limited to, phosphate and citrate. Suitable antioxidants are those as described herein, including bisulfite and sodium metabisulfite. Suitable local anesthetics include, but are not limited to, procaine hydrochloride. Suitable suspending and dispersing agents are those as described herein, including sodium carboxymethylcelluose, hydroxypropyl methylcellulose, and polyvinylpyrrolidone. Suitable emulsifying agents include those described herein, including polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan monooleate 80, and triethanolamine oleate. Suitable sequestering or chelating agents include, but are not limited to EDTA. Suitable pH adjusting agents include, but are not limited to, sodium hydroxide, hydrochloric acid, citric acid, and lactic acid. Suitable complexing agents include, but are not limited to, cyclodextrins, including α-cyclodextrin, β-cyclodextrin, hydroxypropyl-β-cyclodextrin, sulfobutylether-β-cyclodextrin, and sulfobutylether 7-β-cyclodextrin (CAPTISOL®, CyDex, Lenexa, KS).

[00225] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are formulated for single or multiple dosage administration. The single dosage formulations are packaged in an ampule, a vial, or a syringe. 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.

[00226] In some embodiments, pharmaceutical compositions for use with the methods disclosed herein are provided as ready-to-use sterile solutions. In some embodiments, pharmaceutical compositions for use with the methods disclosed herein 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, pharmaceutical compositions for use with the methods disclosed herein are provided as ready-to-use sterile suspensions. In yet another embodiment, pharmaceutical compositions for use with the methods disclosed herein are provided as sterile dry insoluble products to be reconstituted with a vehicle prior to use. In still another embodiment, pharmaceutical compositions for use with the methods disclosed herein are provided as ready-to-use sterile emulsions.

Cancers

[00227] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) an antiangiogenic agent. In some

embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00228] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00229] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00230] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient

response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00231] In some embodiments, the methods disclosed herein are used in the treatment of cancer in a human. In some embodiments, the methods disclosed herein are used in the treatment of a hematological cancer in a human. In some embodiments, the methods disclosed herein are used in the treatment of a solid tumor in a human.

[00232] Hematological cancers include cancers of the blood or bone marrow, such as leukemia or lymphoma.

[00233] A lymphoma is a cancer that begins in cells of the immune system. There are two basic categories of lymphomas. One kind is Hodgkin lymphoma, which is marked by the presence of a type of cell called the Reed-Sternberg cell. The other category is non-Hodgkin lymphomas, which includes a large, diverse group of cancers of immune system cells. Non-Hodgkin lymphomas can be further divided into cancers that have an indolent (slow-growing) course and those that have an aggressive (fast-growing) course.

[00234] A leukemia is a cancer that starts in blood-forming tissue such as the bone marrow and causes large numbers of blood cells to be produced and enter the bloodstream.

[00235] In one aspect, the cancer is a solid tumor or a lymphoma or leukemia. In one aspect, the cancer is a carcinoma, a sarcoma, a lymphoma, a leukemia, a germ cell tumor, a blastic tumor or blastoma.

[00236] In some embodiments, the methods disclosed herein are used in the treatment of a solid tumor. In some embodiments, the methods disclosed herein are used in the treatment of a metstatic solid tumor. In some embodiments, the methods disclosed herein are used in the treatment of an advanced solid tumor.

[00237] In some embodiments, the methods disclosed herein are used in the treatment of a sarcoma.

[00238] In some embodiments, the methods disclosed herein are used in the treatment of a cancer selected from: Cardiac: sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; Lung: bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma; Gastrointestinal: esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors,

Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma); Genitourinary tract: kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma); Liver: hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastom, angiosarcoma, hepatocellular adenoma, hemangioma; Bone: osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor, chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell tumors; Nervous system: skull (osteoma, hemangioma, granuloma, xanthoma, osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiforme, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord (neurofibroma, meningioma, glioma, sarcoma); Gynecological: uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, endometrioid tumors, celioblastoma, clear cell carcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma [embryonal rhabdomyosarcoma], fallopian tubes (carcinoma); Hematologic: blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]; Skin: malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Karposi's sarcoma, moles, dysplastic nevi, lipoma, angioma, dermatofibroma, keloids, psoriasis; Adrenal glands: neuroblastoma; gallbladder carcinomas.

[00239] In one aspect, the cancer is breast cancer, colon cancer, colorectal carcinomas, non-small cell lung cancer, small-cell lung cancer, liver cancer, ovarian cancer, prostate cancer, uterine cervix cancer, urinary bladder cancer, gastric carcinomas, gastrointestinal stromal tumors, pancreatic cancer, germ cell tumors, mast cell tumors, neuroblastoma, mastocytosis, testicular cancers, glioblastomas, astrocytomas, lymphomas, melanoma, myelomas, acute

myelocytic leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome, and chronic myelogenous leukemia (CML).

[00240] In some embodiments, the cancer is a renal cell carcinoma.

[00241] In some embodiments, the cancer is ovarian cancer.

[00242] In one aspect, the cancer is a lymphoma. In one aspect, the lymphoma is a B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma, or non-Hodgkin's lymphoma.

[00243] In one aspect, the cancer is a T-cell lymphoma or leukemia.

[00244] In one aspect, the T-cell lymphoma is peripheral T cell lymphoma. In another aspect, the T-cell lymphoma or leukemia is T cell lymphoblastic leukemia/lymphoma. In yet another aspect, the T-cell lymphoma is cutaneous T cell lymphoma. In another aspect, the T-cell lymphoma is adult T cell lymphoma. In one aspect, the T-cell lymphoma is peripheral T cell lymphoma, lymphoblastic lymphoma, cutaneous T cell lymphoma, NK/T-cell lymphoma, or adult T cell leukemia/lymphoma.

[00245] In one embodiment, the cancer is a sarcoma. A sarcoma is a cancer that begins in the muscle, fat, fibrous tissue, blood vessels, or other supporting tissue of the body. Sarcomas include any one of the following: alveolar soft part sarcoma, angiosarcoma, dermatofibrosarcoma, desmoid tumor, desmoplastic small round cell tumor, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, fibrosarcoma, hemangiopericytoma, hemangiosarcoma, kaposi's sarcoma, leiomyosarcoma, liposarcoma, lymphangiosarcoma, malignant fibrous histiocytoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, askin's tumor, ewing's, malignant hemangioendothelioma, malignant schwannoma, osteosarcoma, chondrosarcoma. In some embodiments, the sarcoma is a soft-tissue sarcoma.

[00246] In some embodiments, the methods disclosed herein are used in the treatment of a soft tissue sarcoma in a human.

[00247] In some embodiments, the methods disclosed herein are used in the treatment of myelodysplastic syndrome (MDS) in a human.

[00248] In some embodiments, the methods disclosed herein are used in the treatment of chronic myelogenous leukemia (CML) in a human.

[00249] In some embodiments, the methods disclosed herein are used in the treatment of non-Hodgkin lymphoma in a human. In some embodiments, the methods disclosed herein are used in the treatment of Hodgkin Disease in a human.

[00250] In some embodiments, the methods disclosed herein are used in the treatment of multiple myeloma in a human.

[00251] In some embodiments, the methods disclosed herein are used in the treatment of chronic lymphocytic leukemia. In some embodiments, the methods disclosed herein are used in the treatment of acute lymphocytic leukemia.

[00252] In some embodiments, the methods disclosed herein are used in the treatment of a solid tumor in a human.

[00253] In some embodiments, the methods disclosed herein are used in the treatment of a sarcoma in a human.

Combination Therapies

[00254] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00255] Disclosed herein, in certain embodiments, are methods of increasing the effectiveness of pazopanib, or a salt thereof, in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00256] Additionally disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) an antiangiogenic agent. In some embodiments, the antiangiogenic agent is pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent;

allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.

[00257] Further disclosed herein, in certain embodiments, are methods of treating cancer comprising administering (a) a cycle of abexinostate, or a salt thereof; and (b) pazopanib, or a salt thereof. In some embodiments, the method reduces resistance to pazopanib, or a salt thereof; delays the development of resistance to pazopanib, or a salt thereof; delays the onset of the cancer becoming refractory to pazopanib, or a salt thereof; prolongs the usefulness of pazopanib, or a salt thereof; allows use of pazopanib, or a salt thereof, in the treatment of cancers that generally develop, or have developed, resistance to pazopanib, or a salt thereof; increases patient response to pazopanib, or a salt thereof; increases cellular response to pazopanib, or a salt thereof; decreases the effective dosage of pazopanib, or a salt thereof; or any combination thereof.

[00258] In one embodiment, the compositions and methods described herein are also used in conjunction with other therapeutic reagents that are selected for their particular usefulness against the cancer that is being treated. In general, the compositions described herein and, in embodiments where combinational therapy is employed, other agents do not have to be administered in the same pharmaceutical composition, and are, because of different physical and chemical characteristics, administered by different routes. In one embodiment, the initial administration is made according to established protocols, and then, based upon the observed effects, the dosage, modes of administration and times of administration, further modified.

[00259] In certain embodiments, the particular choice of compounds used depends on the diagnosis of the attending physicians and their judgment of the condition of the patient and the appropriate treatment protocol. In various embodiments, the compounds are administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the cancer, the condition of the patient, and the actual choice of compounds used. In certain embodiments, the determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is based upon evaluation of the disease being treated and the condition of the patient.

[00260] In one embodiment, it is understood that the dosage regimen to treat the cancer is modified in accordance with a variety of factors. These factors include the type of cancer from which the human suffers, as well as the age, weight, sex, diet, and medical condition of the human. Thus, in one embodiment, the dosage regimen actually employed varies widely and

therefore deviates from the dosage regimens set forth herein. In certain embodiments, treatment of a cancer with a combination of an HDAC inhibitor (e.g. abexinostat) and a second agent allows for the effective amount of the HDAC inhibitor (e.g. abexinostat) and/or the second agent to be decreased.

[00261] The formulations described herein are administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the method of administration, scheduling of administration, and other factors known to medical practitioners.

[00262] Contemplated pharmaceutical compositions provide a therapeutically effective amount of an HDAC inhibitor (e.g. abexinostat) enabling, for example, once-a-day, twice-a-day, three times a day, etc. administration. In one aspect, pharmaceutical compositions provide an effective amount of an HDAC inhibitor (e.g. abexinostat) enabling once-a-day dosing.

[00263] In some embodiments, the methods disclosed herein further comprise administering an additional agent in combination with abexinostat (or a salt thereof), and pazopanib (or a salt thereof).

[00264] In certain embodiments, the therapeutic effectiveness of the methods disclosed herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). In some embodiments, the benefit experienced by a patient is increased by administering an another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. In specific embodiments, increased therapeutic benefit results by also providing the patient with other therapeutic agents or therapies for cancer. In various embodiments, use of an additional agent provides the individual with, e.g., an additive or synergistic benefit.

[00265] Therapeutically-effective dosages vary when the drugs are used in treatment combinations. Determination of therapeutically-effective dosages of drugs and other agents when used in combination treatment regimens is achieved in any manner. For example, the use of metronomic dosing, i.e., providing more frequent, lower doses in order to minimize toxic side effects can be utilized. In certain instances, the combination therapy allows for any or all of the active agents to have a therapeutically effective amount that is lower than would be obtained when administering either agent alone.

[00266] A combination treatment regimen encompasses, by way of non-limiting example, treatment regimens in which administration of abexinostat (or a salt thereof), and pazopanib (or a salt thereof) is initiated prior to, during, or after treatment with an additional agent, and continues until any time during treatment with the additional agent or after termination of

treatment with the additional agent. It also includes treatments in which abexinostat (or a salt thereof), and pazopanib (or a salt thereof) and the additional agent being used in combination are administered simultaneously or at different times and/or at decreasing or increasing intervals during the treatment period. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient.

[00267] In any case, the multiple therapeutic agents are administered in any order, including, e.g., simultaneously. If administration is simultaneous, the multiple therapeutic agents are provided, in various embodiments, in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills). In various embodiments, one of the therapeutic agents is given in multiple doses, or both are given as multiple doses. In certain embodiments wherein administration of the multiple agents is not simultaneous, the timing between administration of the multiple agents is of any acceptable range including, e.g., from more than zero weeks to less than four weeks. Any number of additional agents may be used in combination with the methods disclosed herein,

[00268] In certain embodiments, the initial administration is via oral administration, such as, for example, a pill, a capsule, a tablet, a solution, a suspension, and the like, or combination thereof. In certain embodiments, the methods disclosed herein are used as soon as is practicable after the onset of a cancer is detected or suspected, and for a length of time necessary for the treatment of the cancer. In certain embodiments, the methods disclosed herein are continued for any length of time necessary for the treatment of the cancer including, by way of non limiting example, for at least 2 weeks, at least 1 month, or more than 1 month.

[00269] Additional therapeutic agents are selected from among DNA-damaging agents; topoisomerase I or II inhibitors; alkylating agents; PARP inhibitors; proteasome inhibitors; RNA/DNA antimetabolites; antimitotics; immunomodulatory agents; antiangiogenics; aromatase inhibitors; hormone-modulating agents; apoptosis inducing agents; kinase inhibitors; monoclonal antibodies; abarelix; ABT-888; aldesleukin; aldesleukin; alemtuzumab; alitretinoin; allopurinol; altretamine; amifostine anastrozole; arsenic trioxide; asparaginase; azacitidine; AZD-2281; bendamustine; bevacizumab; bexarotene; bleomycin; bortezomib; BSI-201; busulfan; busulfan; calusterone; capecitabine; carboplatin; carfilozib; carmustine; carmustine; celecoxib; cetuximab; chlorambucil; cisplatin; cladribine; clofarabine; cyclophosphamide; cytarabine; cytarabine liposomal; dacarbazine; dactinomycin; darbepoetin alfa; dasatinib; daunorubicin liposomal; daunorubicin; decitabine; denileukin; dexrazoxane; docetaxel; doxorubicin; doxorubicin liposomal; dromostanolone propionate; epirubicin; epoetin alfa; erlotinib; estramustine; etoposide phosphate; etoposide; exemestane; filgrastim; floxuridine; fludarabine; fluorouracil; fulvestrant; gefitinib; gemcitabine; gemtuzumab ozogamicin; goserelin

acetate; histrelin acetate; hydroxyurea; Ibritumomab tiuxetan; idarubicin; ifosfamide; imatinib mesylate; interferon alfa 2a; Interferon alfa-2b; irinotecan; lenalidomide; letrozole; leucovorin; leuprolide Acetate; levamisole; lomustine; meclorethamine; megestrol acetate; melphalan; mercaptopurine; methotrexate; methoxsalen; mitomycin C; mitomycin C; mitotane; mitoxantrone; nandrolone phenpropionate; nelarabine; NPI-0052; nofetumomab; oprelvekin; oxaliplatin; paclitaxel; paclitaxel protein-bound particles; palifermin; pamidronate; panitumumab; pegademase; pegaspargase; pegfilgrastim; pemetrexed disodium; pentostatin; pipobroman; plicamycin, mithramycin; porfimer sodium; procarbazine; quinacrine; RAD001; rasburicase; rituximab; sargramostim; Sargramostim; sorafenib; streptozocin; sunitinib malate; tamoxifen; temozolomide; teniposide; testolactone; thalidomide; thioguanine; thiotepa; topotecan; toremifene; tositumomab; tositumomab/I-131 tositumomab; trastuzumab; tretinoin; uracil Mustard; valrubicin; vinblastine; vincristine; vinorelbine; vorinostat; zoledronate; and zoledronic acid.

[00270] In some embodiments, the additional agent is a topoisomerase inhibitor, tubulin interactor, DNA-interactive agent, DNA-alkylating agent, and/or platinum complex.

[00271] In some embodiments, the additional agent is oxaliplatin, tyrosine kinase inhibitor, irinotecan (CPT-11), azacitidine, fludaribine, or bendamustine.

[00272] Tyrosine kinase inhibitors include, but are not limited to, erlotinib, gefitinib, lapatinib, vandetanib, neratinib, lapatinib, neratinib, axitinib, sunitinib, sorafenib, lestaurtinib, semaxanib, cediranib, imatinib, nilotinib, dasatinib, bosutinib, lestaurtinib, vatalanib and soratinib.

[00273] In some embodiments, the additional agent is a DNA damaging anti-cancer agent and/or radiation therapy.

[00274] DNA damaging anti-cancer agents and/or radiation therapy include, but is not limited to, ionizing radiation, radiomimetic drugs, monofunctional alkylators (e.g. alkylsulphonates, nitrosoureas, temozolomide), bifunctional alkylators (nitrogen mustard, mitomycin C, cisplatin), antimetabolites (e.g. 5-fluorouracil, thiopurines, folate analogues), topoisomerase inhibitors (e.g. camptothecins, etoposide, doxorubicin), replication inhibitors (e.g. aphidicolin, hydroxyurea), cytotoxic/cytostatic agents, antiproliferative agents, prenyl-protein transferase inhibitors, nitrogen mustards, nitroso ureas, angiogenesis inhibitors, inhibitors of cell proliferation and survival signaling pathway, apoptosis inducing agents, agents that interfere with cell cycle checkpoints, biphosphonates, or any combination thereof.

[00275] In some embodiments, the additional agent is an inhibitor of inherent multidrug resistance (MDR), in particular MDR associated with high levels of expression of transporter proteins. Such MDR inhibitors include inhibitors of p-glycoprotein (P-gp), such as LY335979, XR9576, OC144-093, R101922, VX853 and PSC833 (valspodar).

[00276] In some embodiments, the additional agent is anti-emetic agents to treat nausea or emesis, including acute, delayed, late-phase, and anticipatory emesis, which may result from the use of an HDAC inhibitor (e.g. abexinostat), alone or with radiation therapy. Anti-emetic agents include neurokinin-1 receptor antagonists, 5HT3 receptor antagonists (such as ondansetron, granisetron, tropisetron, Palonosetron, and zatisetron), $GABA_B$ receptor agonists (such as baclofen), corticosteroids (such as dexamethasone, prednisone, prednisolone, or others such as disclosed in U.S.Patent Nos. 2,789,118; 2,990,401; 3,048,581; 3,126,375; 3,929,768; 3,996,359; 3,928,326 and 3,749,712), dopamine antagonists (such as, domperidone, droperidol, haloperidol, chlorpromazine, promethazine, prochlorperazine, metoclopramide), antihistamines (H1 histamine receptor antagonists, such as cyclizine, diphenhydramine, dimenhydrinate, meclizine, promethazine, hydroxyzine), cannabinoids (such as cannabis, marinol, dronabinol), and others (such as trimethobenzamide; ginger, emetrol, propofol).

[00277] In some embodiments, the additional agent is an anti-emesis agent selected from among a neurokinin-1 receptor antagonist, a 5HT3 receptor antagonist and a corticosteroid.

[00278] In some embodiments, the additional agent is an agent useful in the treatment of anemia. Such an anemia treatment agent is, for example, a continuous eythropoiesis receptor activator (such as epoetin-α).

[00279] In some embodiments, the additional agent is an agent useful in the treatment of neutropenia. Examples of agents useful in the treatment of neutropenia include, but are not limited to, a hematopoietic growth factor which regulates the production and function of neutrophils such as a human granulocyte colony stimulating factor, (G-CSF). Examples of a G-CSF include filgrastim.

[00280] In some embodiments, the additional agent is an inhibitor of at least one CYP enzyme. In situations where the abexinostat (or a salt thereof), or pazopanib (or a salt thereof) is metabolized by one or more CYP enzymes, coadministration with a CYP inhibitor reduces in vivo metabolism and improves the pharmacokinetic properties of the agent.

[00281] Other combination therapies are disclosed in WO 08/082856 and WO 07/109178, both of which are herein incorporated by reference in their entirety.

Radiation Therapy

[00282] In some embodiments, the methods disclosed herein further comprise radiation therapy. Radiation therapy, also called radiotherapy, is the treatment of cancer and other diseases with ionizing radiation. Ionizing radiation deposits energy that injures or destroys cells in an area being treated (a "target tissue") by damaging their genetic material, making it impossible for these cells to continue to grow. Although radiation damages both cancer cells and normal cells, the latter are better able to repair themselves and function properly. Radiotherapy

can be used to treat localized solid tumors, such as cancers of the skin, tongue, larynx, brain, breast, prostate, colon, uterus and/or cervix. It can also be used to treat leukemia and lymphoma (cancers of the blood-forming cells and lymphatic system, respectively).

[00283] A technique for delivering radiation to cancer cells is to place radioactive implants directly in a tumor or body cavity. This is called internal radiotherapy (brachytherapy, interstitial irradiation, and intracavitary irradiation are types of internal radiotherapy.) Using internal radiotherapy, the radiation dose is concentrated in a small area, and the patient stays in the hospital for a few days. Internal radiotherapy is frequently used for cancers of the tongue, uterus, prostate, colon, and cervix.

[00284] The term "radiotherapy" or "ionizing radiation" include all forms of radiation, including but not limited to α, β, and γ radiation and ultra violet light. Radiotherapy with or without concurrent or sequential chemotherapy is an effective modality for head and neck, breast, skin, anogenital cancers, and certain nonmalignant diseases such as keloid, desmoid tumor, hemangioma, arteriovenous malformation, and histocytosis X.

[00285] In some embodiments,the methods disclosed herein reduce side effect caused by at least one other therapeutic treatment, such as radiation-induced normal tissue fibrosis or chemotherapy-induced tissue necrosis, and the methods provided herein also synergistically inhibit tumor cell growth with radiotherapy and other anti-cancer agents.

RAD51

[00286] DNA damage causes chromosomal instability, ontogenesis, cell death, and severe dysfunction of cells. The DNA repair system is crucially important for the survival of living cells. The two major DNA repair mechanisms involved in the repair of double stranded DNA breaks are homologous recombination (HR) and non-homologous end-joining (NHEJ). The eukaryotic *RAD51* gene is an ortholog of *Escherichia coli* RecA, and the gene product RAD51 protein plays a central role in homologous recombination.

[00287] Many therapeutic treatments, such as anti-cancer agents, exert their therapeutic effects through their capability of producing DNA damage to cells. If the cells, such as cancer cells, have active DNA repair mechanisms, the therapeutic effects of such treatments may be compromised and high dosages may be needed for achieving the desired therapeutic effects.

[00288] In some embodiments, the methods disclosed herein are used to decrease cellular DNA repair activity in a human with cancer.

[00289] In some embodiments, the methods disclosed herein decrease cellular DNA repair activity in combination therapy. In some embodiments, the methods disclosed herein interfere with a DNA repairing mechanism involving RAD51 or BRCA1.

[00290] In some embodiments, the methods disclosed herein treat cancers associated with a defect in non-homologous end joining of DNA. In some embodiments, the methods disclosed herein further comprise administering a treatment capable of damaging cellular DNA.

[00291] The defect in non-homologous end joining of DNA comprises a defect in a gene selected from the group consisting of: Ku70, Ku80, Ku86, Ku, PRKDC, LIG4, XRCC4, DCLRE1C, and XLF. In one aspect, the cancer is selected from Burkitt's lymphoma, chronic myelogenous leukemia, and B-cell lymphoma. In one aspect, the cancer is described herein.

[00292] In some embodiments, the methods disclosed herein are used in the treatment of an alternative lengthening of telomere (ATL) positive cancer in a human.

[00293] Additional combination therapies, treatment strategies, and the like that include inhibiting RAD51 activity (e.g. an HDAC inhibitor (e.g. abexinostat)) are disclosed in US patent publication number 20080153877 and WO 08/082856 (both of which are herein incorporated by reference).

Kits/Articles of Manufacture

[00294] For use in the therapeutic methods of use described herein, kits and articles of manufacture are also described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[00295] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include, e.g., U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, pumps, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated.

[00296] Such kits optionally comprise an identifying description or label or instructions relating to its use in the methods described herein.

[00297] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific

therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[00298] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert.

EXAMPLES

[00299] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Synthesis of Abexinostat

[00300] Abexinostat was prepared as outlined in Example 7 of US Patent No. 7,276,612, the contents of which are incorporated herein by reference in its entirety.

Example 1: IV Solution of Abexinostat HCl

[00301] Abexinostat HCl was formulated as an intravenous (IV) solutions for initial clinical trials in humans. The IV solution is an aqueous solution formulation intended for infusion administration after dilution with isotonic saline. Each single use vial contains 25 mL of a 5 mg/mL (0.5%) solution of abexinostat HCl in isotonic saline and 50 mM lactate buffer, pH 4.0-4.5. All the excipients in the clinical formulations are compendial and are commonly used in parenteral formulations. The quantitative composition of the formulation is given in Table 1. The recommended storage condition is 2-8 °C.

Table 1. Quantitative Composition of IV Solution (5 mg/mL)

Ingredient	Percent (% w/w)	mg/g (w/w)	Typical Batch (57.5 kg)
Abexinostat HCl	0.5	5.0	0.288 kg
Lactic acid	0.45	4.5	0.259 kg
Sodium chloride	0.665	6.65	0.382 kg
Water for injection	-	-	Q.S. to volume
1N sodium hydroxide* and/or 1N hydrochloric acid* Q.S. to pH 4.0-4.5 ± 0.2	-	-	Q.S. to pH

Example 2: Immediate Release Capsules

[00302] Immediate release capsules are formulated by mixing abexinostat HCl with microcrystalline cellulose, lactose, and magnesium stearate and then adding the mixture into gelatin capsules (see Table 2). The capsules are manufactured in two strengths. A 20 mg dosage strength includes 20 mg of abexinostat HCl in a size 4 Swedish orange hard gelatin capsule. A 100 mg dosage strength includes 100 mg of abexinostat HCl in a size 2 dark green hard gelatin capsule. The capsules are packaged in 30 cc HDPE bottles and sealed with an induction seal and capped with a child resistant screw top cap. The 20 mg dosage strength is packaged at 50 capsules per bottle. The 100 mg dosage strength is packaged at 30 capsules per bottle. The bottles are stored at controlled room temperature 20-25 °C (68-77 °F).

Table 2. Immediate Release Capsules

Component	Quality Standard	Mg/Capsule		Function
Abexinostat HCl	Manufacturer's Specification	20 mg[(a)]	100 mg[(a)]	Active Pharmaceutical Ingredient
Avicel PH113 (microcrystalline cellulose)	NF	68 mg	76 mg	Disintegrant
Lactose, Anhydrous	NF	15.7 mg	17.6 mg	Diluent
Magnesium Stearate	NF	1.3 mg	1.5 mg	Lubricant

[(a)] The quantity of abexinostat per capsule is adjusted for water content and purity.

Example 3: Multiparticulate Pulsatile Formulation with Timed Release

[00303] 80 grams of sodium chloride and 24 grams of polyvinylpyrrolidone are dissolved in 1.2 kilograms of water and 400 grams of pulverized abexinostat HCl are suspended therein.

[00304] In a fluidized bed coater, 400 grams of starch/sugar seeds (30/50 mesh) are suspended in warm air and spray coated with the abexinostat HCl suspension until the seeds are uniformly coated with the desired drug potency.

[00305] Magnesium stearate in isopropyl alcohol is mixed with Eudragit NE30D (Rohm Pharma of Weiterstadt, Germany), in a proportion of two to 1 of dried polymer to magnesium stearate. A sufficient amount of the polymer suspension is sprayed onto the active cores to provide a particular film coating thickness to achieve a particular lag time and rate of release for a population of pellets. The final coated pellets are dried at 50° C for 2 hours to assure complete removal of moisture to stabilize the core contents.

[00306] The procedure is repeated with at least one more batch using a different coating thickness to have a different lag time and rate of release. In this example, two populations are prepared, one with a 10% weight gain and one with a 30% weight gain of coating. Unit doses

are prepared by mixing the two populations together in predetermined proportions and filling capsules with the mixture.

[00307] After oral administration of a unit dose to a human, the first population of pellets does not begin to release abexinostat until an initial lag time of about 2-3 hours has elapsed. The second population of pellets does not begin to release abexinostat until an initial lag time of about 6-7 hours has elapsed. The mean release time (the time when half of the drug has been released) of each population of pellets should be separated from one another by at least 3-4 hours.

[00308] Fluidized bed coaters are well known in the art, however other coating apparatus and methods well known in the art may be used instead.

Example 4: Alternative Multiparticulate Pulsatile Formulation with Timed Release

[00309] The active cores are prepared as in Example 3. Magnesium stearate and triacetin plasticizer are mixed with Eudragit RS 30D suspension in a dry weight ratio of 1:0.6:2. The polymer suspension is coated on the cores as in Example 3, preparing a plurality of populations, each having a particular coating thickness to provide a particular lag time and rate of release of drug in an aqueous environment of use.

[00310] The different population of pellets are mixed and the mixture used to fill capsules as described in Example 3.

Example 5: Pulsatile Formulation – Tablets in Capsule

[00311] A pulsatile release dosage form for administration of abexinostat HCl is prepared by (1) formulating two individual compressed tablets, each having a different release profile, followed by (2) encapsulating the two tablets into a gelatin capsule and then closing and sealing the capsule. The components of the two tablets are as follows.

Table 3. Tablet 1 (Without Coating)

Component	Function	Amount per tablet
abexinostat HCl	Active agent	20.0 mg
Dicalcium phosphate dihydrate	Diluent	38.5 mg
Microcrystalline cellulose	Diluent	38.5 mg
Sodium starch glycolate	Disintegrant	2.4 mg
Magnesium Stearate	Lubricant	0.6 mg

[00312] The tablets are prepared by wet granulation of the individual drug particles and other core components as may be done using a fluid-bed granulator, or are prepared by direct compression of the admixture of components. Tablet 1 is an immediate release dosage form, releasing the active agent completely within 1-2 hours following administration.

[00313] Half of the immediate release tablets are coated with Delayed Coating No. 1 to provide Tablet 2. Tablet 2 delays the release of abexinostat HCl by about 3-5 hours after administration. Half of the immediate release tablets are coated with Delayed Coating No. 2 to provide Tablet 3. Tablet 3 delays the release of abexinostat HCl by about 4-9 hours after administration. The coating is carried out using conventional coating techniques such as spray-coating or the like.

Table 4. Tablet 2 (with Coating)

Component	Function	Weight
Tablet 1	"Core" containing the active agent	100.0 mg
Eudragit RS30D	Delayed release coating material	8.0 mg
Talc	Coating component	6.0 mg
Triethyl citrate	Coating component	2.0 mg

Table 5. Tablet 3 (with Coating)

Component	Function	Weight
Tablet 1	"Core" containing the active agent	100.0 mg
Eudragit RS30D	Delayed release coating material	12 mg
Talc	Coating component	7 mg
Triethyl citrate	Coating component	3.0 mg

[00314] Oral administration of the capsule to a patient should result in a release profile having two pulses, with initial release of abexinostat HCl occurring about 3-5 hours following administration, and release of abexinostat from the second tablet occurring about 7-9 hours following administration.

Example 6: Pulsatile Formulation – Beads in Capsule or Tablet

[00315] The method of Example 5 is repeated, except that drug-containing beads are used in place of tablets. Immediate release beads are prepared by coating an inert support material such as lactose with the drug. The immediate release beads are coated with an amount of enteric coating material sufficient to provide a drug release-free period of about 3-5 hours. A second fraction of beads is prepared by coating immediate release beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period of about 7-9 hours. The two groups of coated beads are encapsulated as in Example 5, or compressed, in the presence of a cushioning agent, into a single pulsatile release tablet.

Example 7: Sustained Release Tablet

[00316] Sustained release tablets of abexinostat are prepared by first preparing a sustained release excipient. The sustained release excipient is prepared by dry blending the requisite amounts of xanthan gum, locust bean gum, a pharmaceutically acceptable hydrophobic polymer and an inert diluent in a high-speed mixer/granulator for 2 minutes. While running choppers/impellers, the water was added and the mixture was granulated for another 2 minutes. The granulation was then dried in a fluid bed dryer to a loss on drying weight ("LOD") of

between 4 and 7%. The granulation was then milled using 20 mesh screens. The ingredients of the sustained release excipients are set forth in Table 6 below:

Table 6. Sustained Release Excipient Mixture

Component	% by Weight
Xanthan Gum	10
Locust Bean Gum	10
Carboxymethylcellulose	30
Dextrose	50
Water	23*

* removed during processing

[00317] Next, the sustained release excipient prepared as detailed above is dry blended with a desired amount of abexinostat in a V-blender for 10 minutes. A suitable amount of tableting lubricant Pruv® (sodium stearyl fumarate, NF) for the following examples is added and the mixture is blended for another 5 minutes. This final mixture is compressed into tablets, each tablet containing 10% by weight, of abexinostat. The tablets produced weighed 500 mg (Diameter is 3/8 inches; hardness is 2.6 Kp). The proportions of the tablets are set forth in Table 7 below.

Table 7. Sustained Release Tablets

Component	% by Weight
sustained release excipient mixture of Table 6	88.5
abexinostat	10
Sodium Stearyl Fumarate	1.5

[00318] Dissolution tests are then carried out on the tablets. The dissolution tests are conducted in an automated USP dissolution apparatus (Paddle Type II, pH 7.5 buffer, 50 rpm in 500 mL.). The tablets should release about 30% of abexinostat by 2 hours, followed by a sustained release such that about 98% of abexinostat is released at the end of 12 hours.

Example 8: Coated Sustained Release Tablet

[00319] A sustained release excipient was prepared as described above by dry blending the requisite amounts of xanthan gum, locust bean gum and an inert diluent. An extra 2 minutes of granulation was used after the addition of the components (for 4 total minutes of post-addition granulation). Ethylcellulose aqueous dispersion was substituted for water in the above methods. The components of the sustained release excipient is described in Table 8.

Table 8. Sustained Release Excipient

Component	% by Weight
Xanthan Gum	12
Locust Bean Gum	18
Dextrose	65
Ethylcellulose Aqueous Dispersion	5*

* Ethylcellulose Aqueous Dispersion contains approx. 25% by weight of solids. The amount added to the formulation (i.e. 5%) is solids only.

[00320] The xanthan gum and locust bean gum are dry blended in a V-blender for 10 minutes, the dextrose is added and the mixture blended for another 5 minutes. The ethylcellulose aqueous dispersion is then added, followed by an additional 5 minutes of blending. The resulting granulation is then compressed into tablets with sodium stearyl fumarate, as a tableting lubricant. The tablets are then coated with additional ethylcellulose aqueous dispersion. To accomplish this, ethylcellulose (Surelease®, 400 g) is mixed with water (100 g) to form an aqueous suspension. Thereafter, the tablets are coated in a Keith Machinery coating pan (diameter 350 mm; pan speed 20 rpm; spray-gun nozzle 0.8 mm; tablets bed temperature 40°-50° C.; charge per batch 1 kg; dry air - Conair Prostyle 1250, 60°-70° C.). The tablets are coated to a weight gain of about 5%. The tablets should weigh about 500 mg. The proportions of the tablets are set forth in Table 9 below:

Table 9. Coated Sustained Release Tablets

Component	% by Weight
sustained release excipient mixture of Table 8	83.5
abexinostat	10
Ethylcellulose	5
Sodium Stearyl Fumarate	1.5

[00321] The dissolution tests are conducted in an automated USP dissolution apparatus in such a way as to model passage through the gastrointestinal tract. The coated tablets should not release more than 10% abexinostat during the first 1-2 hours, and then should release abexinostat at a steady rate such that about 90% to 100% of abexinostat is released after 12 hours.

Example 9: In Vitro Release Profiles

[00322] The dissolution profiles are obtained using the United States Pharmacopeia Apparatus I at 37 °C and 100 RPM. The dissolution media is varied with time beginning with 0.1N HCl for 0-2 hours. From 2 to 4 hours the media is pH 6.5 phosphate buffer and from 4 to 24 hours the media was PH 7.5 phosphate buffer.

[00323] Alternatively, dissolution profiles are performed using a USP Type III (VanKel Bio-Dis II) apparatus.

Example 10: In vitro Fed/Fast Dissolution Protocol

[00324] The test formulations are evaluated under a variety of dissolution conditions to determine the effects of pH, media, agitation and apparatus. Dissolution tests are performed using a USP Type III (VanKel Bio-Dis II) apparatus. In order to determine the differences, if any, in dissolution kinetics between a fed state and a fasting state for the series of formulations, in vitro dissolution experiments are carried out in a solution containing 30% peanut oil ("fed") to model a gastrointestinal tract with a typical dietary fat load. The control determined the dissolution rates in a solution lacking the fat load ("fasted"). The pH-time protocol (ranging from acid to alkaline to model digestive processes) is set forth below in Table 10, below. Agitation is 15 cpm. Volume of the sample tested is 250 mL.

Table 10. Fed/Fast Dissolution Protocol

Apparatus Media			
"Fed"	**"Fasted"**	**Time**	**pH**
30% Peanut Oil	No Peanut oil	0-1 hour	1.5
30% Peanut Oil	No Peanut oil	1-2 hour	3.5
30% Peanut Oil	No Peanut oil	2-4 hour	5.5
30% Peanut Oil	No Peanut oil	4-12 hour	7.5

[00325] An enteric coating on the tablet is expected to provide a tablet that provides dissolution rates that are not significantly different in the fasted and fed states.

Example 11: Phase 1 Trial

Study objectives

[00326] Determine the safety, tolerability and maximum tolerated dose (MTD) of pazopanib HCl in combination with abexinostat HCl in patients with advanced solid tumors

[00327] Characterize the pharmacokinetics of abexinostat HCl , pazopanib HCl, and the combination of the two.

[00328] Evaluate preliminary efficacy using clinical benefit rate=CR+PR+SD, objective response proportion, and progression-free survival.

[00329] Explore the relationship of changes in expression levels of histone acetylation in blood and biopsied tumors and expression of biomarkers including VEGF, VEGFR, HIF, and RAD51 in plasma in responders and nonresponders.

[00330] Explore variations of single-nucleotide polymorphisms (SNPs) in relationship to potential toxicities.

[00331] Evaluate functional imaging using FLT PET (3'deoxy-3'-18F-Fluorothymidine positron emission tomography) to measure changes in rates of cell division and correlation with tumor response.

Overview of Study Design

[00332] Open label, non-randomized, dose escalation and expansion Phase I trial to evaluate the safety of the combination of abexinostat and Pazopanib and to determine the recommended Phase II dose of the combination.

[00333] Pazopanib HCl will be given once daily days 1-28 and should be taken orally without food at least one hour before or two hours after a meal. Abexinostat HCl will be given orally twice a day during d1-5, 8-12, 15-19. Each cycle will be 28 days in duration. A cycle duration is 28 days. Patients will continue on treatment until disease progression.

Inclusion criteria

[00334] Phase Ia: Patients must have histologically or cytologically documented metastatic solid tumor malignancies.

[00335] Phase Ib: Patients must have histologically or cytologically confirmed locally advanced, unresectable or metastatic sarcoma or renal cell carcinoma

[00336] Measurable disease by RECIST 1.1

[00337] Patients may have de novo metastatic disease, or progressed despite any number of prior therapies

[00338] Eastern Cooperative Oncology Group (ECOG) performance status of 0-1

[00339] Resolution of all chemotherapy or radiation-related toxicities to Grade 1 severity or lower except for alopecia

[00340] Patient must be at least 2 weeks or five half-lives (whichever is longer) from last standard or experimental therapy, including radiotherapy

[00341] Patients who have received prior pazopanib HCl are eligible but must not have received it in the last two weeks

Exclusion Criteria

[00342] Patients with other untreated, current primary malignancies, other than carcinoma in situ of the cervix or non-melanoma skin cancer

[00343] History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 4 weeks prior to first dose of study drug.

[00344] Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding.

[00345] Corrected QT interval (QTc) > 480 msecs using Friedrichs's formula

[00346] Use of medications that are known to prolong cause QT prolongation

[00347] History of any one or more of the following cardiovascular conditions within the past 6 months:

a. Cardiac angioplasty or stenting
b. Myocardial infarction
c. Unstable angina
d. Coronary artery bypass graft surgery
e. Symptomatic peripheral vascular disease

[00348] Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].

[00349] History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.

a. Note: Patients with recent DVT who have been treated with therapeutic anticoagulation for at least 6 weeks are eligible

[00350] Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject's safety, provision of informed consent, or compliance to study procedures

[00351] Unable or unwilling to discontinue use of prohibited medications for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study

Patient cohorts and dose escalation rules

[00352] This trial proposes to use abexinostat HCl to increase efficacy and potentially reverse mechanisms of resistance to angiogenesis inhibitors, in this study, pazopanib HCl. To accommodate optimal dosing and to reach steady level of abexinostat HCl, abexinostat HCl will be taken orally twice daily on Days 1-5, 8-12, 15-19 of 28 Days. Pazopanib will be taken daily on Days 1-28 of 28 Days. Cycles will be repeated every 28 Days.

[00353] Patients will receive alternating escalating doses of abexinostat HCl and pazopanib HCl. Dose escalations will occur based on the table below. The following dose cohorts are planned, however if >2 DLT are observed in any cohort and no DLT was seen in the previous cohort, an intermediate dose level will be explored (e.g: 2 DLTs are observed at 45 mg,and no DLT at 30 mg, we will explore 35 mg).

[00354] If a DLT likely related to pazopanib HCl is observed in the first cohort, pazopanib HCl dose will be lowered first. If there is evidence that the toxicity is likely due to abexinostat HCl, the abexinostat HCl dose will be lowered to 30 mg (cohort -1).

[00355] During Phase Ia, patients must receive 20 days of pazopanib HCl (≥75%) and 10 days of abexinostat HCl (≥75%) during the first cycle in order to be evaluable for DLT. If therapy is

delayed >14 days during the first cycle attributable to study drug, this is considered a DLT and the patient will not be replaced. If therapy is delayed due to another reason, the patient will be replaced.

Cohorts	Number of pts	Pazopanib HCl	Abexinostat HCl
-1	(6)	400 mg po qd	30 mg/m2 PO BID d1-5, 8-12, 15-19
1*	1 (+2)	400 mg po qd	45 mg/m2 PO BID d1-5, 8-12, 15-19
2	1 (+2)	600 mg po qd	45 mg/m2 PO BID d1-5, 8-12, 15-19
3	3	600 mg po qd	60 mg/m2 PO BID d1-5, 8-12, 15-19
4	3	800 mg po qd	60 mg/m2 PO BID d1-5, 8-12, 15-19
5	6	800 mg po qd	75 mg/m2 PO BID d1-5, 8-12, 15-19
MTD	**20 each in sarcoma, RCC, and other**	xxx mg po qd	xxx mg/m2 PO BID d1-5, 8-12, 15-19

*starting dose

[00356] Starting at dose level 1, if 1 patient experiences DLT (as defined in section 4.5) that dose level will be expanded to include 2 additional patients. If the additional patients have no DLTs, the dose will be expanded to the next level. If 2/3 patients have a DLT the dose will be de-escalated to dose -1. At dose level 3, expansion part I will occur in a standard 3+3 design. Three patients will be treated at dose level 3 and 4. If 0/3 patients experience DLT, 3 patients will be treated at the next dose level. If DLT attributable to the treatment is experienced in 1/3 patients, three more patients (for a total of six patients) will be treated at that dose level. If no additional DLT are observed at the expanded dose level (i.e. 1/6 with DLT), the dose will be escalated. Escalation will terminate as soon as two or more patients experience any DLT attributable to study drugs, at a given dose level. If dose level 5 is reached 6 patients will be enrolled. Once the MTD is defined, dose expansion part II will occur.

[00357] No intra cohort dose escalations will be permitted. Dose escalation will be followed according to the outlined escalation steps: abexinostat HCl should be started in the morning of Day 1 and continued on Days 2-5 of a 28 Day Cycle. Pazopanib will be given on Day 2 after the morning dose of abexinostat HCl in Cycle 1 only and then daily for 28 days. A four-week treatment is defined as one Cycle. Responses will be assessed after two Cycles. A medication diary by the patient will be assessed after each Cycle.

[00358] If at any dose, DLTs are observed and no DLTs were observed at the previous dose level, we may explore a dose that is intermediate after discussion with the CHR, PI and the sponsor.

[00359] There will be no more than 2 patients dosed for the first time within the same week and patients in the next higher cohorts will not be enrolled until the last patient of the lower cohort has completed the DLT period

Estimated Patient numbers

[00360] The total number of patients to be enrolled on the study will be between 46 and 90.

Duration of intervention and evaluation

[00361] Patients will be on the study until progression of disease as defined by RECIST 1.1, intolerable toxicity, request to withdraw, or withdrawal per the Principal Investigator.

[00362] Patients will continue to be followed periodically (approximately every 6 months) through medical records, and subsequent cancer treatments, progression of cancer, and survival outcome will be updated. Follow-up will occur until death or for at least ten years.

Dose Limiting Toxicities

[00363] This is a combination trial which may have different toxicities resulting from the pazopanib HCl and abexinostat HCl dose escalation or those resulting from the combination. Special consideration should be given to toxicities arising from the dose escalations. The rationale of this trial is to increase the efficacy of each drug by combination therapy and to reverse resistance mechanisms to angiogenesis inhibitors. Every effort should be made not to delay drug dosing. Prior approval by the Principal Investigator is required to delay dosing. If toxicities can be clearly linked to one drug only, only the offending agent should be dose-modified.

[00364] Adverse Events and other symptoms will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.03 (NCI, CTC web site http://ctep.info.nih.gov).

[00365] A dose limiting toxicity (DLT) will be defined as any one of the following adverse events 31 occurring during Cycle 1 when association to therapy that is part of this study is related or possibly related:

[00366] Hematologic dose-limiting toxicity

a. Grade 4 neutropenia lasting for ≥7 days in duration despite growth factor support. GCSF (Filgrastim) or Pegylated-GCSF (Neulasta) may be administered after day 7 Cycle 1 to treat an ANC ≤1000, and prophylactically after Cycle 1 at the discretion of the treating physician. When administered, this does not constitute a DLT.

b. Grade 4 neutropenia with fever >38.5° C and infection requiring antibiotic or anti-fungal treatment
c. Grade 4 thrombocytopenia (≤25.0 x 109/L)
d. Grade 3 thrombocytopenia complicated by bleeding and/or requiring platelet or blood transfusion

[00367] Non-hematologic dose-limiting toxicity - this will be defined as any Grade ≥3 non-hematologic toxicity, with specific exceptions.

[00368] The following will also be considered DLT:

a. Symptomatic bradycardia
b. Persistent increases in QTc interval (>60 milliseconds from baseline and/or >500ms)
c. Treatment delay of greater than 14 days
d. Failure to administer ≥75% of the planned study drugs during cycle 1 as a result ≥ Grade 2 treatment-related toxicity
e. Subjects who fail to complete the first cycle due to reasons other than toxicity will be classified as not evaluable for toxicity, and will be replaced. No dose reductions can occur within the DLT window.

Maximum Tolerated Dose

[00369] The maximum tolerated dose (MTD) will be defined as the highest tested dose level at which less than 33% of patients experience DLT in Cycle 1.

Visit Schedule and Assessments

Test/Study	Pre-study	Cycle 1 Day 1-28				Cycle 2 Day 1-28				Every 8 wks until 6 months on study	Every 8 wks after 6 months on study	Prior to Day 1 of each Cycle	End of Treat-ment
		Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 1**	**Week 2**	**Week 3**	**Week 4**				
History and drug diary	X[1]	X[1]				X[Error! Bookmark not defined.]						X[Error! Bookmark not defined.]	X

Physical Exam[3]	X[1]	X[1]				X[Error! Bookmark not defined.]						X[Error! Bookmark not defined.]	X
Toxicity assessment[4]	X[1]	X	X	X	X	X						X	X
CBC, Diff.[5]	X[1]	X[1]				X						X	X
Chemistry[6]	X[1]	X[1]	X[Error! Bookmark not defined.]			X						X	X
TSH and T4[7]	X					X				X	X		X
INR/PT[8]	X[1]												
Urine protein[9]	X[1]											X	
Echo/ MUGA[10]	X								X		?		X
EKG[11, 12]	X	X[Error! Bookmark not defined.]	X[Error! Bookmark not defined.]	X[Error! Bookmark not defined.]	X[Error! Bookmark not defined.]	X[Error! Bookmark not defined.]						X[Error! Bookmark not defined.]	X
Pregnancy Test[13]	X					X						X	X
Staging Studies[14]	X								X	X	X		
Pazopanib PK[15]		X			X								
Abexinostat PK[16]		X											

PD markers[17]	X^{18}	$X^{18,19,}$	X^{18}			$X^{Error! Bookmark not defined.}$						$X^{Error! Bookmark not defined.}$	X
FLT/PET[21]		X							X				
Tumor biopsy[22]	X	X											

[1] Pre-study tests, history and physical exam may be used for Day 1 tests if within 2 weeks and no significant changes have occured

[2] D1 physical exam and history in subsequent Cycles may be done within 7 Days prior to next Cycle

[3] Physical Exam includes ECOG status and vital signs

[4] Toxicity will be assessed by CTCAE v4.03

[5] Hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential

[6] BUN, creatinine, sodium, potassium, chloride, CO2 (HCO3), glucose, calcium, albumin, total protein, total bilirubin, alkaline phosphatase, LDH (melanoma only), AST/SGOT, ALT/SGPT, phosphorous, magnesium If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed. Biochemistry tests should be obtained after patient has fasted, if possible. LFTs including total bilirubin, alkaline phosphatase, LDH (melanoma only), AST/SGOT, ALT/SGPT should also be obtained during Cycle 1 Week 2.

[7] Thyroid functions tests: TSH, FT4 every 8 weeks

[8] For patients taking warfarin, the coagulation profile includes a prothrombin time or International Normalized Ratio (INR)

[9] Urine protein should be measured by protein quantification in urinalysis

[10] MUGA or ECHO should be performed at baseline and the end of Cycle 2 (± 1 week) and only repeated with subsequent cycles if EF changes ± 10%.

[11] Cycle 1 weekly triplicate EKGs at two timepoints: pre- abexinostat HCl and 3 hours (± 15 min.) post- abexinostat HCl.

[12] Cycles ≥ 2: Single EKGs if no cardiac problems identified on pre-dose Day 1 EKG.

[13] For women of childbearing potential. Pregnancy test will be repeated after each two Cycles if clinically indicated.

[14] Baseline evaluations should be performed not more than 30 Days prior to the beginning of the treatment.

[15] Pazopanib PK: final schedule TBD Phase Ia only

Day 3: predose, after dose: 30 minutes, 2, 4, 8, 24 hours

Day 8: predoses (with abexinostat HCl), after doses: 30 minutes, 1 hour, 2 hours, 4 hours, 8 hours

Day 22: predose, after dose: 30 minutes, 2, 4, 8, 24 hours

[16] abexinostat HCl PK: final schedule TBD Phase Ia only

Day 1: predose, after dose: 30 minutes, 1, 2, 4, 6, 8 24 hours

Day 8: see #15

[17] PD markers will include histone acetylation, expression of VEGF, VEGFR, HIF, RAD51, pharmacogenomics

[18] PD markers for abexinostat HCl:

Pre-treatment: up to 10 Days prior

Day 1: 2-hours (+15 min) post abexinostat HCl

Day 8: pre- and 2-hours (+15 min) post abexinostat HCl

[19] PD markers for pazopanib HCl: plasma to be drawn with each Cycle

[20] Pharmacogenomics: whole blood to be drawn Cycle 1 Day 1

[21] Tumor FNA:

Day 1 (up to 10 Days prior), and Day 5 at 120 min (+30 min) post abexinostat HCl.

Tumor FNA or tumor biopsies are optional for dose escalation, mandatory for dose expansion

[22] FLT PET (3'deoxy-3'-18F-Fluorothymidine positron emission tomography) can be performed with baseline imaging and then prior to Cycle 2 with follow-up imaging.

PK schedule	Dosing	Cycle 1 (Days 1-28)				
		D1	D2	D3	D22	D23
Pazopanib (po)	Once a Day			X	X	X
PCI-24781 (po)	Twice a Day	X	X	X		

Pazopanib schedule: pre, 30 min, hr 2, 4, 8, 24

Abexinostat HCl schedule: pre, 30 min, hr 2, 4, 8, 24

Efficacy assessments

Criteria for response, progression and relapse

[00370] Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee 33. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in RECIST 1.1. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

[00371] For the purposes of this study, patients should be evaluated for response every 8 weeks, prior to the start of odd-numbered Cycles after Cycle 1. In addition to a baseline scan, confirmatory scans should also be obtained ≥4 weeks following initial documentation of objective response.

Evaluation of Target lesions

[00372] Complete Response (CR): Disappearance of all target lesions

[00373] Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

[00374] Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

[00375] Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Tumor samples and PBMCs

[00376] Tumor samples by fine needle aspirations (FNA) will be obtained by the study cytopathologist based on the schedule of assessments post- abexinostat HCl. Diff-Quick air-dry method (FNA) at time of aspiration will be used by the study cytopathologist to confirm the presence of tumor cells in the specimen. An accessible lesion for the purpose of this study is defined as a subcutaneous nodule or lymph node or a lesion accessible to FNA with CT guidance with low risk to the patient (Includes CT/ultrasound guided FNA of lymph nodes in the neck, axilla, groin, tumor masses in the breast, liver or adrenals). This decision will be at the discretion of the treating physician in consultation with the principal investigator. If no tumor nodule is visible and/or palpable or accessible as defined above, then no biopsy will be done.

[00377] Tissues will be evaluated for the effects of PCI24781 on tumor and PBMC histone acetylation. PBMCs and tumor aspirates will be processed in Pamela Munster's laboratory at UCSF using immunofluorescence and Western Blot analysis (IF) analysis. Cells will also be stained for HDAC enzyme expression.

[00378] Other correlative study methods will be added later.

Safety assessments

[00379] Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, vital signs, ECOG performance status, and the regular physical examinations and ECG assessments.

[00380] Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version4.03.

[00381] A serious adverse event is any adverse drug experience occurring at any dose that:

a. results in death;
b. is life-threatening;
c. results in in-patient hospitalization or prolongation of existing hospitalization (admissions for elective surgeries or procedure do not qualify);
d. results in a persistent or significant disability/incapacity; or
e. results in congenital anomaly/birth defect.

[00382] An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

[00383] The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine: the severity grade (mild, moderate, severe) or (grade 1-4); its relationship to the study drug(s) (suspected/not suspected); its duration (start and end dates or if continuing at final exam); action taken (no action taken, study drug dosage adjusted/temporarily interrupted, study drug permanently discontinued due to this adverse event, concomitant medication taken, non-drug therapy given, hospitalization/prolonged hospitalization); and whether it constitutes a serious adverse event (SAE).

[00384] All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more

frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

[00385] Information about all serious adverse events will be collected and recorded.

Endpoints

[00386] DLT will be assessed by monitoring for adverse events, scheduled laboratory assessments, vital sign measurements, ECGs, and physical examinations. The severity of the toxicities will be graded according to the NCI CTCAE v4.03, published 14-Jun-2010. Adverse events and clinically significant laboratory abnormalities (meeting Grade 3, 4, or 5 criteria according to CTCAE) will be summarized by maximum intensity and relationship to study drug for each treatment group. Safety will be assessed weekly for the first 4 weeks and then every 4 weeks. Simple descriptive statistics will be utilized to display the data on toxicity seen from the combination of pazopanib HCl and abexinostat HCl.

[00387] Noncompartmental pharmacokinetics of abexinostat HCl, pazopanib HCl, and the combination will be assessed by measuring and calculating the volume of distribution (Vd), bioavailability (F), clearance (CL), half-life (t1/2), and area under the curve (AUC).

[00388] Clinical Benefit Rate=CR+PR+SD. Evaluated by imaging criteria RECIST 1.1

[00389] Objective response rate. Will be calculated as a proportion, the number of patients by best response (who had clinical benefit) divided by the total number of patients on study.

[00390] Progression-free survival. Time to progression will be calculated as the time from study enrollment until the time of disease relapse, progression, or death from any cause, or until last contact if no relapse, progression or death occurred.

[00391] Overall survival. OS time will be calculated as the time from study enrollment until the time of death from any cause, or until last contact if the patient did not die.

[00392] Histone acetylation as measured by changes in HDAC1, HDAC2, HDAC3, and HDAC6 expression in PBMC and tumor biopsies

[00393] Other PD biomarkers: plasma for VEGF, VEGFR, HIF, and RAD51 expression

[00394] Pharmacogenomics: one time collection of blood for evaluation of SNP variations and correlation with toxicities

[00395] Changes in FLT PET (3'deoxy-3'-18F-Fluorothymidine positron emission tomography)

Example 11: In Vitro Assay of Effects of Pazopabnib + Abexinostat

[00396] The effects of the combination of pazopanib + abexinostat (PCI-24781) were assayed in 786-O human kidney carcinoma cells. Results are presented in Figure 1. The combination was administered to cells for three continuouse days, after which alamarBlue levels were measured.

Example 12: In Vitro Assay of Effects of Pazopabnib + Abexinostat

[00397] The effects of the combination of pazopanib + abexinostat (PCI-24781) was assayed in U2-OS osteosarcoma cells. Results are presented in Figure 2. The combination was administered to cells for three continuouse days, after which alamarBlue levels were measured.

[00398] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of disclosure and scope of the appended claims. As will be appreciated by those skilled in the art, the specific components listed in the above examples may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, coatings, and the like.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of increasing the effectiveness of an antiangiogenic agent in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat or a salt thereof, and (b) an antiangiogenic agent.
2. The method of claim 1, wherein the antiangiogenic agent is pazopanib, or a salt thereof.
3. The method of claim 2, wherein the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.
4. The method of claim 2, wherein the salt of abexinostat is abexinostat HCl.
5. The method of claim 2, wherein abexinostat, or a salt thereof, and the antiangiogenic agent are administered separately, concurrently or sequentially.
6. The method of claim 2, wherein the subject is in an interdigestive state.
7. The method of claim 2, wherein the abexinostat, or a salt thereof, and the antiangiogenic agent, are administered one hour before a meal or 2 hours after a meal.
8. The method of claim 2, wherein the cycle of abexinostat, or a salt thereof, is 5 days.
9. The method of claim 2, wherein at least one dose of abexinostat, or a salt thereof, is administered each day of the abexinostat cycle.
10. The method of claim 9, wherein the dose of abexinostat, or a salt thereof, is sufficient to maintain an effective plasma concentration of abexinostat, or the salt thereof, in the individual for at least about 6 consecutive hours to about 8 consecutive hours.
11. The method of claim 2, comprising administering a first dose of abexinostat, or a salt thereof, and a second dose of abexinostat, or a salt thereof, 4 to 8 hours apart.
12. The method of claim 2, wherein the cancer is a hematological cancer, solid tumor or a sarcoma.
13. The method of claim 2, wherein the cancer is a solid tumor.
14. The method of claim 13, wherein the cancer is a metastatic solid tumor or an advanced solid tumor.
15. The method of claim 2, wherein the cancer is a sarcoma.
16. The method of claim 2, wherein the cancer is soft tissue sarcoma.

17. The method of claim 2, wherein the cancer is renal cell carcinoma or ovarian cancer.
18. The method of claim 2, further comprising administering at least one additional therapy selected from anti-cancer agents, anti-emetic agents, radiation therapy, or combinations thereof.
19. A method of treating a cancer in an individual in need thereof, comprising co-administering to the individual (a) a cycle of abexinostat or a salt thereof, and (b) an antiangiogenic agent.
20. The method of claim 19, wherein the antiangiogenic agent is pazopanib or a salt thereof.
21. The method of claim 20, wherein the method reduces resistance to the antiangiogenic agent; delays the development of resistance to the antiangiogenic agent; delays the onset of the cancer becoming refractory to the antiangiogenic agent; prolongs the usefulness of the antiangiogenic agent; allows use of the antiangiogenic agent in the treatment of cancers that generally develop, or have developed, resistance to the antiangiogenic agent; increases patient response to the antiangiogenic agent; increases cellular response to the antiangiogenic agent; decreases the effective dosage of the antiangiogenic agent; or any combination thereof.
22. The method of claim 20, wherein the salt of abexinostat is abexinostat HCl.
23. The method of claim 20, wherein abexinostat, or a salt thereof, and the antiangiogenic agent are administered separately, concurrently or sequentially.
24. The method of claim 20, wherein the subject is in an interdigestive state.
25. The method of claim 20, wherein the abexinostat, or a salt thereof, and the antiangiogenic agent, are administered one hour before a meal or 2 hours after a meal.
26. The method of claim 20, wherein the cycle of abexinostat, or a salt thereof, is 5 days.
27. The method of claim 20, wherein at least one dose of abexinostat, or a salt thereof, is administered each day of the abexinostat cycle.
28. The method of claim 27, wherein the dose of abexinostat, or a salt thereof, is sufficient to maintain an effective plasma concentration of abexinostat, or the salt thereof, in the individual for at least about 6 consecutive hours to about 8 consecutive hours.
29. The method of claim 20, comprising administering a first dose of abexinostat, or a salt thereof, and a second dose of abexinostat, or a salt thereof, 4 to 8 hours apart.
30. The method of claim 20, wherein the cancer is a hematological cancer, solid tumor or a sarcoma.
31. The method of claim 20, wherein the cancer is a solid tumor.
32. The method of claim 31, wherein the cancer is a metastatic solid tumor or an advanced solid tumor.

33. The method of claim 20, wherein the cancer is a sarcoma.

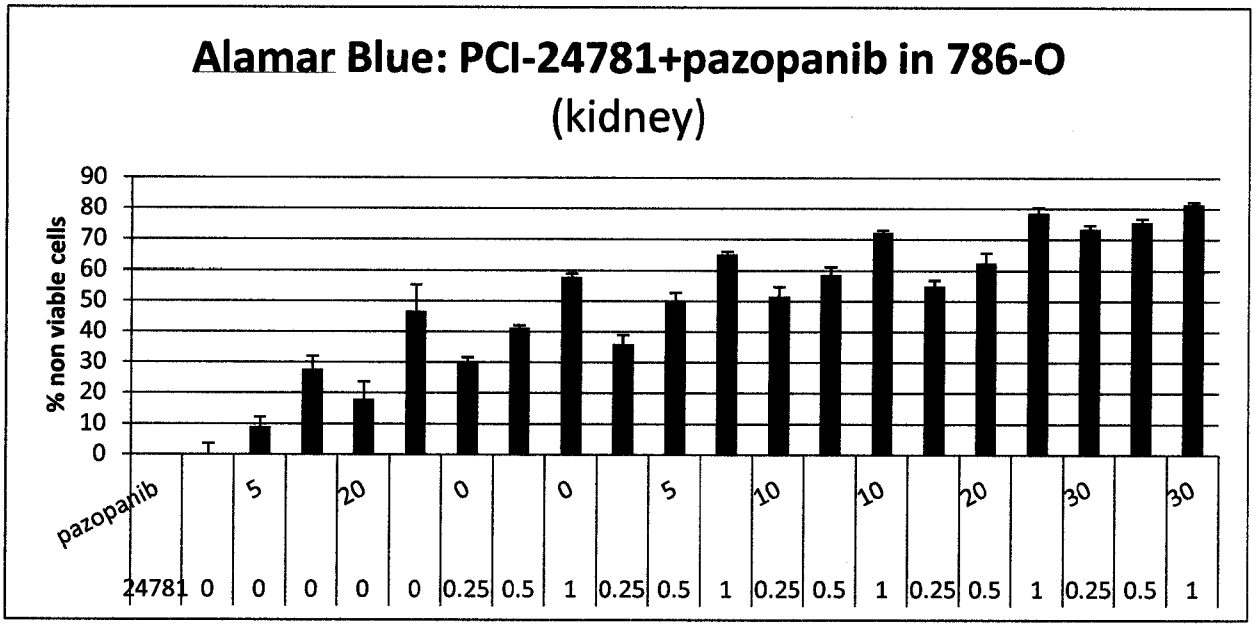
34. The method of claim 20, wherein the cancer is soft tissue sarcoma.

35. The method of claim 20, wherein the cancer is renal cell carcinoma or ovarian cancer.

36. The method of claim 1208, wherein the cancer is resistant to the antiangiogenic agent; partially resistant to the antiangiogenic agent; or refractory to the antiangiogenic agent.

37. The method of claim 20, further comprising administering at least one additional therapy selected from anti-cancer agents, anti-emetic agents, radiation therapy, or combinations thereof.

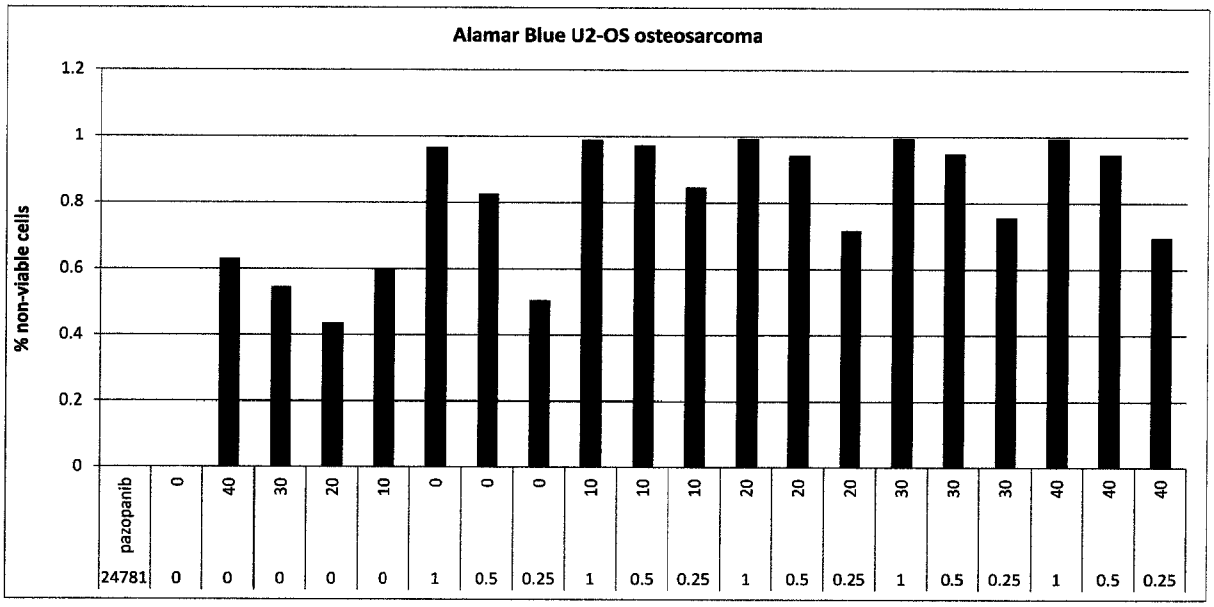
FIG. 1



24781	pazopanib	CI	24781	pazopanib	CI	24781	pazopanib	CI
0.25	5	0.883	0.5	5	0.817	1	5	0.719
0.25	10	0.516	0.5	10	0.604	1	10	0.526
0.25	20	0.608	0.5	20	0.623	1	20	0.406
0.25	30	0.315	0.5	30	0.37	1	30	0.373

3 day continuous treatment, concentrations in micromolar

FIG. 2



24781	pazopanib	CI	24781	pazopanib	CI	24781	pazopanib	CI
0.25	10	0.489	0.5	10	0.446	1	10	#######
0.25	20	0.675	0.5	20	0.621	1	20	0.478
0.25	30	0.621	0.5	30	0.598	1	30	0.469
0.25	40	0.704	0.5	40	0.605	1	40	0.476

3 day continuous treatment, concentrations in micromolar

PATENT COOPERATION TREATY

PCT

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

(PCT Article 17(2)(a), Rules 13*ter*.1(c) and (d) and 39)

Applicant's or agent's file reference	**IMPORTANT DECLARATION**	Date of mailing (*day/month/year*)
25922-852601		18 June 2013 (18.06.2013)
International application No.	International filing date (*day/month/year*)	(Earlist) Priority date *(day/month/year)*
PCT/US2013/026462	**15 February 2013 (15.02.2013)**	17 February 2012 (17.02.2012)

International Patent Classification (IPC) or both national classification and IPC

A61K 31/506(2006.01)i, A61K 31/517(2006.01)i, A61P 35/00(2006.01)i

Applicant

PHARMACYCLICS, INC.

This International Searching Authority hereby declares, according to Article 17(2)(a), that **no international search report will be established** on the international application for the reasons indicated below.

1. ☒ The subject matter of the international application relates to:
   - a. ☐ scientific theories.
   - b. ☐ mathematical theories.
   - c. ☐ plant varieties.
   - d. ☐ animal varieties.
   - e. ☐ essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
   - f. ☐ schemes, rules or methods of doing business.
   - g. ☐ schemes, rules or methods of performing purely mental acts.
   - h. ☐ schemes, rules or methods of playing games.
   - i. ☒ methods for treatment of the human body by surgery or therapy.
   - j. ☐ methods for treatment of the animal body by surgery or therapy.
   - k. ☐ diagnostic methods practised on the human or animal body.
   - l. ☐ mere presentation of information.
   - m. ☐ computer programs for which this International Searching Authority is not equipped to search prior art.
2. ☐ The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:

   ☐ the description ☐ the claims ☐ the drawings
3. ☐ A meaningful search could not be carried out without the sequence listing; the applicant did not, within the prescribed time limit:
   - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
   - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b)
4. Further coments:

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Facsimile No. 82-42-472-7140

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(12)发明专利申请

(10)申请公布号 CN 104244952 A
(43)申请公布日 2014.12.24

(21)申请号 201380020595.0
(22)申请日 2013.02.15
(30)优先权数据
61/600,491 2012.02.17 US
61/602,544 2012.02.23 US
(85)PCT国际申请进入国家阶段日
2014.10.17
(86)PCT国际申请的申请数据
PCT/US2013/026462 2013.02.15
(87)PCT国际申请的公布数据
WO2013/123413 EN 2013.08.22
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(51)Int.Cl.
A61K 31/506(2006.01)
A61K 31/517(2006.01)
A61P 35/00(2006.01)

权利要求书2页 说明书56页 附图2页

(54)发明名称

组蛋白脱乙酰酶抑制剂与帕唑帕尼的组合及其用途

(57)摘要

在此描述了包括HDAC抑制剂或其药学上可接受的盐以及帕唑帕尼(或其盐;例如,帕唑帕尼盐酸盐)的给药方案、治疗方法、控释制剂和联合治疗。

CN 104244952 A

1. 一种在有需要的个体中增加抗血管生成剂的有效性的方法，其包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。

2. 根据权利要求 1 所述的方法，其中所述抗血管生成剂是帕唑帕尼或其盐。

3. 根据权利要求 2 所述的方法，其中所述方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

4. 根据权利要求 2 所述的方法，其中所述 abexinostat 的盐是 abexinostat 盐酸盐。

5. 根据权利要求 2 所述的方法，其中 abexinostat 或其盐与抗血管生成剂分开、同时或相继施用。

6. 根据权利要求 2 所述的方法，其中受试者处于消化间期状态。

7. 根据权利要求 2 所述的方法，其中所述 abexinostat 或其盐与抗血管生成剂在餐前 1 小时或餐后 2 小时施用。

8. 根据权利要求 2 所述的方法，其中所述 abexinostat 或其盐的周期为 5 天。

9. 根据权利要求 2 所述的方法，其中在所述 abexinostat 周期的每一天施用至少一个剂量的 abexinostat 或其盐。

10. 根据权利要求 9 所述的方法，其中所述 abexinostat 或其盐的剂量足以在个体中维持 abexinostat 或其盐的有效血浆浓度至少连续约 6 小时至连续约 8 小时。

11. 根据权利要求 2 所述的方法，其包括间隔 4-8 小时施用第一剂量的 abexinostat 或其盐以及第二剂量的 abexinostat 或其盐。

12. 根据权利要求 2 所述的方法，其中所述癌症是血液系统癌症、实体瘤或肉瘤。

13. 根据权利要求 2 所述的方法，其中所述癌症是实体瘤。

14. 根据权利要求 13 所述的方法，其中所述癌症是转移性实体瘤或晚期实体瘤。

15. 根据权利要求 2 所述的方法，其中所述癌症是肉瘤。

16. 根据权利要求 2 所述的方法，其中所述癌症是软组织肉瘤。

17. 根据权利要求 2 所述的方法，其中所述癌症是肾细胞癌或卵巢癌。

18. 根据权利要求 2 所述的方法，其进一步包括施用选自抗癌剂、止吐剂、放射治疗或它们的组合的至少一种额外的疗法。

19. 一种在有需要的个体中治疗癌症的方法，其包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。

20. 根据权利要求 19 所述的方法，其中所述抗血管生成剂是帕唑帕尼或其盐。

21. 根据权利要求 20 所述的方法，其中所述方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

22. 根据权利要求 20 所述的方法，其中所述 abexinostat 盐是 abexinostat 盐酸盐。

23. 根据权利要求 20 所述的方法，其中 abexinostat 或其盐与抗血管生成剂分开、同时

或相继施用。

24. 根据权利要求 20 所述的方法，其中受试者处于消化间期状态。

25. 根据权利要求 20 所述的方法，其中所述 abexinostat 或其盐与抗血管生成剂在餐前 1 小时或餐后 2 小时施用。

26. 根据权利要求 20 所述的方法，其中所述 abexinostat 或其盐的周期为 5 天。

27. 根据权利要求 20 所述的方法，其中在所述 abexinostat 周期的每一天施用至少一个剂量的 abexinostat 或其盐。

28. 根据权利要求 27 所述的方法，其中所述 abexinostat 或其盐的剂量足以在个体中维持 abexinostat 或其盐的有效血浆浓度至少连续约 6 小时至连续约 8 小时。

29. 根据权利要求 20 所述的方法，其包括间隔 4-8 小时施用第一剂量的 abexinostat 或其盐以及第二剂量的 abexinostat 或其盐。

30. 根据权利要求 20 所述的方法，其中所述癌症是血液系统癌症、实体瘤或肉瘤。

31. 根据权利要求 20 所述的方法，其中所述癌症是实体瘤。

32. 根据权利要求 31 所述的方法，其中所述癌症是转移性实体瘤或晚期实体瘤。

33. 根据权利要求 20 所述的方法，其中所述癌症是肉瘤。

34. 根据权利要求 20 所述的方法，其中所述癌症是软组织肉瘤。

35. 根据权利要求 20 所述的方法，其中所述癌症是肾细胞癌或卵巢癌。

36. 根据权利要求 1208 所述的方法，其中所述癌症对抗血管生成剂具有抗性；对抗血管生成剂具有部分抗性；或者是抗血管生成剂难治性的。

37. 根据权利要求 20 所述的方法，其进一步包括施用选自抗癌剂、止吐剂、放射治疗或它们的组合的至少一种额外的疗法。

组蛋白脱乙酰酶抑制剂与帕唑帕尼的组合及其用途

交叉引用

[0001] 本申请要求 2012 年 2 月 17 日提交的系列号为 61/600,491 的美国临时专利申请及 2012 年 2 月 23 日提交的系列号为 61/602,544 的美国临时专利申请的权益，这两篇临时申请均在此全文引入作为参考。

背景技术

[0002] 核小体组蛋白的乙酰化状态调控基因表达。核小体组蛋白的脱乙酰化由一组被称为组蛋白脱乙酰酶 (HDAC) 的酶催化，这些酶有 11 种已知的同工型。组蛋白脱乙酰化导致染色质凝聚，从而引起转录抑制，而乙酰化在特定的染色体区域内诱导局部松弛，以允许更好地接近转录机器以利于转录。

[0003] 在肿瘤细胞中，有报道称，使用 HDAC 酶的选择性抑制剂会导致组蛋白高乙酰化。这改变了一部分基因的转录调节，这些基因包括许多肿瘤抑制基因、涉及细胞周期控制、细胞分裂和凋亡的基因。进一步地，已经报道了 HDAC 抑制剂在体内抑制肿瘤生长。肿瘤生长的抑制伴随着组蛋白和微管蛋白的高乙酰化，并且可能涉及多个机制。

[0004] HDAC 抑制剂在体外和体内均阻断癌细胞增殖。N- 羟基 -4-{2-[3-(N,N- 二甲基氨基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基 }- 苯甲酰胺（也被称为 PCI-24781 或 abexinostat) 是一种用于治疗人类癌症的基于异羟肟酸酯的 HDAC 抑制剂。

发明内容

[0005] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期 (cycle)，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼 (pazopanib) 或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。在一些实施方案中，abexinostat 的盐是 abexinostat 盐酸盐。在一些实施方案中，abexinostat 或其盐与抗血管生成剂分开、同时或相继施用。在一些实施方案中，受试者处于消化间期状态。在一些实施方案中，abexinostat 或其盐与抗血管生成剂在餐前 1 小时或餐后 2 小时施用。在一些实施方案中，abexinostat 或其盐的周期为 5 天。在一些实施方案中，在 abexinostat 周期的每一天施用至少一个剂量的 abexinostat 或其盐。在一些实施方案中，abexinostat 或其盐的剂量足以在个体中维持 abexinostat 或其盐的有效血浆浓度至少连续约 6 小时至连续约 8 小时。如权利要求 2 所述的方法，包括间隔 4-8 小时施用第一剂量的 abexinostat 或其盐以及第二剂量的 abexinostat 或其盐。在一些实施方案中，所述癌症是血液系统癌症、实体瘤或肉瘤。在一些实施方案中，所述癌症是实体瘤。在一些实施方案中，所述癌症是转移性实体瘤或晚期实体瘤。在一些实施方案中，所述癌症是肉瘤。在一些

实施方案中，所述癌症是软组织肉瘤。在一些实施方案中，所述癌症是肾细胞癌或卵巢癌。在一些实施方案中，该方法还包括施用选自抗癌剂、止吐剂、放射治疗或它们的组合的至少一种额外的疗法。

[0006] 在某些实施方案中，本文公开了在有需要的个体中治疗癌症的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。在一些实施方案中，abexinostat 的盐是 abexinostat 盐酸盐。在一些实施方案中，abexinostat 或其盐与抗血管生成剂分开、同时或相继施用。在一些实施方案中，受试者处于消化间期状态。在一些实施方案中，abexinostat 或其盐与抗血管生成剂在餐前 1 小时或餐后 2 小时施用。在一些实施方案中，abexinostat 或其盐的周期为 5 天。在一些实施方案中，在 abexinostat 周期的每一天施用至少一个剂量的 abexinostat 或其盐。在一些实施方案中，abexinostat 或其盐的剂量足以在个体中维持 abexinostat 或其盐的有效血浆浓度至少连续约 6 小时至连续约 8 小时。在一些实施方案中，该方法还包括间隔 4-8 小时的第一剂量的 abexinostat 或其盐以及第二剂量的 abexinostat 或其盐。在一些实施方案中，所述癌症是血液系统癌症、实体瘤或肉瘤。在一些实施方案中，所述癌症是实体瘤。在一些实施方案中，所述癌症是转移性实体瘤或晚期实体瘤。在一些实施方案中，所述癌症是肉瘤。在一些实施方案中，所述癌症是软组织肉瘤。在一些实施方案中，所述癌症是肾细胞癌或卵巢癌。在一些实施方案中，所述癌症对抗血管生成剂具有抗性；对抗血管生成剂具有部分抗性；或者是抗血管生成剂难治性的。在一些实施方案中，该方法还包括施用选自抗癌剂、止吐剂、放射治疗或它们的组合的至少一种额外的疗法。

[0007] 在某些实施方案中，本文公开了在有需要的个体中治疗癌症的方法，包括：施用 (a)abexinostat（或其盐）的周期，及 (b) 帕唑帕尼（或其盐）。在一些实施方案中，abexinostat（或其盐）与帕唑帕尼（或其盐）分开施用。在一些实施方案中，abexinostat（或其盐）与帕唑帕尼（或其盐）同时或相继施用。在一些实施方案中，abexinostat（或其盐）的周期是连续 1 至 14 天、连续 2 至 14 天、连续 3 至 14 天、连续 4 至 14 天、连续 5 至 14 天、连续 6 至 14 天、连续 7 至 14 天、连续 8 至 14 天、连续 9 至 14 天、连续 10 至 14 天、连续 11 至 14 天、连续 12 至 14 天或连续 13 至 14 天。在一些实施方案中，abexinostat（或其盐）的周期是连续 2 天、连续 3 天、连续 4 天、连续 5 天、连续 6 天、连续 7 天、连续 8 天、连续 9 天、连续 10 天、连续 11 天、连续 12 天、连续 13 天或连续 14 天。在一些实施方案中，该方法还包括在 abexinostat（或其盐）周期之后的 abexinostat（或其盐）休药期。在一些实施方案中，abexinostat（或其盐）的休药期是连续 1 至 14 天、连续 2 至 14 天、连续 3 至 14 天、连续 4 至 14 天、连续 5 至 14 天、连续 6 至 14 天、连续 7 至 14 天、连续 8 至 14 天、连续 9 至 14 天、连续 10 至 14 天、连续 11 至 14 天、连续 12 至 14 天或连续 13 至 14 天。在一些实施方案中，abexinostat（或其盐）的休药期是连续 2 天、连续 3 天、连续 4 天、连续 5 天、连续 6 天、连续 7 天、连续 8 天、连续 9 天、连续 10 天、连续 11 天、连

续 12 天、连续 13 天或连续 14 天。在一些实施方案中，在 abexinostat 周期的每一天施用至少一个剂量的 abexinostat（或其盐）。在一些实施方案中，abexinostat 的剂量足以在个体中维持 abexinostat（或其盐）的有效血浆浓度至少连续约 6 小时。在一些实施方案中，abexinostat（或其盐）的剂量足以在个体中维持 abexinostat（或其盐）的有效血浆浓度至少连续约 8 小时。在一些实施方案中，abexinostat（或其盐）的剂量足以在个体中维持 abexinostat（或其盐）的有效血浆浓度连续约 6 小时至连续约 8 小时。在一些实施方案中，该方法包括施用第一剂量的 abexinostat（或其盐）和第二剂量的 abexinostat（或其盐），其中该第一剂量和第二剂量间隔 4-8 小时施用。在一些实施方案中，该方法包括施用第一剂量的 abexinostat（或其盐）、第二剂量的 abexinostat（或其盐）和第三剂量的 abexinostat（或其盐），其中该第一剂量、第二剂量和第三剂量间隔 4-8 小时施用。在一些实施方案中，abexinostate（或其盐）被配制为口服剂型。在一些实施方案中，abexinostate（或其盐）被配制为速释口服剂型或控释口服剂型。在一些实施方案中，该方法包括施用含有 abexinostat（或其盐）的第一速释口服剂型和含有 abexinostat（或其盐）的第二速释口服剂型，其中该第二速释口服剂型与第一速释口服剂型间隔约 4 小时至约 8 小时施用。在一些实施方案中，所述口服剂型在给药后约 2 小时至约 10 小时的时期内完全释放 abexinostate（或其盐）。在一些实施方案中，该方法包括在禁食模式下施用 abexinostat（或其盐）。在一些实施方案中，该方法包括在禁食模式下施用帕唑帕尼（或其盐）。在一些实施方案中，该方法包括在餐前一小时或餐后两小时施用 abexinostate（或其盐）。在一些实施方案中，该方法包括在餐前一小时或餐后两小时施用帕唑帕尼（或其盐）。在一些实施方案中，该方法包括一日两次施用约 30mg/m^2 至约 75mg/m^2 的 abexinostat（或其盐）。在一些实施方案中，abexinostat（或其盐）的日剂量介于约 60mg/m^2 至约 150mg/m^2 之间。在一些实施方案中，该方法包括施用约 400mg 至约 800mg 的帕唑帕尼。在一些实施方案中，abexinostat 的盐是 abexinostat 盐酸盐。在一些实施方案中，帕唑帕尼的盐是帕唑帕尼盐酸盐。在一些实施方案中，该方法包括施用约 433.4mg 至约 866.8mg 的帕唑帕尼盐酸盐。在一些实施方案中，所述癌症为血液系统癌症、实体瘤或肉瘤。在一些实施方案中，所述癌症是肉瘤。在一些实施方案中，所述癌症是软组织肉瘤。在一些实施方案中，所述癌症选自：乳腺癌、结肠癌、结直肠癌、非小细胞肺癌、小细胞肺癌、肝癌、卵巢癌、前列腺癌、宫颈癌、膀胱癌、胃癌、胃肠道间质瘤、胰腺癌、生殖细胞瘤、肥大细胞瘤、神经母细胞瘤、肥大细胞增多症、睾丸癌、胶质母细胞瘤、星形细胞瘤、B 细胞淋巴瘤、T 细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、黑色素瘤、骨髓瘤、急性粒细胞性白血病 (AML)、急性淋巴细胞性白血病 (ALL)、骨髓增生异常综合征、慢性髓性白血病和肾细胞癌。在一些实施方案中，所述癌症选自：乳腺癌、结肠癌、结直肠癌、非小细胞肺癌、肝癌、卵巢癌、宫颈癌、胃癌、胰腺癌、胶质母细胞瘤、B 细胞淋巴瘤、T 细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、骨髓瘤、骨髓增生异常综合征 (MDS) 和肾细胞癌。在一些实施方案中，所述癌症是肾细胞癌或卵巢癌。在一些实施方案中，该方法还包括施用选自抗癌剂、止吐剂、放射治疗或它们的组合的至少一种额外的疗法。在一些实施方案中，该方法还包括施用至少一种选自下述的额外的治疗剂：DNA 损伤剂；拓扑异构酶 I 或 II 抑制剂；烷化剂；PARP 抑制剂；蛋白酶体抑制剂；RNA/DNA 抗代谢物；抗有丝分裂；免疫调节剂；抗血管生成剂；芳香酶抑制剂；激素调节剂；细胞凋亡诱导剂；激酶抑制剂；单克隆抗体；阿巴瑞克；ABT-888；阿地白介素；阿地白介素；阿仑珠

单抗；阿利维 A 酸；别嘌呤醇；六甲蜜胺；氨磷汀阿那曲唑；三氧化二砷；天冬酰胺酶；阿扎胞苷；AZD-2281；苯达莫司汀；贝伐珠单抗；贝沙罗汀；博来霉素；硼替佐米；BSI-201；白消安；白消安；卡芦睾酮；卡培他滨；卡铂；卡非佐米（carfilozib）；卡莫司汀；卡莫司汀；塞来昔布；西妥昔单抗；苯丁酸氮芥；顺铂；克拉屈滨；氯法拉滨；环磷酰胺；阿糖胞苷；阿糖胞苷脂质体；达卡巴嗪；更生霉素；达依泊汀 α；达沙替尼；柔红霉素脂质体；柔红霉素；地西他滨；地尼白介素；右丙亚胺；多西他赛；多柔比星；多柔比星脂质体；丙酸屈他雄酮；表柔比星；依泊汀 α；厄洛替尼；雌莫司汀；磷酸依托泊苷；依托泊苷；依西美坦；非格司亭；氟尿苷；氟达拉滨；氟尿嘧啶；氟维司群；吉非替尼；吉西他滨；吉妥珠单抗奥佐米星；醋酸戈舍瑞林；醋酸组氨瑞林；羟基脲；替伊莫单抗；伊达比星；异环磷酰胺；甲磺酸伊马替尼；干扰素 α-2a；干扰素 α-2b；伊立替康；来那度胺；来曲唑；甲酰四氢叶酸；醋酸亮丙瑞林；左旋咪唑；洛莫司汀；甲氮芥；醋酸甲地孕酮；美法仑；巯基嘌呤；氨甲喋呤；甲氧沙林；丝裂霉素 C；丝裂霉素 C；米托坦；米托蒽醌；苯丙酸诺龙；奈拉滨；NPI-0052；诺非单抗；奥普瑞白介素；奥沙利铂；紫杉醇；紫杉醇蛋白质结合颗粒；帕利夫明；帕米膦酸盐；帕尼单抗；培加酶；培门冬酶；培非司亭；培美曲塞二钠；喷司他丁；哌泊溴烷；普卡霉素，光辉霉素；卟吩姆钠；丙卡巴肼；奎纳克林；RAD001；拉布立酶；利妥昔单抗；沙格司亭；沙格司亭；索拉非尼；链佐星；苹果酸舒尼替尼；他莫昔芬；替莫唑胺；替尼泊苷；睾内酯；沙利度胺；硫鸟嘌呤；塞替派；托泊替康；托瑞米芬；托西莫单抗；托西莫单抗 /I-131 托西莫单抗；曲妥珠单抗；维甲酸；尿嘧啶氮芥；戊柔比星；长春碱；长春新碱；长春瑞滨；伏林司他；唑来膦酸盐；以及唑来膦酸。

附图说明

[0008] 图 1 举例说明了施用帕唑帕尼 +abexinostat(PCI-24781) 的组合对 786-O 人肾癌细胞的效果。通过测量阿拉玛蓝 (AlamarBlue) 将该组合的效果可视化。

[0009] 图 2 举例说明了施用帕唑帕尼 +abexinostat(PCI-24781) 的组合对 U2-OS 骨肉瘤细胞的效果。通过测量阿拉玛蓝将该组合的效果可视化。

发明详述

[0010] 抗血管生成剂常用于多种癌症的治疗。与抗血管生成剂相关的一个常见问题是在治疗过程中不断增加的肿瘤细胞对该药剂的抗性。帕唑帕尼，一种抗血管生成剂，是一种酪氨酸激酶抑制剂。在癌症治疗期间经常产生对帕唑帕尼的抗性，从而降低了帕唑帕尼的功效，并最终使患者无法使用可能挽救生命的药物疗法。对于减少或降低对诸如帕唑帕尼的抗血管生成剂的抗性的影响的新治疗模式存在需求。

[0011] HDAC 抑制剂对肿瘤细胞基因组产生不同的表观遗传修饰。这些修饰可能导致与 HDAC 抑制剂联合施用的任何化疗剂的功效增加。例如，HDAC 抑制剂增加 DNA 对于多种化学治疗剂的可及性，从而增加了化疗药物的细胞毒性。N- 羟基 -4-{2-[3-(N,N- 二甲基氨基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基 }- 苯甲酰胺（也被称为 PCI-24781 或 abexinostat）是用于治疗人类癌症的基于氧肟酸盐的 HDAC 抑制剂。

[0012] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管

生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0013] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0014] 在某些实施方案中，本文另外还公开了治疗癌症的方法，包括施用 (a) abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0015] 在某些实施方案中，本文进一步公开了治疗癌症的方法，包括施用 (a) abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

某些术语

[0016] 术语“药物组合物”指活性剂（或成分）与其它非活性化学成分如载体、稳定剂、稀释剂、分散剂、悬浮剂、增稠剂、包衣和 / 或赋形剂的混合物。药物组合物有助于对人施用化合物。在一个方面，活性剂为 HDAC 抑制剂（例如 abexinostat）。在一个方面，活性剂为 abexinostat 的盐酸盐。

[0017] 本文所使用的“控释”是指任何不是完全速释的释放谱 (release profile)。

[0018] “生物利用度”指施用的 HDAC 抑制剂（例如 abexinostat）或药学上可接受的盐被递送至所研究的动物或人的体循环的重量百分比。在静脉内给药时，药物的总暴露 ($AUC_{(0-\infty)}$) 通常被定义为 100％生物利用 (F％)。“口服生物利用度”指与静脉内注射相比，当口服药物组合物时，HDAC 抑制剂（例如 abexinostat）或药学上可接受的盐被吸收至体循环的程度。

[0019] “血浆浓度”指 HDAC 抑制剂（例如 abexinostat）或药学上可接受的盐在受试者血液的血浆成分中的浓度。应当理解，由于与代谢相关的变化和 / 或与其它治疗剂的相互作用，HDAC 抑制剂（例如 abexinostat）或药学上可接受的盐的血浆浓度可能在受试者之

间显著变化。在一个方面，HDAC 抑制剂（例如 abexinostat）或药学上可接受的盐的血浆浓度随受试者不同而不同。类似地，诸如最大血浆浓度（C_{max}）或达到最大血浆浓度的时间（T_{max}）或血浆浓度时间曲线下总面积（$AUC_{(0-\infty)}$）等值也随受试者不同而不同。由于这种变化，在一个实施方案中，构成 HDAC 抑制剂（例如 abexinostat）或药学上可接受的盐的“治疗有效量”所需的量也随受试者不同而不同。

[0020] HDAC 抑制剂的“有效血浆浓度”指的是血浆中能导致有效治疗癌症的暴露水平的 HDAC 抑制剂的量。

[0021] “药物吸收”或“吸收”一般是指药物从药物的给药部位跨越障碍进入血管或作用部位的移动过程，例如，药物从胃肠道移动到门静脉或淋巴系统内。

[0022] “可检测的血清浓度”或“可检测的血浆浓度”描述了在给药后吸收到血流中的血清或血浆浓度，一般以 mg、μg 或 ng 治疗剂 /ml、dl 或 l 血清进行测量。如在此使用的，可检测的血浆浓度一般用 ng/ml 或 μg/ml 进行测量。

[0023] “药效学”指决定相对于作用部位处的药物浓度所观察到的生物响应的因素。

[0024] “药代动力学”指决定在作用部位处达到和维持药物的合适浓度的因素。

[0025] “休药期”是指暂时减少或暂时中止药物的给药一段时间。休药期的长度可以在 2 天到 1 年之间不等，仅举例来说，包括 2 天、3 天、4 天、5 天、6 天、7 天、10 天、12 天、15 天、20 天、28 天、35 天、50 天、70 天、100 天、120 天、150 天、180 天、200 天、250 天、280 天、300 天、320 天、350 天和 365 天。在其它实施方案中，休药期期间的剂量减少为约 10％至约 100％，仅举例来说，包括约 10％、约 15％、约 20％、约 25％、约 30％、约 35％、约 40％、约 45％、约 50％、约 55％、约 60％、约 65％、约 70％、约 75％、约 80％、约 85％、约 90％、约 95％和约 100％。

[0026] “禁食模式 (fast mode)”或“消化间期 (intergestive)”是胃呈现出被称为消化间期移行性复合运动 (IMMC) 的周期性活动的生理状态。该周期性活动在四个阶段发生：I 期是最静止期，持续 45 至 60 分钟，并发生很少的收缩或不发生收缩；II 期以发生不规则的间歇性扫描式收缩为特征，其收缩强度逐渐增强；III 期持续 5 至 15 分钟，以出现同时涉及胃和小肠的蠕动波的强烈爆发为特征；IV 期是活动逐渐减少的过渡期，持续到下一个周期开始。总周期时间为大约 90 分钟，因此，在消化间期模式期间，强烈的蠕动波每 90 分钟清出胃的内容物。IMMC 可以作为肠的管家发挥作用，将吞咽的唾液、胃分泌物和碎片清扫至小肠和结肠，使上消化道为下一餐做好准备，同时防止细菌过度生长。胰肽和促胃动素的胰外分泌也与这些运动模式同步循环。

[0027] “进食模式 (fed mode)”或“餐后 (postprandial)”是由食物摄取引发的生理状态。其开始于上胃肠道的运动模式的改变，所述改变在约 30 秒至 1 分钟的时间内发生。胃产生每分钟 3-4 次连续的规律性收缩，这与消化间期模式中的收缩相似，但幅度仅为其大约一半。在胃内容物到达小肠远端之前，几乎同时在胃肠道的所有部位发生变化。液体和小颗粒不断从胃流入肠。胃的收缩导致一个允许液体和小颗粒通过部分打开的幽门的筛分过程。大于幽门尺寸的难以消化的颗粒退回 (retropelled) 并滞留于胃中。尺寸超过约 1cm 的颗粒因此滞留于胃中大约 4-6 小时。

[0028] 如本文所使用的，增加活性剂（例如，抗血管生成剂，更具体地，帕唑帕尼）的有效性包括，降低对活性剂的抗性；延缓对活性剂的抗性的发展；延缓变为活性剂难治性的癌

症的发生；延长活性剂的有用性；允许在治疗通常发展或已经发展出对活性剂的抗性的癌症中使用活性剂；提升患者对活性剂的响应；增加细胞对活性剂的应答；降低活性剂的有效剂量；或它们的任意组合。

Abexinostat

[0029] Abexinostat（或PCI-24781）是基于氧肟酸盐的HDAC抑制剂。Abexinostat的化学名称为3-[（二甲基氨基）甲基]-N-{2-[4-（羟基氨基甲酰基）苯氧基]乙基}-1-苯并呋喃-2-甲酰胺。

[0030] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用(a)abexinostat或其盐的周期，及(b)抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0031] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用(a)abexinostat或其盐的周期，及(b)帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0032] 在某些实施方案中，本文另外还公开了治疗癌症的方法，包括施用(a)abexinostat或其盐的周期，及(b)抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0033] 在某些实施方案中，本文进一步公开了治疗癌症的方法，包括施用(a)abexinostat或其盐的周期，及(b)帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0034] 癌症可能由诸如基因突变和缺失和染色体异常等遗传缺陷所引起，这类遗传缺陷导致肿瘤抑制基因的功能丧失和/或癌基因的功能获得或超活化。

[0035] 癌症通常以肿瘤内全基因组范围的基因表达改变为特征。这些改变增强了肿瘤超越细胞周期进展、避免细胞凋亡或变得耐受化学治疗的能力。HDAC抑制剂已经显示出能够

逆转这些改变中的几种，并恢复更类似于正常细胞的模式。

[0036] 人类基因组由复杂的基因网络组成，这些基因根据细胞的需要被打开或关闭。基因打开或关闭的一种途径是借助于组蛋白的化学修饰。组蛋白是染色体的结构成分，并形成一个框架，在该框架上安置遗传物质 DNA。充分研究的组蛋白修饰是乙酰化和脱乙酰化，这是由被称为组蛋白乙酰基转移酶和组蛋白脱乙酰酶的酶家族催化的修饰。

[0037] abexinostat 对 HDAC 酶的抑制使平衡倾向于乙酰化状态——一种允许转录发生的状态，其可被认为是将基因“打开”。当用 abexinostat 处理细胞时，一个个之前沉默的基因开始被打开。这些基因中的一些自身是调节子，会激活或抑制其它基因的表达。结果是基因表达的组合 (orchestra) 改变 ：一些基因被打开，而其它基因保持关闭状态。

[0038] 在化学治疗和 / 或放射治疗后，作为肿瘤适应治疗并耐受细胞死亡的一种策略，一些患者的肿瘤可能打开某些基因。在很多癌症中发生的遗传改变的一个例子是 DNA 修复基因 RAD51 的激活。响应于 DNA 损伤性化学治疗或放射治疗，肿瘤会经常打开 DNA 修复基因 (包括 RAD51) 作为适应策略，以帮助肿瘤修复由这些因素造成的 DNA 损伤。在临床前模型中，abexinostat 能够关闭 RAD51(和其它 DNA 修复基因)，从而有效阻断肿瘤修复其损伤的 DNA 的能力，使得肿瘤对化学治疗和放射治疗敏感。

[0039] 在临床前研究中，已发现 abexinostat 及其盐 (例如 abexinostat 盐酸盐) 具有有显著肿瘤特异性的抗癌活性。这些早期研究提供了关于 abexinostat 及其盐 (如 abexinostat 盐酸盐) 的体外和体内活性的重要信息，并确定了抗癌效果潜在的分子机理。

[0040] 体外 ：abexinostat 及其盐 (例如 abexinostat(或其盐 ；例如 abexinostat 盐酸盐) 盐酸盐) 对多种肿瘤细胞系都有活性，且在肺、结肠、前列腺、胰及脑肿瘤的小鼠模型中是有效的。

[0041] 离体 ：abexinostat 及其盐 (例如 abexinostat 盐酸盐) 在来自罹患结肠、卵巢、肺和很多血液系统癌症的患者的原发性人类肿瘤中具有活性。

[0042] 在多种动物物种中已经进行了充分的安全性和毒理学研究。研究了 abexinostat 及其盐 (例如 abexinostat 盐酸盐) 的作用机理，其涉及对肿瘤细胞的多重攻击 ：p21 和其它肿瘤抑制子和细胞周期基因的上调 ；活性氧的诱导和抗氧化途径的减弱 ；钙稳态的改变和增加的 ER 应激 ；DNA 修复途径的下调和增加的 DNA 损伤 ；通过死亡受体对细胞凋亡的直接诱导和胱天蛋白酶的激活。

[0043] 在涉及癌症病人的临床试验中，溶液形式的 abexinostat 以 2mg/kg 作为单一口服剂量和多次 2- 小时静脉内输注剂量给药。以 $AUC_{0-\infty}$ 测量的静脉内和口服给药的全身暴露分别为 5.9μM*hr 和 1.45μM*hr，表明人的口服生物利用度为约 27％。

治疗方案

[0044] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性 ；延缓抗血管生成剂抗性的发展 ；延缓变为抗血管生成剂难治性的癌症的发生 ；延长抗血管生成剂的有用性 ；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂 ；提升患者对抗血管生成剂的响应 ；增加细胞对抗血管生成剂的应答 ；降低抗血管生成剂的有效剂量 ；或它们的任意组合。

[0045] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0046] 在某些实施方案中，本文另外还公开了治疗癌症的方法，包括施用 (a) abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0047] 在某些实施方案中，本文进一步公开了治疗癌症的方法，包括施用 (a) abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0048] 在一些实施方案中，所述癌症是血液系统癌症、实体瘤或肉瘤。

[0049] 在一些实施方案中，所述癌症是肉瘤。在一些实施方案中，所述癌症是软组织肉瘤。

[0050] 在一些实施方案中，所述癌症选自：乳腺癌、结肠癌、结直肠癌、非小细胞肺癌、小细胞肺癌、肝癌、卵巢癌、前列腺癌、宫颈癌、膀胱癌、胃癌、胃肠道间质瘤、胰腺癌、生殖细胞瘤、肥大细胞瘤、神经母细胞瘤、肥大细胞增多症、睾丸癌、胶质母细胞瘤、星形细胞瘤、B 细胞淋巴瘤、T 细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、黑色素瘤、骨髓瘤、急性髓细胞性白血病 (AML)、急性淋巴细胞性白血病 (ALL)、骨髓增生异常综合征、慢性髓性白血病以及肾细胞癌。

[0051] 在一些实施方案中，所述癌症选自：乳腺癌、结肠癌、结直肠癌、非小细胞肺癌、肝癌、卵巢癌、宫颈癌、胃癌、胰腺癌、胶质母细胞瘤、B 细胞淋巴瘤、T 细胞淋巴瘤、霍奇金淋巴瘤、非霍奇金淋巴瘤、骨髓瘤、骨髓增生异常综合征 (MDS) 以及肾细胞癌。在一些实施方案中，所述癌症是肾细胞癌或卵巢癌。

[0052] 在本文公开的方法的一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）以一种剂型（例如，口服剂型）施用。在本文公开的方法的一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开（即，以分开的口服剂型）施用。在 HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐

酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开施用的情况下，它们同时或相继施用。在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开并相继施用。在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开并同时施用。

[0053] 在本文公开的方法的一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）以一种剂型（例如，一种口服剂型）施用。在本文公开的方法的一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开（即，以分开的口服剂型）施用。在 abexinostat（或其盐，例如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开施用的情况下，它们同时或相继施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开并相继施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）及帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）分开并同时施用。

[0054] 在本文公开的方法的一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）以速释剂型施用。在本文公开的方法的一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）以控释剂型施用。在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）以控释剂型施用，而帕唑帕尼或其盐（例如，帕唑帕尼盐酸盐）以速释剂型施用。

[0055] 在本文公开的方法的一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）以速释剂型施用。在本文公开的方法的一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）以速释剂型施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）以控释剂型施用，而帕唑帕尼或其盐（例如，帕唑帕尼盐酸盐）以速释剂型施用。

[0056] 在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过口服（例如，通过胶囊或片剂）施用。在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）通过口服（例如，通过胶囊或片剂）施用。在一些实施方案中，帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过口服（例如，通过胶囊或片剂）施用。

[0057] 在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过口服（例如，通过胶囊或片剂）施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）通过口服（例如，通过胶囊或片剂）施用。在一些实施方案中，帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过口服（例如，通过胶囊或片剂）施用。

[0058] 在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）和 / 或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过静脉内施用。在一些实施方案中，HDAC 抑制剂（例如，abexinostat 或其盐，如 abexinostat 盐酸盐）通过静脉内施用。

在一些实施方案中，帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过静脉内施用。

[0059] 在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）和/或帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过静脉内施用。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）通过静脉内施用。在一些实施方案中，帕唑帕尼（或其盐；例如，帕唑帕尼盐酸盐）通过静脉内施用。

[0060] 在本文公开的方法的一些实施方案中，HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐）在禁食模式下施用。在本文公开的方法的一些实施方案中，帕唑帕尼（或其盐）在禁食模式下施用。在一些实施方案中，HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐）在禁食模式下施用。

[0061] 在本文公开的方法的一些实施方案中，abexinostat（或其盐）在禁食模式下施用。在本文公开的方法的一些实施方案中，帕唑帕尼（或其盐）在禁食模式下施用。在一些实施方案中，abexinostat（或其盐）和帕唑帕尼（或其盐）在禁食模式下施用。

[0062] 在本文公开的方法的一些实施方案中，HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐）在餐前至少约一小时或餐后至少约两小时施用。在本文公开的方法的一些实施方案中，帕唑帕尼（或其盐）在餐前至少约一小时或餐后至少约两小时施用。在一些实施方案中，HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐）和帕唑帕尼（或其盐）在餐前至少约一小时或餐后至少约两小时施用。

[0063] 在本文公开的方法的一些实施方案中，abexinostat（或其盐）在餐前至少约一小时或餐后至少约两小时施用。在本文公开的方法的一些实施方案中，帕唑帕尼（或其盐）在餐前至少约一小时或餐后至少约两小时施用。在一些实施方案中，abexinostat（或其盐）和帕唑帕尼（或其盐）在餐前至少约一小时或餐后至少约两小时施用。

[0064] 在一些实施方案中，本文公开的方法包括一日两次施用约30mg/m^{2}至约75mg/m^{2}的HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐）。在一些实施方案中，本文公开的方法包括施用约400mg至约800mg的帕唑帕尼（或其盐）。在一些实施方案中，本文公开的方法包括一日两次施用约30mg/m^{2}至约75mg/m^{2}的HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐），以及约200mg至约800mg的帕唑帕尼（或其盐）。在一些实施方案中，本文公开的方法包括一日两次施用约30mg/m^{2}至约75mg/m^{2}的HDAC抑制剂（例如，abexinostat或其盐，如abexinostat盐酸盐），以及约216.7mg至约866.8mg的帕唑帕尼盐酸盐。

[0065] 在一些实施方案中，本文公开的方法包括一日两次施用约30mg/m^{2}至约75mg/m^{2}的abexinostat（或其盐）。在一些实施方案中，本文公开的方法包括施用约400mg至约800mg的帕唑帕尼（或其盐）。在一些实施方案中，本文公开的方法包括一日两次施用约30mg/m^{2}至约75mg/m^{2}的abexinostat（或其盐），以及约200mg至约800mg的帕唑帕尼（或其盐）。在一些实施方案中，本文公开的方法包括一日两次施用约30mg/m^{2}至约75mg/m^{2}的abexinostat（或其盐），以及约216.7mg至约866.8mg的帕唑帕尼盐酸盐。

[0066] 在一些实施方案中，本文公开的方法包括持续5天一日两次施用约30mg/m^{2}至约75mg/m^{2}的abexinostat（或其盐），随后2天不施用abexinostat（或其盐）。在一些实施方案中，本文公开的方法包括施用约400mg至约800mg的帕唑帕尼（或其盐）。在一些实施方案中，本文公开的方法包括(a)持续5天一日两次施用约30mg/m^{2}至约75mg/

m^2 的 abexinostat（或其盐），随后 2 天不施用 abexinostat（或其盐），以及 (b) 施用约 200mg 至约 800mg 的帕唑帕尼（或其盐）。在一些实施方案中，本文公开的方法包括 (a) 持续 5 天一日两次施用约 30mg/m^2 至约 75mg/m^2 的 abexinostat（或其盐），随后 2 天不施用 abexinostat（或其盐），以及 (b) 施用约 216.7mg 至约 866.8mg 的帕唑帕尼盐酸盐。

[0067] 在一些实施方案中，持续使用本文公开的方法直到癌症缓解。在一些实施方案中，持续使用本文公开的方法直到病情进展、出现无法接受的毒性或基于个人选择。在一些实施方案中，长期持续使用本文公开的方法。

Abexinostat

[0068] 在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 1 至 14 天、连续 2 至 14 天、连续 3 至 14 天、连续 4 至 14 天、连续 5 至 14 天、连续 6 至 14 天、连续 7 至 14 天、连续 8 至 14 天、连续 9 至 14 天、连续 10 至 14 天、连续 11 至 14 天、连续 12 至 14 天或连续 13 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 1 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 2 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 3 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 4 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 5 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 6 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 7 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 8 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 9 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 10 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 11 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 12 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 13 至 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是 5 至 9 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是 6 至 8 天。

[0069] 在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 2 天、连续 3 天、连续 4 天、连续 5 天、连续 6 天、连续 7 天、连续 8 天、连续 9 天、连续 10 天、连续 11 天、连续 12 天、连续 13 天或连续 14 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 2 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 3 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 4 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 5 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 6 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 7 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 8 天。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的周期是连续 9 天。在一些实施方案中，abexinostat（或其

盐，例如abexinostat盐酸盐）的周期是连续10天。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的周期是连续11天。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的周期是连续12天。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的周期是连续13天。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的周期是连续14天。

[0070] 在一些实施方案中，在abexinostat（或其盐，例如abexinostat盐酸盐）的周期内，每天一次施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，在abexinostat（或其盐，例如abexinostat盐酸盐）的周期内，每天两次施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，在abexinostat（或其盐，例如abexinostat盐酸盐）的周期内，每天三次施用abexinostat（或其盐，例如abexinostat盐酸盐）。在某些情况下，相比于一天三次给药，一天两次给药减少血小板减少症的发生率。

[0071] 在一些实施方案中，在abexinostat（或其盐，例如abexinostat盐酸盐）的周期内，每天两次施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的各剂量间隔4-8小时施用。在一些实施方案中，任何在本文中公开的方法包括施用第一剂量的abexinostat（或其盐，例如abexinostat盐酸盐）和第二剂量的abexinostat（或其盐，例如abexinostat盐酸盐），其中该第一剂量和第二剂量间隔4-8小时施用。

[0072] 在一些实施方案中，在abexinostat（或其盐，例如abexinostat盐酸盐）的周期内，每天三次施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的各剂量间隔4-8小时施用。在一些实施方案中，任何在本文中公开的方法包括施用第一剂量的abexinostat（或其盐，例如abexinostat盐酸盐）、第二剂量的abexinostat（或其盐，例如abexinostat盐酸盐）和第三剂量的abexinostat（或其盐，例如abexinostat盐酸盐），其中该第一剂量、第二剂量及第三剂量间隔4-8小时施用。

[0073] 为了达到治疗效果，在给药日，人体内abexinostat的有效血浆浓度应当维持每天至少连续6小时、至少连续7小时或至少连续8小时。在给药日维持abexinostat的有效血浆浓度约连续6小时至约连续8小时增强了肿瘤细胞生长抑制的功效并使血小板减少症的发生率降至最低。

[0074] 在一些实施方案中，在给药日，人体内abexinostat的有效血浆浓度维持每天至少连续6小时。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的剂量足以在个体中维持HDAC抑制剂的有效血浆浓度至少约连续6小时。

[0075] 在一些实施方案中，在给药日，人体内abexinostat的有效血浆浓度维持每天至少连续7小时。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的剂量足以在个体中维持HDAC抑制剂的有效血浆浓度至少约连续7小时。

[0076] 在一些实施方案中，在给药日，人体内abexinostat的有效血浆浓度维持每天至少连续8小时。在一些实施方案中，abexinostat（或其盐，例如abexinostat盐酸盐）的剂量足以在个体中维持HDAC抑制剂的有效血浆浓度至少约连续8小时。

[0077] 在一些实施方案中，在给药日，人体内abexinostat的有效血浆浓度维持至少连

续 6 小时但不超过连续 12、13 或 14 小时。在给药日维持 abexinostat 的有效血浆浓度至少连续 6 小时但不超过连续 14 小时增强了肿瘤细胞生长抑制的功效并使血小板减少症的发生率降至最低。

[0078] 作为速释胶囊或口服溶液施用的 abexinostat 在人体中的口服生物利用度经测定为约 27％。在实验动物中观察到禁食状态和进食状态之间的药代动力学区别。abexinostat 表现出优先在肠内吸收。

[0079] 对人施用的 abexinostat 的日剂量范围为约 10mg/mm^2 至约 200mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 30mg/mm^2 至约 90mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 60mg/mm^2 至约 150mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 20mg/mm^2、约 30mg/mm^2、约 40mg/mm^2、约 50mg/mm^2、约 60mg/mm^2、约 70mg/mm^2、约 80mg/mm^2、约 90mg/mm^2、约 100mg/mm^2、约 110mg/mm^2、约 120mg/mm^2、约 130mg/mm^2、约 140mg/mm^2 或约 150mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 20mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 30mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 40mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 50mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 60mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 70mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 80mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 90mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 100mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 110mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 120mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 130mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 140mg/mm^2。在一些实施方案中，abexinostat 的日剂量为约 150mg/mm^2。

[0080] 在一些实施方案中，abexinostat 的日剂量为约 40mg 至约 60mg 的 abexinostat。

[0081] 施用的 abexinostat（或其盐，例如 abexinostat 盐酸盐）的日剂量随着下述因素而变化，作为非限制性的实例，该因素包括使用的制剂的类型、癌症的类型及其严重程度、患者特征（例如，体重、年龄）和 / 或给药途径。

[0082] 在本文公开的方法的一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）以速释剂型施用。在本文公开的方法的一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）以控释剂型施用。

[0083] 在一些实施方案中，所述剂型在给药后约 2 小时至约 10 小时的时期内完全释放 abexinostat（或其盐）。

[0084] 在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）通过口服（例如，通过胶囊或片剂）施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）通过速释口服剂型（例如，通过胶囊或片剂）施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）通过控释口服剂型（例如，通过胶囊或片剂）施用。

[0085] 在本文公开的方法的一些实施方案中，该方法包括施用含有 abexinostat（或其盐）的第一速释口服剂型和含有 abexinostat（或其盐）的第二速释口服剂型，其中该第二速释口服剂型与第一速释口服剂型间隔约 4 小时至约 8 小时施用。

[0086] 在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）通过静脉

内施用。

[0087] 在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）在个体处于禁食模式时施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）在餐前至少约 1 小时施用。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）在餐后至少约 2 小时施用。

[0088] 在一些实施方案中，施用 abexinostat（或其盐）直到癌症缓解。在一些实施方案中，施用 abexinostat（或其盐）直到病情进展、出现无法接受的毒性或基于个人选择。在一些实施方案中，长期施用 abexinostat（或其盐）。

Abexinostat 休药期

[0089] 在某些情况下，血小板减少症是在接受 HDAC 抑制剂化合物治疗的人中观察到的副作用。4 级血小板减少症一般包括病人血小板计数少于 25,000/mm^2 的情况。血小板减少症可通过降低 abexinostat 的日剂量而得以改善或避免。在一些实施方案中，本文公开的方法进一步包括在 abexinostat（或其盐，例如 abexinostat 盐酸盐）周期之后的 abexinostat（或其盐；例如 abexinostat 盐酸盐）休药期。在一些实施方案中，abexinostat（或其盐，例如 abexinostat 盐酸盐）的休药期不会损害 abexinostat（或其盐，例如 abexinostat 盐酸盐）治疗方案的功效。

[0090] 在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 1 至 14 天、连续 2 至 14 天、连续 3 至 14 天、连续 4 至 14 天、连续 5 至 14 天、连续 6 至 14 天、连续 7 至 14 天、连续 8 至 14 天、连续 9 至 14 天、连续 10 至 14 天、连续 11 至 14 天、连续 12 至 14 天或连续 13 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 1 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 2 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 3 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 4 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 5 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 6 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 7 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 8 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 9 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 10 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 11 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 12 至 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 13 至 14 天。

[0091] 在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 2 天、连续 3 天、连续 4 天、连续 5 天、连续 6 天、连续 7 天、连续 8 天、连续 9 天、连续 10 天、连续 11 天、连续 12 天、连续 13 天或连续 14 天。在一些实施方案中，abexinostat（或其盐；例如 abexinostat 盐酸盐）的休药期是连续 2 天。在一些实施方案

中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续3天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续4天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续5天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续6天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续7天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续8天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续9天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续10天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续11天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续12天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续13天。在一些实施方案中，abexinostat（或其盐；例如abexinostat盐酸盐）的休药期是连续14天。

[0092] 在一些实施方案中，本文公开的方法包括连续5-9天每日施用abexinostat（或其盐，例如abexinostat盐酸盐），然后连续5-9天不施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，本文公开的方法包括连续5-9天每日施用abexinostat（或其盐，例如abexinostat盐酸盐），然后连续2-9天不施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，本文公开的方法包括连续6-8天每日施用abexinostat（或其盐，例如abexinostat盐酸盐），然后连续6-8天不施用abexinostat（或其盐，例如abexinostat盐酸盐）。在一些实施方案中，本文公开的方法包括连续6-8天每日施用abexinostat（或其盐，例如abexinostat盐酸盐），然后连续2-8天不施用abexinostat（或其盐，例如abexinostat盐酸盐）。

[0093] 在一些实施方案中，本文公开的方法包括连续7天每日施用abexinostat（或其盐，例如abexinostat盐酸盐），然后连续7天不施用abexinostat（或其盐，例如abexinostat盐酸盐）。

[0094] 在一些实施方案中，本文公开的方法包括连续5天每日施用abexinostat（或其盐，例如abexinostat盐酸盐），然后连续2天不施用abexinostat（或其盐，例如abexinostat盐酸盐）。

帕唑帕尼

[0095] 帕唑帕尼，5-[[4-[(2,3-二甲基-2H-吲唑-6-基)(甲基)氨基]嘧啶-2-基]氨基]-2-甲基苯磺酰胺一盐酸盐，是一种口服血管生成抑制剂，其靶向与血管内皮生长因子受体(VEGFR)-1、-2和-3、血小板衍生生长因子受体(PDGFR)-α和PDGFR-β以及干细胞因子受体(C-KIT)相关联的酪氨酸激酶活性。

[0096] 在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）与abexinostat（或其盐，例如abexinostat盐酸盐）联合施用于个体。在一些实施方案中，帕唑帕尼与abexinostat（或其盐，例如abexinostat盐酸盐）联合施用于个体。在一些实施方案中，帕唑帕尼盐酸盐与abexinostat（或其盐，例如abexinostat盐酸盐）联合施用于个体。在一些实施方案中，帕唑帕尼盐酸盐与abexinostat的盐（例如abexinostat盐酸盐）联合施用于个体。

[0097] 在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）连续施用于个体，例如，无休药期。在一些实施方案中，在不施用 abexinostat 期间（即，在 abexinostat 的休药期内）并不停止施用帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）。在一些实施方案中，在不施用 abexinostat 期间（即，在 abexinostat 的休药期内）停止施用帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）。

[0098] 在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）以速释剂型施用。在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）以控释剂型施用。

[0099] 在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）通过口服（例如，通过胶囊或片剂）施用。在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）通过速释口服剂型（例如，通过胶囊或片剂）施用。在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）通过控释口服剂型（例如，通过胶囊或片剂）施用。

[0100] 在一些实施方案中，帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）通过静脉内施用。

[0101] 在一些实施方案中，施用 abexinostat（或其盐）直到癌症缓解。在一些实施方案中，施用 abexinostat（或其盐）直到病情进展、出现无法接受的毒性或基于个人选择。在一些实施方案中，长期施用 abexinostat（或其盐）。

[0102] 在一些实施方案中，在个体处于禁食模式时施用帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）。在一些实施方案中，在餐前至少约一小时施用帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）。在一些实施方案中，在餐后至少约两小时施用帕唑帕尼（或其盐，例如帕唑帕尼盐酸盐）。

[0103] 在一些实施方案中，帕唑帕尼（或其盐）每天一次、每天两次、每天三次或每天四次施用。在一些实施方案中，帕唑帕尼（或其盐）每天两次施用。在一些实施方案中，帕唑帕尼（或其盐）每天三次施用。在一些实施方案中，帕唑帕尼（或其盐）每天四次施用。

[0104] 在一些实施方案中，帕唑帕尼（或其盐）每天两次施用。在一些实施方案中，帕唑帕尼（或其盐）的各剂量间隔 4-8 小时施用。在一些实施方案中，任何在本文中公开的方法包括施用第一剂量的帕唑帕尼（或其盐）和第二剂量的帕唑帕尼（或其盐），其中该第一剂量和第二剂量间隔 4-8 小时施用。

[0105] 在一些实施方案中，帕唑帕尼（或其盐）每天三次施用。在一些实施方案中，帕唑帕尼（或其盐）的各剂量间隔 4-8 小时施用。在一些实施方案中，任何在本文中公开的方法包括施用第一剂量的帕唑帕尼（或其盐）、第二剂量的帕唑帕尼（或其盐）和第三剂量的帕唑帕尼（或其盐），其中该第一剂量、第二剂量和第三剂量间隔 4-8 小时施用。

[0106] 在一些实施方案中，帕唑帕尼（或其盐）每天四次施用。在一些实施方案中，帕唑帕尼（或其盐）的各剂量间隔 4-8 小时施用。在一些实施方案中，任何在本文中公开的方法包括施用第一剂量的帕唑帕尼（或其盐）、第二剂量的帕唑帕尼（或其盐）、第三剂量的帕唑帕尼（或其盐）和第四剂量的帕唑帕尼（或其盐），其中该第一剂量、第二剂量、第三剂量和第四剂量间隔 4-8 小时施用。

[0107] 在一些实施方案中，帕唑帕尼的日剂量是约 200mg 至约 800mg、约 400mg 至约 800mg 或者约 600mg 至约 800mg。在一些实施方案中，帕唑帕尼的日剂量是约 200mg 至约 800mg。在一些实施方案中，帕唑帕尼的日剂量是约 400mg 至约 800mg。在一些实施方案中，帕唑帕尼的日剂量是约 600mg 至约 800mg。

[0108] 在一些实施方案中，帕唑帕尼的日剂量是约200mg、约400mg、约600mg或约800mg。在一些实施方案中，帕唑帕尼的日剂量是约200mg。在一些实施方案中，帕唑帕尼的日剂量是约400mg。在一些实施方案中，帕唑帕尼的日剂量是约600mg。在一些实施方案中，帕唑帕尼的日剂量是约800mg。

[0109] 在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约216.7mg至约866.8mg、约433.4mg至约866.8mg或者约650.1mg至约866.8mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约216.7mg至约866.8mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约433.4mg至约866.8mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约650.1mg至约866.8mg。

[0110] 在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约216.7mg、约433.4mg、约650.1mg或约866.8mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约216.7mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约433.4mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约650.1mg。在一些实施方案中，帕唑帕尼盐酸盐的日剂量是约866.8mg。

[0111] 施用的abexinostat（或其盐，例如abexinostat盐酸盐）的日剂量随着下述因素而变化，作为非限制性的实例，该因素包括使用的制剂的类型、癌症的类型及其严重程度、患者的特征（例如，体重、年龄）和/或给药途径。

HDAC抑制剂化合物

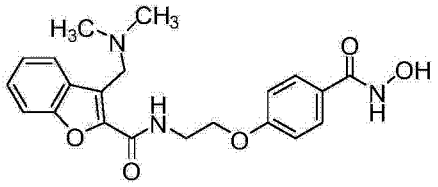
[0112] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用(a)HDAC抑制剂或其盐的周期，及(b)抗血管生成剂。在一些实施方案中，该HDAC抑制剂是abexinostat。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0113] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用(a)HDAC抑制剂或其盐的周期，及(b)帕唑帕尼或其盐。在一些实施方案中，该HDAC抑制剂是abexinostat。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0114] 在某些实施方案中，本文另外还公开了治疗癌症的方法，包括施用(a)HDAC抑制剂或其盐的周期，及(b)抗血管生成剂。在一些实施方案中，该HDAC抑制剂是abexinostat。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0115] 在某些实施方案中，本文进一步公开了治疗癌症的方法，包括施用 (a)HDAC 抑制剂或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该 HDAC 抑制剂是 abexinostat。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0116] N- 羟基 -4-{2-[3-(N,N- 二甲基氨基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基} 苯甲酰胺 (abexinostat) 具有如下结构：



Abexinostat。

[0117] 在一个方面，abexinostat 在本文公开的方法中作为药学上可接受的盐使用。在一个方面，abexinostat 作为盐酸盐使用。

[0118] Abexinostat 的另外的药学上可接受的盐包括：(a) 当 abexinostat 的酸性质子被替换为金属离子例如碱金属离子（如锂、钠、钾）、碱土金属离子（如镁或钙）或铝离子或者被替换为铵阳离子 (NH_4^+) 时形成的盐；(b) 通过 abexinostat 与药学上可接受的有机碱（包括烷基胺，如乙醇胺、二乙醇胺、三乙醇胺、氨丁三醇、N- 甲基葡糖胺、二环己基胺、三（羟甲基）甲胺）反应而形成的盐，以及与诸如精氨酸、赖氨酸等氨基酸形成的盐；(c) 通过 abexinostat 与提供酸加成盐的药学上可接受的酸反应而形成的盐。药学上可接受的酸包括盐酸、氢溴酸、硫酸、硝酸、磷酸、偏磷酸等；或有机酸，如，例如，乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、琥珀酸、苹果酸、马来酸、富马酸、三氟乙酸、酒石酸、柠檬酸、苯甲酸、3-(4- 羟基苯甲酰基）苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、1,2- 乙二磺酸、2- 羟基乙磺酸、苯磺酸、甲苯磺酸、2- 萘磺酸、4- 甲基双环 -[2.2.2] 辛 -2- 烯 -1- 甲酸、葡庚糖酸、4,4'- 亚甲基双 -(3- 羟基 -2- 烯 -1- 甲酸）、3- 苯基丙酸、三甲基乙酸、叔丁基乙酸、月桂基硫酸、葡糖酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸、粘康酸等。

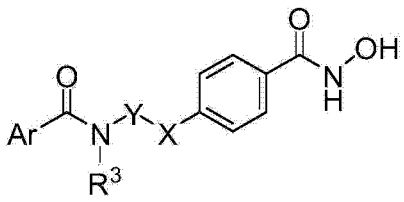
[0119] 另外的药学上可接受的盐包括描述于 Berge 等人，J.Pharm.Sci.1977,66,1-19；和“Handbook of Pharmaceutical Salts,Properties,and Use,”Stah 和 Wermuth 编；Wiley-VCH 和 VHCA,Zurich,2002 中的盐。

[0120] 在一些实施方案中，对在此描述的化合物的芳环部分上对多种代谢反应敏感的位点进行修饰，从而使该多种代谢反应减少、减至最少或消除。这类修饰包括在芳环结构上引入合适的取代基，例如，仅举例来说，卤素、氘等等。在一个方面，在此描述的 HDAC 抑制剂化合物在对代谢反应敏感的位点上进行氘化。

[0121] 在此描述的化合物包括同位素标记的化合物，后者与此处显示的各通式和结构中所列举的那些化合物相同，但是一个或多个原子被替换为原子质量或质量数与自然界通常发现的原子质量或质量数不同的原子。可引入本发明化合物的同位素的例子包括氢、碳、氮、氧、氟和氯的同位素，例如，分别为 ^{2}H、^{3}H、^{13}C、^{14}C、^{15}N、^{18}O、^{17}O、^{35}S、^{18}F、^{36}Cl。在此描述的某

些同位素标记的化合物，例如那些引入了放射性同位素如 ^{3}H 和 ^{14}C 的化合物，可用于药物和/或基质组织分布分析。进一步地，用例如氘（即，^{2}H）的同位素取代可以产生某些由更高的代谢稳定性所导致的治疗优势，例如增加的体内半衰期或降低的剂量需求。

[0122] 预期用于药物组合物、药代动力学策略、给药方案、治疗方法和联合治疗的其它 HDAC 抑制剂化合物包括具有式（I）结构的那些化合物：



式(I)

其中：

X 为 -O-、$-NR^{2}-$ 或 $-S(O)_{n}$，其中 n 为 0、1 或 2 且 R^{2} 为氢、$-CH_{3}$、$-CH_{2}CH_{3}$；

Y 为亚乙基、亚丙基、1- 甲基亚丙基、2- 甲基亚丙基、$-CH(C_{2}H_{5})CH_{2}-$、$-CH(CH(CH_{3})_{2})CH_{2}-$ 和 $-CH(CH_{3})CH_{2}-$；

R^{3} 为氢、$-CH_{3}$ 或 $-CH_{2}CH_{3}$；

Ar 为苯基、萘基、喹啉基、苯并呋喃基、苯并噻吩基、反式苯基 CH ＝ CH- 或反式（苯并呋喃 -2- 基）CH ＝ CH，其中 Ar 任选地被一个或两个取代基所取代，该取代基独立地选自氯、氟、三氟甲基、甲基、乙基、甲氧基、乙氧基、亚甲基二氧基、-OH、1- 环丙基哌啶 -4- 基氧基、1-(2,2,2- 三氟乙基）哌啶 -4- 基氧基、N,N- 二甲基氨基甲基、N,N- 二乙基氨基甲基、2- 甲氧基乙氧基甲基、苯氧基甲基、2- 甲氧基乙氧基、2- 吗啉 -4- 基乙氧基、吡啶 -3- 基甲氧基、2- 羟基乙氧基、2-N,N- 二甲基氨基乙氧基、甲氧基甲基、3- 异丙氧基甲基、吗啉 -4- 基甲基、3- 羟基丙氧基甲基、2- 氟苯氧基甲基、3- 氟苯氧基甲基、4- 氟苯氧基 - 甲基、3- 甲氧基丙氧基甲基、吡啶 -4- 基氧甲基、2,4,6- 三氟苯氧基甲基、2- 氧代吡啶 -1- 基甲基、2,2,2- 三氟乙氧基甲基、4- 咪唑 -1- 基苯氧基甲基、4-[1.2.4- 三嗪 -1- 基 - 苯氧基甲基、2- 苯基乙基、吡咯烷 -1- 基甲基、哌啶 -1- 基甲基、4- 三氟甲基哌啶 -1- 基甲基、4- 甲基哌嗪 -1- 基甲基、3,3,3- 三氟丙氧基甲基、4- 氟苯硫基甲基、4- 氟苯基亚磺酰基甲基、4- 氟苯基磺酰基甲基、吡啶 -3- 基甲氧基甲基、四氢吡喃 -4- 基氧基、2,2,2- 三氟乙氧基、2- 吡咯烷 -1- 基乙氧基、哌啶 -4- 基氧基、N- 甲基 -N- 苄基氨基甲基、N- 甲基 -N-2- 苯基乙基氨基甲基、3- 羟基丙硫基甲基、3- 羟基丙基亚磺酰基甲基、3- 羟基丙基磺酰基 - 甲基、N- 甲基 -N-2- 吲哚 -3- 基乙基氨基甲基、2-(4- 三氟甲基苯基）乙基、2-(3- 三氟甲氧基苯基）乙基、N- 羟基氨基羰基 - 甲基氨基甲基或 3-(2- 羧基乙基氨基 - 甲基）；或

其药学上可接受的盐。

[0123] 在一些实施方案中，Ar 为苯并呋喃 -2- 基且在苯并呋喃 -2- 基环的 3 位上被以下基团单取代：N,N- 二甲基氨基甲基、N,N- 二乙基氨基甲基、2- 氟苯氧基甲基、3- 氟苯氧基甲基、4- 氟苯氧基 - 甲基、羟基 -4- 基氧甲基、2,4,6- 三氟苯氧基 - 甲基、2- 氧代吡啶 -1- 基甲基、2,2,2- 三氟乙氧基 - 甲基、4- 咪唑 -1- 基苯氧基 - 甲基、4-[1.2.4- 三嗪 -1- 基 - 苯氧基甲基、2- 苯基乙基、3- 羟基丙氧基甲基、2- 甲氧基乙氧基甲基、吡咯烷 -1- 基甲基、哌啶 -1- 基甲基、4- 三氟甲基哌啶 -1- 基甲基、4- 甲基哌嗪 -1- 基甲基、3,3,3- 三氟丙氧基甲

基、4- 氟苯硫基甲基、4- 氟苯基亚磺酰基甲基、4- 氟苯基磺酰基甲基、2-(3- 三氟甲氧基苯基乙基)，N- 甲基 -N- 苄基氨基甲基、N- 甲基 -N-2- 苯基乙基氨基甲基、3- 羟基丙基 - 硫甲基、3- 羟基丙基亚磺酰基 - 甲基、3- 羟基丙基磺酰基甲基、N- 甲基 -N-2- 吲哚 -3- 基乙基氨基甲基、2-(4- 三氟甲基苯基) 乙基、N- 羟基氨基羰基 - 甲基氨基甲基或 2- 羧基乙基氨基甲基。

[0124] 在一些实施方案中，Ar 为苯并呋喃 -2- 基且在苯并呋喃 -2- 基环的 3 位被以下基团单取代 :N,N- 二甲基氨基甲基、N,N- 二乙基氨基甲基、2- 甲氧基乙氧基甲基、甲氧基甲基、3- 异丙氧基甲基、吗啉 -4- 基甲基、3- 羟基丙氧基甲基、3- 甲氧基丙氧基甲基、吡咯烷 -1- 基甲基或哌啶 -1- 基甲基。

[0125] 在一些实施方案中，Ar 为苯并呋喃 -2- 基且在苯并呋喃 -2- 基环的 5 位上被以下基团单取代 :1- 环丙基哌啶 -4- 基氧基、哌啶 -4- 基氧基、四氢吡喃 -4- 基氧基、2,2,2- 三氟乙氧基、2- 吡咯烷 -1- 基乙氧基或 1-(2,2,2- 三氟乙基) 哌啶 -4- 基氧基。

[0126] 在一些实施方案中，Ar 为反式苯基 CH ＝ CH，其中该苯基任选地被独立地选自甲基、乙基、甲氧基、乙氧基、亚甲基二氧基或 - OH 的一个或两个取代基所取代。在一些实施方案中，Ar 为反式苯基 CH ＝ CH-。

[0127] 在一些实施方案中，Ar 为萘基，其中该萘基任选地被一个或两个取代基取代。

[0128] 在一些实施方案中，Ar 为喹啉基，其中该喹啉基任选地被一个或两个取代基取代。

[0129] 在一些实施方案中，Ar 为喹啉基，其中该喹啉基任选地被一个或两个取代基所取代，该取代基独立地选自氯、氟、三氟甲基、甲基、乙基、甲氧基、乙氧基、亚甲基二氧基、-OH、2- 甲氧基乙氧基、2- 羟基乙氧基、甲氧基甲基、3- 异丙氧基甲基、3- 羟基丙氧基甲基、3- 甲氧基丙氧基甲基或 3,3,3- 三氟丙氧基甲基。

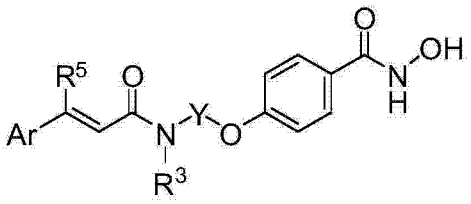
[0130] 在一些实施方案中，X 为 - O- 且 R^3 为氢。

[0131] 在一些实施方案中，X 为 $-S(O)_n$ 且 R^3 为氢。

[0132] 在一些实施方案中，Y 为亚乙基。在一些实施方案中，Y 为亚乙基或 $-CH(C_2H_5)CH_2-$。在一些实施方案中，Y 为 $-CH(C_2H_5)CH_2-$。

[0133] 在一些实施方案中，X 为 - O- ；R^3 为氢 ；且 Y 为亚乙基或 $-CH(C_2H_5)CH_2-$。

[0134] 预期用于该药物组合物、药代动力学策略、给药方案、治疗方法和联合治疗的另一些 HDAC 抑制剂化合物包括那些具有式 (II) 结构的化合物 ：



式(II)

其中 ：

X 为 - O-、$-NR^2-$ 或 $-S(O)_n$，其中 n 为 0、1 或 2 且 R^2 为氢、$-CH_3$、$-CH_2CH_3$ ；

Y 为亚乙基、亚丙基、1- 甲基亚丙基、2- 甲基亚丙基、$-CH(C_2H_5)CH_2-$、$-CH(CH(CH_3)_2)CH_2$ 和 $-CH(CH_3)CH_2-$ ；

R^3 为氢、$-CH_3$，或 $-CH_2CH_3$ ；

Ar 为苯基、萘基、喹啉基、苯并呋喃基或苯并噻吩基，其中 Ar 任选地被独立地选自氯、氟、三氟甲基、甲基、乙基、甲氧基、乙氧基、亚甲基二氧基、-OH 的一个或两个取代基所取代；

R^5 为三氟甲基、甲基、乙基、N,N- 二甲基氨基甲基、N,N- 二乙基氨基甲基、2- 甲氧基乙氧基甲基、苯氧基甲基、甲氧基甲基、3- 异丙氧基甲基、吗啉 -4- 基甲基、3- 羟基丙氧基甲基、2- 氟苯氧基甲基、3- 氟苯氧基甲基、4- 氟苯氧基 - 甲基、3- 甲氧基丙氧基甲基、吡啶 -4- 基氧甲基、2,4,6- 三氟苯氧基甲基、2- 氧代吡啶 -1- 基甲基、2,2,2- 三氟乙氧基甲基、4- 咪唑 -1- 基苯氧基甲基、2- 苯基乙基、吡咯烷 -1- 基甲基、哌啶 -1- 基甲基、4- 三氟甲基哌啶 -1- 基甲基、4- 甲基哌嗪 -1- 基甲基、3,3,3- 三氟丙氧基甲基、4- 氟苯硫基甲基、4- 氟苯基亚磺酰基甲基、4- 氟苯基磺酰基甲基、吡啶 -3- 基甲氧基甲基、N- 甲基 -N- 苄基氨基甲基、N- 甲基 -N-2- 苯基乙基氨基甲基、3- 羟基丙硫基甲基、3- 羟基丙基亚磺酰基甲基、3- 羟基丙基磺酰基 - 甲基、N- 甲基 -N-2- 吲哚 -3- 基乙基氨基甲基、2-(4- 三氟甲基苯基）乙基、2-(3- 三氟甲氧基苯基）乙基、N- 羟基氨基羰基 - 甲基氨基甲基或 3-(2- 羧基乙基氨基 - 甲基）；或

其药学上可接受的盐。

[0135] 在一些实施方案中，Ar 为苯并呋喃基。

[0136] 在一些实施方案中，R^5 为 N,N- 二甲基氨基甲基、N,N- 二乙基氨基甲基、吡咯烷 -1- 基甲基或哌啶 -1- 基甲基。

[0137] 在一些实施方案中，该 HDAC 抑制剂选自：N- 羟基 -4-[2-(4- 甲氧基喹啉 -2- 基羰基氨基）乙氧基］苯甲酰胺；N- 羟基 -4-[2S-（反 - 肉桂酰氨基）丁氧基］苯甲酰胺；N- 羟基 -4-[2R-（反 - 肉桂酰氨基）丁氧基］苯甲酰胺；N- 羟基 -4-{2-[4-(2- 甲氧基乙氧基）喹啉 -2- 基羰基氨基］乙氧基｝苯甲酰胺；N- 羟基 -4-[2S-（苯并噻吩 -2- 基羰基氨基）丁氧基］- 苯甲酰胺；N- 羟基 -4-{2S-［苯并呋喃 -2- 基羰基氨基］丁氧基｝苯甲酰胺；N- 羟基 -4-{2-[3-（甲氧基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝苯甲酰胺；N- 羟基 -4-{2-[3-(N,N- 二甲基氨基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝苯甲酰胺 (abexinostat)；N- 羟基 -4-{2-[3-（异丙氧基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝苯甲酰胺；N- 羟基 -4-{2-[3-(3- 羟基丙氧基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝- 苯甲酰胺；N- 羟基 -4-{2-[3-(2- 甲氧基乙氧基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝- 苯甲酰胺；N- 羟基 -4-{2-[3-（吡咯烷 -1- 基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝- 苯甲酰胺；N- 羟基 -4-{2-[3-（哌啶 -1- 基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝- 苯甲酰胺；N- 羟基 -4-{2-[3-(4- 甲基哌嗪 -1- 基甲基）苯并呋喃 -2- 基羰基氨基］- 乙氧基｝苯甲酰胺；N- 羟基 -4-{2-[5-（四氢吡喃 -4- 基氧基）苯并呋喃 -2- 基羰基氨基］乙氧基｝- 苯甲酰胺；N- 羟基 -4-{2-[5-(2- 吡咯烷 -1- 基乙氧基）苯并呋喃 -2- 基羰基氨基］乙氧基｝- 苯甲酰胺；N- 羟基 -4-{2S-[5-(2- 吡咯烷 -1- 基乙氧基）苯并呋喃 -2- 基羰基氨基］丁氧基｝- 苯甲酰胺；N- 羟基 -4-{2-[5-(2- 吡咯烷 -1- 基乙氧基）苯并呋喃 -2- 基羰基氨基］-1R- 甲基 - 乙氧基｝苯甲酰胺；和 N- 羟基 -4-{2-[(3-（苯并呋喃 -2- 基）-4-（二甲基氨基）- 丁 -2- 烯酰）氨基］- 乙氧基｝苯甲酰胺；或其药学上可接受的盐。

[0138] 在一些实施方案中，该 HDAC 抑制剂是 N- 羟基 -4-{2-[3-(N,N- 二甲基氨基甲基）苯并呋喃 -2- 基羰基氨基］乙氧基｝苯甲酰胺 (abexinostat)。

[0139] 在一些实施方案中，该HDAC抑制剂选自在WO 2004/092115或WO 2005/097770中公开的HDAC抑制剂，二者在此全文引入作为参考。形式和相

[0140] HDAC抑制剂（例如abexinostat），包括其药学上可接受的盐及其药学上可接受的溶剂化物，以多种形式存在，包括但不限于无定形相、部分结晶形式、结晶形式、磨碎形式和纳米颗粒形式。结晶形式被称为多晶型物。多晶型物包括化合物的相同元素组成的不同晶体堆积排列。这种排列可以显著影响物质和赋形剂的生理化学、配制和加工参数以及贮存期或稳定性。多晶型物通常具有不同的X-射线衍射图、红外光谱、熔点、密度、硬度、晶体形状、光学和电学性质、稳定性和溶解度。多种因素如再结晶溶剂、结晶速率和储存温度都会导致单一晶型占优势。在一个方面，在此处公开的药物组合物中使用结晶形式的HDAC抑制剂（例如abexinostat）。在一个方面，在此处公开的药物组合物中使用结晶形式的abexinostat的盐酸盐。在一个方面，在此处公开的药物组合物中使用无定形的abexinostat。在一个方面，在此处公开的药物组合物中使用无定形的abexinostat的盐酸盐。

药物组合物

[0141] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用(a)abexinostat或其盐的周期，及(b)抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0142] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用(a)abexinostat或其盐的周期，及(b)帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0143] 在某些实施方案中，本文另外还公开了在有需要的个体中治疗癌症的方法，包括施用(a)abexinostat或其盐的周期，及(b)抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0144] 在某些实施方案中，本文进一步公开了在有需要的个体中治疗癌症的方法，包括施用(a)abexinostat或其盐的周期，及(b)帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经

发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0145] 使用一种或多种生理学上可接受的载体（即非活性成分）以常规方式配制随本文公开的方法使用的组合物，该载体包括有利于将活性化合物加工成药学上使用的制品的赋形剂和助剂。合适的技术、载体和赋形剂包括在例如Remington:The Science and Practice of Pharmacy, 第 19 版 (Easton,Pa.:Mack Publishing Company,1995)；Hoover,John E.,Remington's Pharmaceutical Sciences,Mack Publishing Co.,Easton,Pennsylvania 1975；Liberman,H.A. 和 Lachman,L. 编，Pharmaceutical Dosage Forms,Marcel Decker,New York,N.Y.,1980； 和 Pharmaceutical Dosage Forms and Drug Delivery Systems, 第7版,(Lippincott Williams&Wilkins1999) 中记载的那些，这些文献在此全文引入作为参考。

[0146] 随本文公开的方法使用的组合物包含 abexinostat（或其盐），和 / 或帕唑帕尼（或其盐），以及下述一种或多种：(a) 粘合剂；(b) 包衣；(c) 崩解剂；(d) 填充剂（稀释剂）；(e) 润滑剂；(f) 助流剂（增流剂）；(g) 压制助剂；(h) 颜料；(i) 甜味剂；(j) 防腐剂；(k) 悬浮 / 分散剂；(l) 成膜剂 / 包衣；(m) 增味剂；(n) 印刷油墨；(o) 胶凝剂；(p) 第二治疗活性剂。

[0147] 在一个方面，随本文公开的方法使用的药物组合物除活性剂（例如，abexinostat、abexinostat 的盐、帕唑帕尼和 / 或帕唑帕尼的盐）外还包含下述一种或多种：(a) 硬脂酸镁；(b) 乳糖；(c) 微晶纤维素；(d) 硅化微晶纤维素；(e) 甘露醇；(f) 淀粉（玉米）；(g) 二氧化硅；(h) 二氧化钛；(i) 硬脂酸；(j) 羟基乙酸淀粉；(k) 明胶；(l) 滑石；(m) 蔗糖；(n) 阿斯巴甜；(o) 硬脂酸钙；(p) 聚维酮；(q) 预胶化淀粉；(r) 羟丙基甲基纤维素；(s)OPA 产品（包衣和油墨）；(t) 交联羧甲纤维素；(u) 羟丙基纤维素；(v) 乙基纤维素；(w) 磷酸钙（二碱性）；(x) 交聚维酮；(y) 虫胶（和釉）；(z) 碳酸钠。

[0148] 在一些实施方案中，随本文公开的方法使用的药物组合物包含在药学上可接受的媒介物、载体、稀释剂或赋形剂或其混合物中的活性成分（例如，abexinostat、abexinostat 的盐、帕唑帕尼和 / 或帕唑帕尼的盐）；和一种或多种在此描述的控释赋形剂。合适的改进释放剂量载体包括但不限于亲水或疏水基质装置、水溶性隔离层包衣、肠溶衣、渗透装置、多颗粒装置及其组合。该药物组合物还可以包含非控释赋形剂。

[0149] 在一些实施方案中，随本文公开的方法使用的药物组合物是薄膜包衣的剂型，其包含组合的活性成分和一种或多种压片赋形剂以使用常规压片工艺形成片剂核芯并随后对该核芯进行包衣。片剂核芯可使用常规造粒方法例如湿法或干法造粒进行生产，任选地对颗粒进行粉碎并随后压制和包衣。造粒方法描述于，例如 Voigt，第 156-69 页。

[0150] 用于生产颗粒的合适的赋形剂为，例如任选地具有流动调节性质的粉状填充剂，例如滑石、二氧化硅，例如 Syloid® 型 (Grace) 合成无定形无水硅酸，例如 SYLOID 244FP，例如 Avicel® 型 (FMC Corp.) 微晶纤维素，例如 AVICEL PH101、102、105、RC581 或 RC 591 型，Emcocel® 型 (Mendell Corp.) 或 Elcema® 型 (Degussa)；碳水化合物，如糖、糖醇、淀粉或淀粉衍生物，例如乳糖、右旋糖、蔗糖、葡萄糖、山梨醇、甘露醇、木糖醇、马铃薯淀

粉、玉米淀粉、大米淀粉、小麦淀粉或支链淀粉、磷酸三钙、磷酸氢钙或三硅酸镁；粘合剂，如明胶、黄蓍胶、琼脂、海藻酸、纤维素醚，例如甲基纤维素、羧甲基纤维素或羟丙基甲基纤维素，聚乙二醇或环氧乙烷均聚物（特别是具有约 $2.0x10^3$ 至 $1.0x10^5$ 聚合度和约 $1.0x10^5$ 至 $5.0x10^6$ 分子量的，例如被称为 Polyox® (Union Carbide) 的赋形剂）、聚乙烯吡咯烷酮或聚维酮（特别是具有约 1000 的平均分子量和约 500 至约 2500 的聚合度的），以及琼脂或明胶；表面活性物质，例如烷基硫酸盐类型的阴离子表面活性剂，例如钠、钾或镁的正十二烷基硫酸盐、正十四烷基硫酸盐、正十六烷基硫酸盐或正十八烷基硫酸盐，烷基醚硫酸盐类型的，例如钠、钾或镁的正十二烷氧基乙基硫酸盐、正十四烷氧基乙基硫酸盐、正十六烷氧基乙基硫酸盐或正十八烷氧基乙基硫酸盐，或链烷磺酸盐类型的，例如钠、钾或镁的正十二烷磺酸盐、正十四烷磺酸盐、正十六烷磺酸盐或正十八烷磺酸盐，或脂肪酸多羟基醇酯类型的非离子表面活性剂，如脱水山梨醇单月桂酸酯、单油酸酯、单硬脂酸酯或单棕榈酸酯，脱水山梨醇三硬脂酸酯或三油酸酯，脂肪酸多羟基醇酯的聚氧乙烯加合物，如聚氧乙烯脱水山梨醇单月桂酸酯、单油酸酯、单硬脂酸酯、单棕榈酸酯、三硬脂酸酯或三油酸酯，聚乙二醇脂肪酸酯，如聚氧乙基硬脂酸酯、聚乙二醇 400 硬脂酸酯、聚乙二醇 2000 硬脂酸酯，特别是普朗尼克® (BWC) 或 Synperonic® (ICI) 型的环氧乙烷 / 环氧丙烷嵌段共聚物。

[0151] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为肠溶衣剂型，其包含组合的活性成分或其药学上可接受的盐、溶剂化物或前药；以及用于肠溶衣剂型的一种或多种控释赋形剂。该药物组合物还可以包含非控释赋形剂。

[0152] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为具有速释成分和至少一种延迟释放成分的剂型，并能够以至少两个间隔时间为 0.5 小时至 8 小时的连续脉冲的形式提供化合物的不连续释放的药物组合物。该药物组合物包含组合的活性成分和一种或多种控释和非控释赋形剂，如那些适于可打破的半透膜和作为可膨胀物质的赋形剂。

[0153] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为用于对受试者口服给药的剂型，其包含组合的活性成分和一种或多种药学上可接受的赋形剂或载体，其包封在中间反应层中，该中间反应层含有部分用碱中和的、抗胃液的分层聚合材料，并且具有阳离子交换能力和抗胃液的外层。

[0154] 在一些实施方案中，随本文公开的方法使用的药物组合物包含肠溶衣颗粒形式的活性成分，作为用于口服给药的延迟释放胶囊。

[0155] 在此提供的药物组合物可作为单位剂量形式或多重剂量形式提供。本文使用的单位剂量形式指适合人和动物受试者给药并且如本领域所知单独包装的物理离散单元。每个单位剂量包含足以产生所期望的治疗效果的预定量的活性成分以及所需的药用载体或赋形剂。单位剂量形式的例子包括独立包装的片剂和胶囊。可分成几份或多次施用单位剂量形式。多重剂量形式是包装在单一容器内从而以分离的单位剂量形式给药的多个相同的单位剂量形式。多重剂量形式的例子包括片剂或胶囊剂的瓶子。

[0156] 药物剂型可以多种方法进行配制，并可以提供多种药物释放谱，包括速释、持续释放和延迟释放。在一些情况下可能需要阻止药物给药后的药物释放，直至一定量的时间逝去（即定时释放），以在预定的时间期限内提供基本上连续的释放（即持续释放），或提供

药物给药后的立即释放（即，速释）。

[0157] 口服制剂以下述形式呈现：片剂、胶囊、丸剂、微丸、珠粒、颗粒、散装粉剂。胶囊包括活性化合物与惰性填充剂和/或稀释剂如药学上可接受的淀粉（例如玉米、马铃薯或木薯淀粉）、糖、人造甜味剂、粉状纤维素（如结晶和微晶纤维素）、面粉、明胶、树胶等的混合物。片剂制剂通过常规压片、湿法造粒或干法造粒方法制备，并利用药学上可接受的稀释剂、粘合剂、润滑剂、崩解剂、表面改性剂（包括表面活性剂）、悬浮剂或稳定剂，包括但不限于硬脂酸镁、硬脂酸、滑石、十二烷基硫酸钠、微晶纤维素、羧甲基纤维素钙、聚乙烯吡咯烷酮、明胶、海藻酸、阿拉伯胶、黄原胶、柠檬酸钠、复合硅酸盐、碳酸钙、甘氨酸、糊精、蔗糖、山梨醇、磷酸二钙、硫酸钙、乳糖、高岭土、甘露醇、氯化钠、滑石、干淀粉和糖粉。在一些实施方案中是表面改性剂，其包括非离子和阴离子表面改性剂。例如，表面改性剂包括但不限于泊洛沙姆188、苯扎氯铵、硬脂酸钙、鲸蜡硬脂醇、聚西托醇乳化蜡、脱水山梨醇酯、胶体二氧化硅、磷酸盐、十二烷基硫酸钠、硅酸镁铝和三乙醇胺。

[0158] 在一个方面，在此描述的口服制剂利用标准的延迟或定时释放制剂来改变活性化合物的吸收。

[0159] 粘合剂或造粒剂赋予片剂凝聚力，以确保片剂在压制后保持完整。合适的粘合剂或造粒剂包括但不限于淀粉，如玉米淀粉、马铃薯淀粉和预胶化淀粉（例如STARCH 1500）；明胶；糖，如蔗糖、葡萄糖、右旋糖、糖蜜和乳糖；天然和合成树胶，如阿拉伯胶、海藻酸、海藻酸盐、角叉菜提取物、Panwar胶、茄替胶（ghatti gum）、依莎贝果（isabgol）外皮的粘液、羧甲基纤维素、甲基纤维素、聚乙烯吡咯烷酮（PVP）、硅酸镁铝（Veegum）、落叶松阿拉伯半乳聚糖、西黄蓍胶粉和瓜尔胶；纤维素，如乙基纤维素、醋酸纤维素、羧甲基纤维素钙、羧甲基纤维素钠、甲基纤维素、羟乙基纤维素（HEC）、羟丙基纤维素（HPC）、羟丙基甲基纤维素（HPMC）；微晶纤维素，如AVICEL®-PH-101、AVICEL®-PH-103、AVICEL® RC-581、AVICEL®-PH-105（FMC Corp.，Marcus Hook，PA）；及其混合物。合适的填充剂包括但不限于滑石、碳酸钙、微晶纤维素、粉状纤维素、葡萄糖结合剂、高岭土、甘露醇、硅酸、山梨醇、淀粉、预胶化淀粉及其混合物。在此提供的药物组合物中的粘合剂水平为约50％至约99％重量。

[0160] 合适的稀释剂包括但不限于磷酸二钙、硫酸钙、乳糖、山梨醇、蔗糖、肌醇、纤维素、高岭土、甘露醇、氯化钠、干淀粉和糖粉。

[0161] 合适的崩解剂包括但不限于琼脂；膨润土；纤维素，如甲基纤维素和羧甲基纤维素；木质产品；天然海绵；阳离子交换树脂；海藻酸；树胶，如瓜尔胶和硅酸镁铝HV；柑橘渣；交联纤维素，如交联羧甲纤维素；交联聚合物，如交聚维酮；交联淀粉；碳酸钙；微晶纤维素，如羟基乙酸淀粉钠；聚克立林钾；淀粉，如玉米淀粉、马铃薯淀粉、木薯淀粉和预胶化淀粉；黏土；aligns；及其混合物。在此提供的药物组合物中崩解剂的量根据制剂类型而不同，且容易被本领域普通技术人员辨识。在一个方面，在此提供的药物组合物包含约0.5％至约15％或约1％至约5％重量的崩解剂。

[0162] 合适的润滑剂包括但不限于硬脂酸钙；硬脂酸镁；矿物油；轻质矿物油；甘油；山梨醇；甘露醇；二醇，如甘油山萮酸酯和聚乙二醇（PEG）；硬脂酸；月桂基硫酸钠；滑石；氢化植物油，包括花生油、棉籽油、葵花籽油、芝麻油、橄榄油、玉米油和大豆油；硬脂酸锌；油

酸乙酯；月桂酸乙酯；琼脂；淀粉；石松；二氧化硅或硅胶，如AEROSIL® 200(W.R.Grace Co.,Baltimore,MD)和CAB-O-SIL® (Boston,Ma的Cabot Co.)；及其混合物。在一个方面，在此提供的药物组合物包含约0.1%至约5%重量的润滑剂。

[0163] 合适的助流剂包括胶体二氧化硅、CAB-O-SIL® (Cabot Co.,Boston,Ma)和无石棉滑石。着色剂包括任何经批准、认证的水溶性FD&C染料，和悬浮在水化氧化铝上的水不溶性FD&C染料，和色淀(color lake)，及其混合物。色淀是将水溶性染料吸附至重金属的含水氧化物的组合，其导致染料的不溶形式。

[0164] 应当理解，即使在同一剂型中很多载体和赋形剂也可能发挥若干功能。

[0165] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为压制的片剂、片剂磨碎物、快速溶解片剂、多重压制片剂或肠溶衣片剂、糖包衣或薄膜包衣片剂。

[0166] 肠溶衣是耐受胃酸作用但在肠内溶解或分解的包衣。

[0167] 在一些实施方案中，随本文公开的方法使用的药物组合物包括肠溶衣。肠溶衣包括下述一种或多种：邻苯二甲酸醋酸纤维素；丙烯酸甲酯-甲基丙烯酸共聚物；琥珀酸醋酸纤维素；邻苯二甲酸羟丙基甲基纤维素；琥珀酸醋酸羟丙基甲基纤维素(琥珀酸醋酸羟丙甲纤维素)；聚醋酸乙烯邻苯二甲酸酯(PVAP)；甲基丙烯酸甲酯-甲基丙烯酸共聚物；甲基丙烯酸共聚物，醋酸纤维素(及其琥珀酸酯和邻苯二甲酸酯形式)；苯乙烯马来酸共聚物；聚甲基丙烯酸/丙烯酸共聚物；邻苯二甲酸羟乙基乙基纤维素；琥珀酸醋酸羟丙基甲基纤维素；四氢邻苯二甲酸醋酸纤维素；丙烯酸树脂；虫胶。

[0168] 肠溶衣是置于片剂、丸剂、胶囊、微球、珠粒、微粒、颗粒等上的包衣，从而使其在到达小肠前不会溶解。

[0169] 糖包衣的片剂是由糖包衣包围的压制片剂，其可以有利于覆盖令人讨厌的味道或气味和保护片剂不被氧化。

[0170] 薄膜包衣的片剂是由水溶性材料的薄层或薄膜覆盖的压制片剂。薄膜包衣包括但不限于羟乙基纤维素、羧甲基纤维素钠、聚乙二醇4000和邻苯二甲酸醋酸纤维素。薄膜包衣提供与糖包衣相同的一般特性。多重压制片剂是通过多于一个的压制循环制备的压制片剂，包括分层的片剂和压制包衣的或干包衣的片剂。

[0171] 片剂剂型可由以下成分制备：单独的或与一种或多种在此描述的载体或赋形剂组合的粉状、晶体状或粒状形式的活性成分，该载体或赋形剂包括粘合剂、崩解剂、控释聚合物、润滑剂、稀释剂和/或着色剂。调味剂和甜味剂在咀嚼片和锭剂的形成中特别有用。

[0172] 在一些实施方案中，随本文公开的方法使用的药物组合物是软胶囊或硬胶囊，其可以由明胶、甲基纤维素、淀粉或藻酸钙制备。硬明胶胶囊，也称为干填充胶囊(DFC)，由两个部分组成，一个部分套在另一个部分上，从而完全包裹活性成分。软弹性胶囊(SEC)是软的球状壳，如明胶壳，其通过加入甘油、山梨醇或相似的多元醇进行塑化。胶囊还可以如本领域技术人员已知的那样进行包衣，以改变或维持活性成分的溶出。

[0173] 着色剂和调味剂可用于所有上述剂型。

[0174] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为速释或改进释放剂型，包括延迟、持续、脉冲、控制、靶向和程序释放形式。

[0175] 在一些实施方案中，随本文公开的方法使用的药物组合物是速释或改进释放剂型

的形式，包括延迟、持续、脉冲、控制、靶向和程序释放形式。

控释

[0176] 在一些实施方案中，随本文公开的方法使用的药物组合物是控释剂型的形式。如在此使用的，术语“控释”指一种剂型，其中当口服给药时，活性成分释放的速率或位置不同于速释剂型。控释剂型包括延迟、延伸 (extended)、延长 (prolonged)、持续、脉冲、改进、靶向、程序释放。控释剂型的药物组合物使用多种本领域技术人员已知的改进释放装置和方法进行制备，包括但不限于，基质控释装置、渗透控释装置、多颗粒控释装置、离子交换树脂、肠溶衣、多层包衣及其组合。活性成分的释放速率还可以通过改变颗粒大小进行改变。

[0177] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为能提供活性剂（例如，abexinostat、abexinostat 的盐、帕唑帕尼和 / 或帕唑帕尼的盐）或其药学上可接受的盐的控制释放。

[0178] 与速释组合物相比，控释组合物允许根据预设的释放谱在延长的一段时间内将药剂递送至人体。这样的释放速率能够在延长的一段时间内提供治疗有效水平的药剂，从而提供更长时间的药理学响应。这种更长时间的响应提供了很多内在的益处，这些益处是相应的短效速释制剂所不能获得的。在一些实施方案中，控释组合物在延长的一段时间内提供治疗有效水平的 HDAC 抑制剂（例如 abexinostat），从而提供更长时间的药理学响应。

[0179] 在一些实施方案中，在此描述的固体剂型可以被配制为肠溶衣包衣的延迟释放口服剂型，即，如在此描述的药物组合物的口服剂型，其利用肠溶衣来影响在胃肠道的小肠中的释放。肠溶衣剂型是压制的或模塑的或挤出的片剂 / 模子（包衣的或不包衣的），其包含活性成分和 / 或其它组合物成分的颗粒、粉末、微丸、珠粒或微粒，它们自身是包衣的或不包衣的。在一个方面，肠溶衣口服剂型可以是含有固体载体或组合物的微丸、珠粒或颗粒（它们自身是包衣的或不包衣的）的胶囊（包衣的或不包衣的）。

[0180] 如在此使用的术语“延迟释放”指能够在肠道中一些通常可预测的位置完成释放的递送，该位置较之如果没有延迟释放改变所完成释放的位置处于更远侧。在一些实施方案中，延迟释放的方法是包衣。任何包衣都应使用足够的厚度从而使整个包衣不会在 pH 低于约 5 的胃肠液中溶解，但是在约 5 和更高的 pH 下溶解。在本发明的实践中预期任何表现出 pH 依赖性的溶解度曲线的阴离子聚合物都可用作肠溶衣以实现向下胃肠道的递送。在一些实施方案中，用于本发明的聚合物为阴离子羧酸聚合物。在其它实施方案中，聚合物及其相容的混合物，和它们的一些性质，包括但不限于：

[0181] 虫胶，也称为纯化虫胶。该包衣溶解于 pH>7 的介质中；

[0182] 丙烯酸聚合物。丙烯酸聚合物的表现（主要是它们在生物液体中的溶解度）可随着取代的程度和类型而变化。合适的丙烯酸聚合物的例子包括甲基丙烯酸共聚物和胺基甲基丙烯酸酯共聚物。Eudragit 系列 E、L、R、S、RL、RS 和 NE(Rohm Pharma) 可用于溶解在有机溶剂、水分散体或干粉中。Eudragit 系列 RL、NE 和 RS 在胃肠道中不可溶，但是有渗透性，主要用于靶向结肠。Eudragit 系列 E 在胃中溶解。Eudragit 系列 L、L-30D 和 S 在胃中不可溶，在肠中溶解；

[0183] 纤维素衍生物。合适的纤维素衍生物的例子为：乙基纤维素；纤维素与邻苯二甲酸酐的部分醋酸酯的反应混合物。其表现可随着取代的程度和类型而变化。邻苯二甲酸醋酸纤维素 (CAP) 在 pH>6 下溶解。Aquateric(FMC) 是基于水的系统，是一种喷雾干燥的 CAP

假乳胶(psuedolatex),其颗粒<1μm。Aquateric中的其它成分可包括普朗尼克、吐温和乙酰化单甘油酯。其它合适的纤维素衍生物包括:偏苯三酸醋酸纤维素(Eastman);甲基纤维素(Pharmacoat,Methocel);邻苯二甲酸羟丙基甲基纤维素(HPMCP);琥珀酸羟丙基甲基纤维素(HPMCS);和琥珀酸醋酸羟丙基甲基纤维素(例如,AQOAT(Shin Etsu))。其表现可随着取代的程度和类型而变化。例如,HPMCP如HP-50、HP-55、HP-55S、HP-55F级是合适的。其表现可随着取代的程度和类型而变化。例如,合适级别的琥珀酸醋酸羟丙基甲基纤维素包括但不限于AS-LG(LF),其在pH 5下溶解;AS-MG(MF),其在pH 5.5下溶解;和AS-HG(HF),其在更高pH下溶解。这些聚合物作为颗粒提供,或作为细粉用于水分散体;

[0184] 聚醋酸乙烯邻苯二甲酸酯(PVAP)。PVAP在pH>5下溶解,其对于水汽和胃液有更低的渗透性。

[0185] 在一些实施方案中,包衣可以并通常包含塑化剂和可能的其它包衣赋形剂如着色剂、滑石和/或硬脂酸镁,它们是本领域已知的。合适的塑化剂包括柠檬酸三乙酯(Citroflex 2)、三醋精(三醋酸甘油酯)、乙酰基柠檬酸三乙酯(Citroflec A2)、Carbowax 400(聚乙二醇400)、邻苯二甲酸二乙酯、柠檬酸三丁酯、乙酰化单甘油酯、甘油、脂肪酸酯、丙二醇和邻苯二甲酸二丁酯。特别地,阴离子羧酸丙烯酸聚合物通常会包含10-25%重量的塑化剂,特别是邻苯二甲酸二丁酯、聚乙二醇、柠檬酸三乙酯和三醋精。使用常规包衣技术如喷雾或锅包衣施加包衣。包衣厚度必须足以确保口服剂型直至到达肠道中期望的局部递送部位之前保持完整。

[0186] 除塑化剂外还可以向包衣中添加着色剂、防粘剂、表面活性剂、

消泡剂、润滑剂(例如,加诺巴蜡或PEG),以增溶或分散包衣材料,和改进包衣表现和包衣的产品。

[0187] 特别合适的甲基丙烯酸共聚物是Eudragit L®,特别是L-30D®和Eudragit 100-55®,它们由德国的Rohm Pharma制造。在Eudragit L-30D®中,游离羧基与酯基的比例约为1:1。进一步地,已知该共聚物不溶于pH低于5.5,通常为1.5-5.5的胃肠液,即,一般存在于上胃肠道的液体中的pH;但是其容易溶解或部分溶解在大于5.5的pH下,即,在小肠中存在的pH值。

[0188] 在一些实施方案中,材料包括虫胶、丙烯酸聚合物、纤维素衍生物、聚醋酸乙烯邻苯二甲酸酯及其混合物。在其它实施方案中,材料包括Eudragit®系列E、L、RL、RS、NE、L、L300、S、100-55、邻苯二甲酸醋酸纤维素、Aquateric、偏苯三酸醋酸纤维素、乙基纤维素、邻苯二甲酸羟丙基甲基纤维素、琥珀酸醋酸羟丙基甲基纤维素、聚醋酸乙烯邻苯二甲酸酯和Cotteric。

[0189] 对于一些类型的药物,优选以“脉冲”方式释放该药物,其中单一剂型提供药物的初始剂量,然后是无释放的间隔,之后释放第二剂量的药物,然后是一个或多个额外的无释放间隔和药物释放“脉冲”。或者,在该剂型给药后的一段时间内没有药物被释放,之后释放一个剂量的药物,然后是一个或多个额外的无释放间隔和药物释放“脉冲”。

[0190] 脉冲药物递送例如可用于具有短半衰期且一天施用两次或三次的活性剂、被预先全身性(presystemically)广泛代谢的活性剂和应维持一定血浆水平以具有最优药效学效果的活性剂。

[0191] 脉冲剂型能在控制的滞后时间后的预设时间点或在特定部位提供一个或多个速释脉冲。使用已经描述的多种脉冲制剂来施用脉冲剂型，该脉冲剂型包括在此描述的含有HDAC抑制剂（例如abexinostat）或其药学上可接受的盐的制剂。例如，这类制剂包括但不限于在美国专利号5,011,692、5,017,381、5,229,135、5,840,329、4,871,549、5,260,068、5,260,069、5,508,040、5,567,441和5,837,284中描述的那些制剂。在一个实施方案中，控释剂型是包括至少两组颗粒（即多颗粒）的脉冲释放固体口服剂型，每组含有在此描述的制剂。第一组颗粒在被哺乳动物摄入后基本上立即提供一定剂量的HDAC抑制剂（例如abexinostat）或其药学上可接受的盐。第一组颗粒可以是未包衣的或包含包衣和/或密封剂。第二组颗粒包括包衣的颗粒，该颗粒在所述制剂中包含按总剂量的重量计约2％至约75％、优选约2.5％至约70％、更优选约40％至约70％的HDAC抑制剂（例如abexinostat）或其药学上可接受的盐，该HDAC抑制剂与一种或多种粘合剂混合。包衣包含药学上可接受的成分，其量足以在第二剂量释放前提供摄入后约2小时至约7小时的延迟。合适的包衣包括一种或多种可差别降解的包衣，例如，仅举例来说，pH敏感的包衣（肠溶衣），如丙烯酸树脂（例如，Eudragit® EPO、Eudragit® L30D-55、Eudragit® FS 30D Eudragit® L100-55、Eudragit® L100、Eudragit® S100、Eudragit® RD100、Eudragit® E100、Eudragit® L12.5、Eudragit® S12.5和Eudragit® NE30D、Eudragit® NE 40D），其单独使用或与纤维素衍生物例如乙基纤维素共混，或具有可变厚度的非肠溶衣，以提供包含HDAC抑制剂（例如abexinostat）或其药学上可接受的盐的制剂的差别释放。

多颗粒控释装置

[0192] 在一些实施方案中，随本文公开的方法使用的药物组合物为多颗粒控释装置，其包括约10μm至约3mm、约50μm至约2.5mm或约100μm至约1mm直径的多种颗粒、微粒或微丸。这些多颗粒通过湿法造粒、干法造粒、挤出/滚圆、滚筒碾压、融化-冷凝、喷雾-包衣核心及其组合进行制造。参见，例如，Multiparticulate Oral Drug Delivery；Marcel Dekker：1994；和Pharmaceutical Pelletization Technology；Marcel Dekker：1989。

[0193] 如在此描述的其它赋形剂或载体与该药物组合物共混以辅助加工和形成多颗粒。得到的颗粒自身可以构成多颗粒装置或者可以用各种成膜材料进行包衣，如肠溶性聚合物、遇水膨胀的和水溶性的聚合物。多颗粒可进一步加工为胶囊或片剂。

[0194] 肠保护药物吸收系统（IPDAS）是一种多颗粒片剂技术，其由压制为片剂形式的高密度控释珠粒组成。珠粒可通过诸如挤出滚圆的技术进行制造，控释可通过使用不同聚合物系统涂覆得到的珠粒来实现。或者，药物还可以涂覆到惰性载体如空白丸芯上，以产生立即释放多颗粒。控释可通过在这些立即释放多颗粒上形成聚合物膜来实现。一旦摄入IPDAS片，其在胃中迅速崩解并分散含药物的珠粒，其随后以受控的和逐渐的方式沿胃肠道进入十二指肠，而不依赖于摄食状态。活性成分从多颗粒中的释放通过经过形成于挤出/滚圆的多颗粒中的聚合物膜和/或聚合物/活性成分微基质的扩散过程而发生。IPDAS的肠保护是由于制剂的多颗粒性质，其保证了药物贯穿胃肠道的广泛分散。

[0195] 球状口服药物吸收系统（SODAS）是一种多颗粒技术，其能够产生订制剂型并直接响应于个体药物候选的需求。其可提供多种定制的药物释放方式，包括药物的速释然后持

续释放，以产生快速起效并维持至少 12 小时。备选地，可得到相反的情况，其中药物释放被延迟数小时。

[0196] 可编程口服药物吸收系统 (PRODAS) 表现为硬明胶胶囊中包含的大量小片剂。其从而在胶囊中组合了制片技术的优势。引入很多不同的小片剂是可能的，其中每一个单独配制并编程为在胃肠道内的不同部位释放药物。这些组合可包括速释、延迟释放和 / 或控释小片剂。还可引入不同大小的小片剂，从而高载药量是可能的。其大小通常为直径 1.5-4mm。

[0197] 本领域普通技术人员已知的许多其它类型的控释系统适用于在此描述的制剂。这些递送系统的例子包括，例如，基于聚合物的系统，如聚乳酸和聚乙醇酸、聚酸酐和聚己内酯；多孔基质，为脂质的基于非聚合物的系统，包括甾醇，如胆固醇、胆固醇酯和脂肪酸，或中性脂肪，例如单 -、二 - 和三甘油酯；水凝胶释放系统；硅橡胶系统；基于肽的系统；蜡涂层、可生物蚀解的剂型、使用常规粘合剂的压制片剂等等。参见，例如，Liberman 等人，Pharmaceutical Dosage Forms, 第 2 版，第 1 卷，第 209-214 页 (1990)；Singh 等人，Encyclopedia of Pharmaceutical Technology, 第 2 版，第 751-753 页 (2002)；美国专利号 4,327,725、4,624,848、4,968,509、5,461,140、5,456,923、5,516,527、5,622,721、5,686,105、5,700,410、5,977,175、6,465,014 和 6,932,983。

基质控释装置

[0198] 在一些实施方案中，随本文公开的方法使用的药物组合物是使用本领域技术人员已知的基质控释装置制造的改进释放剂型（参见，Takada 等人“Encyclopedia of Controlled Drug Delivery,”第 2 卷，Mathiowitz 编，Wiley, 1999)。

[0199] 在一些实施方案中，随本文公开的方法使用的药物组合物使用易蚀的基质装置进行配制，该基质装置为遇水膨胀的、易蚀的或可溶性的聚合物，包括合成聚合物和天然存在的聚合物和衍生物，如多糖和蛋白质。

[0200] 可用于形成易蚀基质的材料包括但不限于几丁质、壳聚糖、葡聚糖和支链淀粉；琼脂胶、阿拉伯胶、刺梧桐胶、刺槐豆胶、黄蓍胶、角叉菜胶、盖提胶、瓜尔胶、黄原胶和硬葡聚糖；淀粉，如糊精和麦芽糊精；亲水胶体，如果胶；磷脂，如卵磷脂；海藻酸盐；海藻酸丙二醇；明胶；胶原蛋白；和纤维素，如乙基纤维素 (EC)、甲基乙基纤维素 (MEC)、羧甲基纤维素 (CMC)、CMEC、羟乙基纤维素 (HEC)、羟丙基纤维素 (HPC)、醋酸纤维素 (CA)、丙酸纤维素 (CP)、丁酸纤维素 (CB)、醋酸丁酸纤维素 (CAB)、CAP、CAT、羟丙基甲基纤维素 (HPMC)、HPMCP、HPMCAS、偏苯三酸醋酸羟丙基甲基纤维素 (HPMCAT) 和乙基羟乙基纤维素 (EHEC)；聚乙烯吡咯烷酮；聚乙烯醇；聚醋酸乙烯酯；甘油脂肪酸酯；聚丙烯酰胺；聚丙烯酸；乙基丙烯酸或甲基丙烯酸的共聚物（EUDRAGIT®，Rohm America, Inc., Piscataway, NJ)；聚 (2- 羟乙基 - 甲基丙烯酸酯）；聚乳酸；L- 谷氨酸和 L- 谷氨酸乙酯的共聚物；可降解的乳酸 - 羟基乙酸共聚物；聚 -D-(-)-3- 羟基丁酸；和其它丙烯酸衍生物，如甲基丙烯酸丁酯、甲基丙烯酸甲酯、甲基丙烯酸乙酯、丙烯酸乙酯、(2- 二甲基氨基乙基）甲基丙烯酸酯和（三甲基氨基乙基）甲基丙烯酸酯氯化物的均聚物和共聚物。

[0201] 在一些实施方案中，随本文公开的方法使用的药物组合物用非易蚀的基质装置进行配制。活性成分被溶解或分散于惰性基质中，一旦给药，主要通过扩散透过惰性基质进行释放。适于用作非易蚀的基质装置的材料包括但不限于，不可溶性塑料，如聚乙烯、聚丙烯、

聚异戊二烯、聚异丁烯、聚丁二烯、聚甲基丙烯酸甲酯、聚甲基丙烯酸丁酯、氯化聚乙烯、聚氯乙烯、丙烯酸甲酯 - 甲基丙烯酸甲酯共聚物、乙烯 - 醋酸乙烯酯共聚物、乙烯 / 丙烯共聚物、乙烯 / 丙烯酸乙酯共聚物、氯乙烯与醋酸乙烯酯的共聚物、偏二氯乙烯、乙烯和丙烯、离聚物聚对苯二甲酸乙二醇酯、丁基橡胶表氯醇橡胶、乙烯 / 乙烯醇共聚物、乙烯 / 醋酸乙烯酯 / 乙烯醇三元共聚物和乙烯 / 乙烯氧基乙醇共聚物、聚氯乙烯、塑化尼龙、塑化聚对苯二甲酸乙二醇酯、天然橡胶、硅橡胶、聚二甲基硅氧烷、硅氧烷碳酸酯共聚物，和亲水聚合物，如乙基纤维素、醋酸纤维素、交聚维酮和交联的部分水解的聚醋酸乙烯酯；和脂肪化合物，如加诺巴蜡、微晶蜡和甘油三酯。

[0202] 在基质控释系统中，期望的释放动力学可以通过例如使用的聚合物类型、聚合物粘度、聚合物和 / 或活性成分的粒径、活性成分与聚合物的比例和组合物中的其它赋形剂或载体进行控制。

[0203] 在一个方面，改进释放剂型通过本领域技术人员已知的方法制备，包括直接压制、干法或湿法造粒后压制、融化 - 造粒后压制。

[0204] 在一些实施方案中，基质控释系统包括肠溶衣，从而在胃中没有药物释放。

渗透控释装置

[0205] 在一些实施方案中，随本文公开的方法使用的药物组合物使用渗透控释装置来制造，包括单室系统、双室系统、不对称膜技术 (AMT) 和挤出核心系统 (ECS)。一般而言，这样的装置具有至少两个组件：(a) 含有活性成分的核心；和 (b) 具有至少一个递送口的半透膜，该半透膜将核心包封。该半透膜控制水从使用的水环境向核心的流入，以便通过经递送口挤出而引起药物释放。

[0206] 除了活性成分以外，渗透装置的核心任选地还包含渗透剂，该渗透剂产生驱动力，用于使水从使用环境转运到该装置的核心内。一类渗透剂是遇水膨胀的亲水性聚合物，其也被称为“渗透聚合物”和“水凝胶”，包括但不限于亲水性乙烯基和丙烯酸聚合物、多糖例如藻酸钙、聚环氧乙烷 (PEO)、聚乙二醇 (PEG)、聚丙二醇 (PPG)、聚 (甲基丙烯酸 2- 羟乙酯)、聚 (丙烯酸)、聚 (甲基丙烯酸)、聚乙烯吡咯烷酮 (PVP)、交联 PVP、聚乙烯醇 (PVA)、PVA/PVP 共聚物、PVA/PVP 与疏水性单体如甲基丙烯酸甲酯和乙酸乙烯酯的共聚物、含有大 PEO 嵌段的亲水性聚氨酯、交联羧甲基纤维素纳、角叉菜胶、羟乙基纤维素 (HEC)、羟丙基纤维素 (HPC)、羟丙基甲基纤维素 (HPMC)、羧甲基纤维素 (CMC) 和羧乙基纤维素 (CEC)、海藻酸钠、聚卡波非 (polycarbophil)、明胶、黄原胶和羟基乙酸淀粉钠。

[0207] 另一类渗透剂是渗透原 (osmogen)，其能够吸水以影响跨周围包衣屏障的渗透压梯度。合适的渗透原包括但不限于无机盐，例如硫酸镁、氯化镁、氯化钙、氯化钠、氯化锂、硫酸钾、磷酸钾、碳酸钠、亚硫酸钠、硫酸锂、氯化钾和硫酸钠；糖，例如右旋糖、果糖、葡萄糖、肌醇、乳糖、麦芽糖、甘露醇、棉籽糖、山梨醇、蔗糖、海藻糖和木糖醇；有机酸，例如抗坏血酸、苯甲酸、富马酸、柠檬酸、马来酸、癸二酸、山梨酸、己二酸、依地酸 (edetic acid)、谷氨酸、对甲苯磺酸、琥珀酸和酒石酸；尿素；和它们的混合物。

[0208] 可以使用具有不同溶出率的渗透剂来影响在开始时多快地由该剂型递送活性成分。例如，可以使用无定形糖，例如 Mannogeme EZ(SPI Pharma, Lewes, DE) 来提供在前数个小时较快地递送，以快速产生所需的治疗效果，而剩下的量逐渐和连续释放以在延长的一段时间内维持治疗或预防效果的所需水平。在这种情况下，活性成分以这样的速率释放以

代替代谢和排泄的活性成分的量。

[0209] 所述核心也可以包含各种各样的如本文所述的其它赋形剂和载体，以增强剂型的性能或提高稳定性或加工。

[0210] 可用于形成半透膜的材料包括各种等级的丙烯酸、乙烯基化合物、醚、聚酰胺、聚酯和纤维素衍生物，它们在生理相关的 pH 下都是水渗透性的和水不溶性的，或者易于通过化学改变（例如交联）而成为水不溶性的。可用于形成包衣的合适聚合物的实例包括增塑的、未增塑的和强化的醋酸纤维素 (CA)、二醋酸纤维素、三醋酸纤维素、醋酸丙酸纤维素、硝酸纤维素、醋酸丁酸纤维素 (CAB)、CA 氨基甲酸乙酯、CAP、CA 氨基甲酸甲酯、CA 琥珀酸酯、偏苯三酸醋酸纤维素 (CAT)、CA 二甲基氨基乙酸酯、CA 碳酸乙酯、CA 氯乙酸酯、CA 草酸乙酯、CA 磺酸甲酯、CA 磺酸丁酯、CA 对甲苯磺酸酯、琼脂乙酸酯、直链淀粉三乙酸酯、乙酸 β 葡聚糖、三乙酸 β 葡聚糖、乙醛二甲基乙酸酯、刺槐豆胶的三乙酸酯、羟基化乙烯 - 乙酸乙烯酯、EC、PEG、PPG、PEG/PPG 共聚物、PVP、HEC、HPC、CMC、CMEC、HPMC、HPMCP、HPMCAS、HPMCAT、聚（丙烯酸）和聚（丙烯酸酯）和聚（甲基丙烯酸）和聚（甲基丙烯酸酯）及其共聚物、淀粉、葡聚糖、糊精、壳聚糖、胶原、明胶、聚烯、聚醚、聚砜、聚醚砜、聚苯乙烯、聚乙烯基卤化物、聚乙烯基酯和醚、天然蜡和合成蜡。

[0211] 半透膜也可以是疏水性微孔膜，其中孔基本上被气体充填并且不为含水介质润湿但水汽可透过，如美国专利号 5,798,119 中所公开的。这样的疏水性但水汽可透过的膜一般由疏水性聚合物如聚烯、聚乙烯、聚丙烯、聚四氟乙烯、聚丙烯酸衍生物、聚醚、聚砜、聚醚砜、聚苯乙烯、聚乙烯基卤化物、聚偏二氟乙烯、聚乙烯基酯和醚、天然蜡和合成蜡组成。

[0212] 半透膜上的递送口可以在包衣后通过机械或激光钻孔而形成。递送口也可以通过腐蚀水溶性材料的塞子或者通过破坏在核心中压痕上方的膜的较薄部分而原位形成。另外，递送口可以在包衣过程中形成，如在美国专利号 5,612,059 和 5,698,220 中公开的类型的不对称膜包衣的情况中。

[0213] 活性成分的释放总量和释放速率可以基本上通过半透膜的厚度和孔隙率、核心的组成以及递送口的数目、大小和位置进行调节。

[0214] 渗透控释剂型的药物组合物还可包含另外的如本文所述的常规赋形剂或载体，以提高制剂的性能或加工。

[0215] 渗透控释剂型可以按照本领域技术人员已知的常规方法和技术来制备（参见 Remington:The Science and Practice of Pharmacy, 同上;Santus 和 Baker,J. Controlled Release,1995,35,1-21;Verma 等人,Drug Development and Industrial Pharmacy,2000,26,695-708;Verma 等人,J.Controlled Release,2002,79,7-27）。

[0216] 在其它实施方案中，将本文提供的药物组合物配制为 AMT 控释剂型，其包含包裹核心的不对称渗透膜，该核心包含活性成分和其它的药学上可接受的赋形剂或载体。参见美国专利号 5,612,059 和 WO2002/17918。AMT 控释剂型可以按照本领域技术人员已知的常规方法和技术来制备，包括直接压制、干法制粒、湿法制粒和浸涂法。

[0217] 在某些实施方案中，将本文提供的药物组合物配制为 ESC 控释剂型，其包含包裹核心的渗透膜，该核心包含活性成分、羟乙基纤维素和其它的药学上可接受的赋形剂或载体。

多层片剂

[0218] 在一些实施方案中，随本文公开的方法使用的药物组合物为多层片剂的形式。多层片剂包括惰性核心，其上施有分层的药物（加上任选的赋形剂），然后是肠溶衣。第二层药物被置于第一肠溶衣上，然后是第二层药物上的第二肠溶衣。肠溶衣应确保药物从每一层的释放间隔至少 3-6 小时的时间。

速释

[0219] 在一些实施方案中，随本文公开的方法使用的药物组合物为速释剂型，该剂型能够释放不少于 75％的治疗活性成分或组合，和 / 或满足片剂核心中含有的特定治疗剂或组合的速释片剂的崩解或溶出需要，如 USP XXII, 1990（美国药典）所述。速释药物组合物包括胶囊、片剂、口服液、粉剂、珠粒、微丸、颗粒等等。

肠胃外给药

[0220] 在一些实施方案中，随本文公开的方法使用的药物组合物通过注射、输注或植入进行肠胃外给药，以供局部或系统给药。本文所用的肠胃外给药包括静脉内、动脉内、腹膜内、鞘内、心室内、尿道内、胸骨内、颅内、肌内、滑膜内和皮下给药。

[0221] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制成适合于肠胃外给药的任何剂型，包括溶液、悬浮液、乳剂、胶束、脂质体、微球体、纳米体系和适合在注射前在液体中制成溶液或悬浮液的固体剂型。这样的剂型可以按照制药科学领域技术人员已知的常规方法制备（参见 Remington:The Science and Practice of Pharmacy，同上）。

[0222] 计划用于肠胃外给药的药物组合物可包含一种或多种药学上可接受的载体和赋形剂，包括但不限于水性载体、水混溶性载体、非水性载体、抵抗微生物生长的抗微生物剂或防腐剂、稳定剂、溶解性增强剂、等渗剂、缓冲剂、抗氧化剂、局部麻醉剂、悬浮剂和分散剂、润湿剂或乳化剂、络合剂、掩蔽剂或螯合剂、冷冻保护剂 (cryoprotectants)、冻干保护剂 (lyoprotectants)、增稠剂、pH 调节剂和惰性气体。

[0223] 合适的水性载体包括但不限于水、盐水、生理盐水或磷酸缓冲盐溶液 (PBS)、氯化钠注射液、林格氏注射液、等渗葡萄糖注射液、无菌的水注射液、葡萄糖和乳酸盐林格氏注射液。非水性载体包括但不限于植物来源的不挥发性油、蓖麻油、玉米油、棉籽油、橄榄油、花生油、薄荷油、红花油、芝麻油、大豆油、氢化植物油、氢化大豆油和椰子油的中链甘油三酯和棕榈籽油。水混溶性载体包括但不限于乙醇、1,3- 丁二醇、液态聚乙二醇（例如聚乙二醇 300 和聚乙二醇 400）、丙二醇、甘油、N- 甲基 -2- 吡咯烷酮、二甲基乙酰胺和二甲亚砜。

[0224] 合适的抗微生物剂或防腐剂包括但不限于苯酚、甲酚、汞制剂、苯甲醇、氯丁醇、对羟基苯甲酸甲酯和对羟基苯甲酸丙酯、硫柳汞、苯扎氯铵、苄索氯铵、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯和山梨酸。合适的等渗剂包括但不限于氯化钠、甘油和右旋糖。合适的缓冲剂包括但不限于磷酸盐和柠檬酸盐。合适的抗氧化剂是如本文所述的那些，包括亚硫酸氢盐和偏亚硫酸氢钠。合适的局部麻醉剂包括但不限于盐酸普鲁卡因。合适的悬浮剂和分散剂是如本文所述的那些，包括羧甲基纤维素钠、羟丙基甲基纤维素和聚乙烯吡咯烷酮。合适的乳化剂包括如本文所述的那些，包括聚氧乙烯脱水山梨醇单月桂酸酯、聚氧乙烯脱水山梨醇单油酸酯 80 和三乙醇胺油酸酯。合适的掩蔽剂或螯合剂包括但不限于 EDTA。合适的 pH 调节剂包括但不限于氢氧化钠、盐酸、柠檬酸和乳酸。合适的络合剂包括但不限于环糊精，包括 α - 环糊精、β - 环糊精、羟丙基 - β - 环糊精、磺基丁基醚 - β - 环糊精和磺基丁基醚 7- β - 环糊精（CAPTISOL®，CyDex, Lenexa, KS）。

[0225] 在一些实施方案中，随本文公开的方法使用的药物组合物被配制为用于单剂量或多剂量给药。单剂量制剂包装于安瓿、小瓶或注射器中。多剂量肠胃外制剂必须含有抑制细菌或抑制真菌的浓度的抗微生物剂。所有的肠胃外制剂都必须是无菌的，正如本领域已知的和实践的。

[0226] 在一些实施方案中，随本文公开的方法使用的药物组合物作为即用型无菌溶液提供。在一些实施方案中，随本文公开的方法使用的药物组合物作为无菌的干燥可溶性产品提供，包括冻干粉剂和皮下注射用片剂，临用前用载体重构。在又一个实施方案中，随本文公开的方法使用的药物组合物作为即用型无菌悬浮液提供。在又一个实施方案中，随本文公开的方法使用的药物组合物作为无菌的干燥不溶性产品提供，临用前用载体重构。在再一个实施方案中，随本文公开的方法使用的药物组合物作为即用型无菌乳剂提供。

癌症

[0227] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0228] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0229] 在某些实施方案中，本文另外还公开了在有需要的个体中治疗癌症的方法，包括施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0230] 在某些实施方案中，本文进一步公开了在有需要的个体中治疗癌症的方法，包括施用 (a)abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0231] 在一些实施方案中，随本文公开的方法使用的药物组合物用于治疗人的癌症。在一些实施方案中，随本文公开的方法使用的药物组合物用于治疗人的血液系统癌症。在一些实施方案中，随本文公开的方法使用的药物组合物用于治疗人的实体瘤。

[0232] 血液系统癌症包括血液或骨髓的癌症，如白血病或淋巴瘤。

[0233] 淋巴瘤是在免疫系统细胞中开始的癌症。淋巴瘤存在两个基本类别。一类是霍奇金淋巴瘤，其标志是存在一种被称为 Reed-Sternberg 细胞的细胞。另一类是非霍奇金淋巴瘤，其包括庞大的、多样化的一组免疫系统细胞癌症。非霍奇金淋巴瘤可进一步分为具有缓慢进展（慢速生长）进程和具有侵袭性（快速生长）进程的癌症。

[0234] 白血病是开始于血液形成组织如骨髓中的癌症，其导致大量血细胞产生并进入血流中。

[0235] 在一个方面，所述癌症为实体瘤或淋巴瘤或白血病。在一个方面，所述癌症为癌、肉瘤、淋巴瘤、白血病、生殖细胞瘤、胚细胞瘤 (blastic tumor) 或母细胞瘤。

[0236] 在一些实施方案中，本文公开的方法用于治疗实体瘤。在一些实施方案中，本文公开的方法用于治疗转移性实体瘤。在一些实施方案中，本文公开的方法用于治疗晚期实体瘤。

[0237] 在一些实施方案中，本文公开的方法用于治疗肉瘤。

[0238] 在一些实施方案中，本文公开的方法用于治疗选自下述的癌症：心脏：肉瘤（血管肉瘤、纤维肉瘤、横纹肌肉瘤、脂肪肉瘤）、粘液瘤、横纹肌瘤、纤维瘤、脂肪瘤和畸胎瘤；肺：支气管癌（鳞状细胞癌、未分化小细胞癌、未分化大细胞癌、腺癌）、肺泡（细支气管）癌、支气管腺瘤、肉瘤、淋巴瘤、软骨错构瘤、间皮瘤；胃肠：食道（鳞状细胞癌、腺癌、平滑肌肉瘤、淋巴瘤）、胃（癌、淋巴瘤、平滑肌肉瘤）、胰腺（导管腺癌、胰岛瘤、胰高血糖素瘤、胃泌素瘤、类癌瘤、舒血管肠肽瘤）、小肠（腺癌、淋巴瘤、类癌瘤、卡波西肉瘤、平滑肌瘤、血管瘤、脂肪瘤、神经纤维瘤、纤维瘤）、大肠（腺癌、管状腺瘤、绒毛状腺瘤、错构瘤、平滑肌瘤）；泌尿生殖道：肾（腺癌、维尔姆斯瘤［肾母细胞瘤］、淋巴瘤、白血病）、膀胱和尿道（鳞状细胞癌、移行细胞癌、腺癌）、前列腺（腺癌、肉瘤）、睾丸（精原细胞瘤、畸胎瘤、胚胎性癌、畸胎癌、绒毛膜癌、肉瘤、间质细胞癌、纤维瘤、纤维腺瘤、腺瘤样瘤、脂肪瘤）；肝：肝细胞瘤（肝细胞癌）、胆管上皮癌、肝母细胞瘤、血管肉瘤、肝细胞腺瘤、血管瘤；骨：成骨性肉瘤（骨肉瘤）、纤维肉瘤、恶性纤维组织细胞瘤、软骨肉瘤、尤因肉瘤、恶性淋巴瘤（网状细胞肉瘤）、多发性骨髓瘤、恶性巨细胞瘤、脊索瘤、骨软骨瘤（骨软骨性外生骨疣）、良性软骨瘤、软骨母细胞瘤、软骨粘液纤维瘤、骨样骨瘤和巨细胞瘤；神经系统：颅骨（骨瘤、血管瘤、肉芽肿、黄瘤、变形性骨炎）、脑膜（脑膜瘤、脑膜肉瘤、神经胶质瘤病）、脑（星形细胞瘤、髓母细胞瘤、神经胶质瘤、室管膜瘤、生殖细胞瘤［松果体瘤］、多形性胶质母细胞瘤、少突神经胶质瘤、神经鞘瘤、视网膜母细胞瘤、先天性肿瘤）、脊髓（神经纤维瘤、脑膜瘤、神经胶质瘤、肉瘤）；妇科：子宫（子宫内膜癌）、子宫颈（宫颈癌、肿瘤前宫颈发育不良）、卵巢（卵巢癌［浆液性囊腺癌、粘液性囊腺癌、子宫内膜样瘤、celioblastoma、透明细胞癌、未分类癌］、粒层－卵泡膜细胞瘤、Sertoli-Leydig 细胞瘤、无性细胞瘤、恶性畸胎瘤）、外阴（鳞状细胞癌、上皮内癌、腺癌、纤维肉瘤、黑色素瘤）、阴道（透明细胞癌、鳞状细胞癌、葡萄状肉瘤［胚胎型横纹肌肉瘤］、输卵管（癌）；血液系统：血液（髓样白血病［急性和慢性］、急性淋巴母细胞性白血病、慢性淋巴细胞性白血病、骨髓增生性疾病、多发性骨髓瘤、骨髓增生异常

综合征）、霍奇金病、非霍奇金淋巴瘤［恶性淋巴瘤］；皮肤：恶性黑色素瘤、基底细胞癌、鳞状细胞癌、卡波西肉瘤、痣、发育异常痣、脂肪瘤、血管瘤、皮肤纤维瘤、瘢痕疙瘩、银屑病；肾上腺：神经母细胞瘤、胆囊癌。

[0239] 在一个方面，所述癌症为乳腺癌、结肠癌、结直肠癌、非小细胞肺癌、小细胞肺癌、肝癌、卵巢癌、前列腺癌、宫颈癌、膀胱癌、胃癌、胃肠道间质瘤、胰腺癌、生殖细胞瘤、肥大细胞瘤、神经母细胞瘤、肥大细胞增多症、睾丸癌、胶质母细胞瘤、星形细胞瘤、淋巴瘤、黑色素瘤、骨髓瘤、急性髓细胞性白血病（AML）、急性淋巴细胞性白血病（ALL）、骨髓增生异常综合征和慢性髓性白血病（CML）。

[0240] 在一些实施方案中，所述癌症是肾细胞癌。

[0241] 在一些实施方案中，所述癌症是卵巢癌。

[0242] 在一个方面，所述癌症是淋巴瘤。在一个方面，该淋巴瘤为 B 细胞淋巴瘤、T 细胞淋巴瘤、霍奇金淋巴瘤或非霍奇金淋巴瘤。

[0243] 在一个方面，所述癌症为 T 细胞淋巴瘤或白血病。

[0244] 在一个方面，所述 T 细胞淋巴瘤为外周 T 细胞淋巴瘤。在另一方面，该 T 细胞淋巴瘤或白血病是 T 细胞淋巴母细胞性白血病 / 淋巴瘤。在又一方面，该 T 细胞淋巴瘤是皮肤 T 细胞淋巴瘤。在另一方面，该 T 细胞淋巴瘤是成体 T 细胞淋巴瘤。在一个方面，该 T 细胞淋巴瘤是外周 T 细胞淋巴瘤、淋巴母细胞性淋巴瘤、皮肤 T 细胞淋巴瘤、NK/T 细胞淋巴瘤或成体 T 细胞白血病 / 淋巴瘤。

[0245] 在一个实施方案中，所述癌症为肉瘤。肉瘤是开始于肌肉、脂肪、纤维组织、血管或身体的其它支持组织的癌症。肉瘤包括以下中的任何一种：软组织腺泡状肉瘤、血管肉瘤、皮肤纤维肉瘤、硬纤维瘤、结缔组织增生性小圆细胞瘤、骨外软骨肉瘤、骨外骨肉瘤、纤维肉瘤、血管外皮细胞瘤、血管肉瘤、卡波西肉瘤、平滑肌肉瘤、脂肪肉瘤、淋巴管肉瘤、恶性纤维组织细胞瘤、神经纤维肉瘤、横纹肌肉瘤、滑膜肉瘤、Askin 瘤、尤因瘤、恶性血管内皮瘤、恶性神经鞘瘤、骨肉瘤、软骨肉瘤。在一些实施方案中，所述肉瘤为软组织肉瘤。

[0246] 在一些实施方案中，本文公开的方法用于治疗人的软组织肉瘤。

[0247] 在一些实施方案中，本文公开的方法用于治疗人的骨髓增生异常综合征（MDS）。

[0248] 在一些实施方案中，本文公开的方法用于治疗人的慢性髓性白血病（CML）。

[0249] 在一些实施方案中，本文公开的方法用于治疗人的非霍奇金淋巴瘤。在一些实施方案中，本文公开的方法用于治疗人的霍奇金病。

[0250] 在一些实施方案中，本文公开的方法用于治疗人的多发性骨髓瘤。

[0251] 在一些实施方案中，本文公开的方法用于治疗慢性淋巴细胞性白血病。在一些实施方案中，本文公开的方法用于治疗急性淋巴细胞性白血病。

[0252] 在一些实施方案中，本文公开的方法用于治疗人的实体瘤。

[0253] 在一些实施方案中，本文公开的方法用于治疗人的肉瘤。

联合治疗

[0254] 在某些实施方案中，本文公开了在有需要的个体中增加抗血管生成剂的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发

生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0255] 在某些实施方案中，本文公开了在有需要的个体中增加帕唑帕尼或其盐的有效性的方法，包括对个体共同施用 (a)abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0256] 在某些实施方案中，本文另外还公开了在有需要的个体中治疗癌症的方法，包括施用 (a)abexinostat 或其盐的周期，及 (b) 抗血管生成剂。在一些实施方案中，该抗血管生成剂是帕唑帕尼或其盐。在一些实施方案中，该方法降低对抗血管生成剂的抗性；延缓抗血管生成剂抗性的发展；延缓变为抗血管生成剂难治性的癌症的发生；延长抗血管生成剂的有用性；允许在通常发展或已经发展出抗血管生成剂抗性的癌症的治疗中使用抗血管生成剂；提升患者对抗血管生成剂的响应；增加细胞对抗血管生成剂的应答；降低抗血管生成剂的有效剂量；或它们的任意组合。

[0257] 在某些实施方案中，本文进一步公开了在有需要的个体中治疗癌症的方法，包括施用 (a)abexinostat 或其盐的周期，及 (b) 帕唑帕尼或其盐。在一些实施方案中，该方法降低对帕唑帕尼或其盐的抗性；延缓对帕唑帕尼或其盐的抗性的发展；延缓变为帕唑帕尼或其盐难治性的癌症的发生；延长帕唑帕尼或其盐的有用性；允许在治疗通常发展或已经发展出对帕唑帕尼或其盐的抗性的癌症中使用帕唑帕尼或其盐；提升患者对帕唑帕尼或其盐的响应；增加细胞对帕唑帕尼或其盐的应答；降低帕唑帕尼或其盐的有效剂量；或它们的任意组合。

[0258] 在一个实施方案中，本文描述的组合物和方法还与为了对所治疗的癌症的特定有效性而选择的其它治疗剂联合使用。通常，在此描述的组合物，和在使用联合治疗的实施方案中不必在同一药物组合物中施用的其它药剂，由于物理和化学特性不同，而通过不同的途径施用。在一个实施方案中，根据确立的方案进行初始给药，然后，基于观察到的效果，对剂量、给药模式和给药药剂进行进一步的调整。

[0259] 在某些实施方案中，所用化合物的具体选择取决于主治医师的诊断和他们对患者病情的判断以及合适的治疗方案。在各种实施方案中，化合物同时（例如，同时、基本上同时或在同一治疗方案中）或相继给药，这取决于癌症的性质、患者的状况和所用化合物的实际选择。在某些实施方案中，给药顺序的确定和在治疗方案中每种治疗剂给药的重复次数取决于对所治疗的疾病和患者状况的评价。

[0260] 在一个实施方案中，应当理解，治疗癌症的给药方案根据多种因素进行调整。这些因素包括患者罹患的癌症的类型，以及患者的年龄、体重、性别、饮食和医疗状况。因此，在一个实施方案中，实际使用的给药方案变化很大并因此偏离了在此所述的给药方案。在某些实施方案中，联合使用 HDAC 抑制剂（例如 abexinostat）和另外的药剂治疗癌症允许减少 HDAC 抑制剂（例如 abexinostat）和 / 或第二药剂的有效量。

[0261] 根据良好的医疗实践对在此描述的制剂进行施用和给药，其中考虑个体患者的临床状况、给药方法、给药日程安排和其他执业医生已知的因素。

[0262] 所关注的药物组合物提供了治疗有效量的 HDAC 抑制剂（例如 abexinostat），其能够例如每天一次、每天两次、每天三次等给药。在一个方面，药物组合物提供了有效量的 HDAC 抑制剂（例如 abexinostat），其能够一天一次给药。

[0263] 在一些实施方案中，本文公开的方法进一步包括与 abexinostat（或其盐）和帕唑帕尼（或其盐）联合施用额外的药剂。

[0264] 在某些实施方案中，通过施用佐剂（即，佐剂本身具有很小的治疗益处，但是联合其它治疗剂时，对患者的整体治疗益处得到增强）来增强本文公开的方法的治疗效果。在一些实施方案中，通过施用同样具有治疗益处的另一种治疗剂（还包括治疗方案）增强患者所获得的益处。在特定的实施方案中，通过对患者提供其它治疗剂或癌症疗法得到增强的治疗益处。在不同的实施方案中，使用额外的药剂为个体提供了例如加成的或协同的益处。

[0265] 当药物在治疗组合中使用时，治疗有效剂量发生变化。当在联合治疗方案中使用时，药物和其它药剂的治疗有效剂量的确定通过任何方式来实现。例如，可以采用节律给药，即提供更频繁的、较低的剂量，以使毒副作用减至最小。在某些情况下，联合治疗允许任何或全部活性剂具有比单独施用任一种药剂时所获得的更低的治疗有效量。

[0266] 作为非限制性的实例，联合治疗方案涵盖了一些治疗方案，其中 abexinostat（或其盐）和帕唑帕尼（或其盐）的给药开始于用额外的药剂进行治疗之前、期间或之后，并且持续至额外的药剂治疗期间的任何时间或在额外的药剂治疗终止之后。其还包括这样的治疗：其中联合使用的 abexinostat（或其盐）和帕唑帕尼（或其盐）及额外的药剂在治疗过程中同时或在不同时间和 / 或以减少或增加的间隔给药。联合治疗进一步包括周期性治疗，其在多个时间开始和停止以辅助对患者的临床处理。

[0267] 在任何情况下，多种治疗剂以任意顺序给药，包括，例如，同时。如果给药是同时的，在各种实施方案中以单一、统一的形式或以多重形式（仅作为示例，作为单一的丸剂或作为两种分离的丸剂）提供多种治疗剂。在不同的实施方案中，治疗剂的一种以多剂量给予，或两种都以多剂量给予。在其中多种药剂不同时给药的某些实施方案中，多种药剂给药之间的时间处于任何能接受的范围，包括例如从多于 0 周到少于 4 周。任意数量的额外的药剂可以与本文公开的方法联合使用。

[0268] 在某些实施方案中，初始给药是通过口服给药，例如、丸剂、胶囊、片剂、溶液、悬浮液，等等，或其组合。在某些实施方案中，在检测到或怀疑癌症发生后一旦可行就应用本文公开的方法，并持续治疗癌症所必须的一段时间。在某些实施方案中，本文公开的方法持续治疗癌症所必须的任意时间长度，作为非限制性的示例，包括至少 2 周、至少 1 个月或多于 1 个月。

[0269] 额外的治疗剂选自：DNA 损伤剂；拓扑异构酶 I 或 II 抑制剂；烷化剂；PARP 抑制剂；蛋白酶体抑制剂；RNA/DNA 抗代谢药物；抗有丝分裂剂；免疫调节剂；抗血管生成剂；芳香酶抑制剂；激素调节剂；细胞凋亡诱导剂；激酶抑制剂；单克隆抗体；阿巴瑞克；ABT-888；阿地白介素；阿地白介素；阿仑珠单抗；阿利维 A 酸；别嘌呤醇；六甲蜜胺；氨磷汀阿那曲唑；三氧化二砷；天冬酰胺酶；阿扎胞苷；AZD-2281；苯达莫司汀；贝伐珠单抗；贝沙

罗汀；博来霉素；硼替佐米；BSI-201；白消安；白消安；卡芦睾酮；卡培他滨；卡铂；卡非佐米（carfilozib）；卡莫司汀；卡莫司汀；塞来昔布；西妥昔单抗；苯丁酸氮芥；顺铂；克拉屈滨；氯法拉滨；环磷酰胺；阿糖胞苷；阿糖胞苷脂质体；达卡巴嗪；更生霉素；达依泊汀 α；达沙替尼；柔红霉素脂质体；柔红霉素；地西他滨；地尼白介素；右丙亚胺；多西他赛；多柔比星；多柔比星脂质体；丙酸屈他雄酮；表柔比星；依泊汀 α；厄洛替尼；雌莫司汀；磷酸依托泊苷；依托泊苷；依西美坦；非格司亭；氟尿苷；氟达拉滨；氟尿嘧啶；氟维司群；吉非替尼；吉西他滨；吉妥珠单抗奥佐米星；醋酸戈舍瑞林；醋酸组氨瑞林；羟基脲；替伊莫单抗；伊达比星；异环磷酰胺；甲磺酸伊马替尼；干扰素 α-2a；干扰素 α-2b；伊立替康；来那度胺；来曲唑；甲酰四氢叶酸；醋酸亮丙瑞林；左旋咪唑；洛莫司汀；甲氮芥；醋酸甲地孕酮；美法仑；巯基嘌呤；氨甲喋呤；甲氧沙林；丝裂霉素 C；丝裂霉素 C；米托坦；米托蒽醌；苯丙酸诺龙；奈拉滨；NPI-0052；诺非单抗；奥普瑞白介素；奥沙利铂；紫杉醇；紫杉醇蛋白结合颗粒；帕利夫明；帕米膦酸盐；帕尼单抗；培加酶；培门冬酶；培非司亭；培美曲塞二钠；喷司他丁；哌泊溴烷；普卡霉素；光辉霉素；卟吩姆钠；丙卡巴肼；奎纳克林；RAD001；拉布立酶；利妥昔单抗；沙格司亭；沙格司亭；索拉非尼；链佐星；苹果酸舒尼替尼；他莫昔芬；替莫唑胺；替尼泊苷；睾内酯；沙利度胺；硫鸟嘌呤；塞替派；托泊替康；托瑞米芬；托西莫单抗；托西莫单抗 /I-131 托西莫单抗；曲妥珠单抗；维甲酸；尿嘧啶氮芥；戊柔比星；长春碱；长春新碱；长春瑞滨；伏林司他；唑来膦酸盐；和唑来膦酸。

[0270] 在一些实施方案中，所述额外的药剂为拓扑异构酶抑制剂、微管蛋白相互作用因子、DNA- 相互作用剂、DNA- 烷化剂和 / 或铂络合物。

[0271] 在一些实施方案中，所述额外的药剂为奥沙利铂、酪氨酸激酶抑制剂、伊立替康（CPT-11）、阿扎胞苷、氟达拉滨或苯达莫司汀。

[0272] 酪氨酸激酶抑制剂包括但不限于厄洛替尼、吉非替尼、拉帕替尼、凡德他尼、来那替尼、拉帕替尼、来那替尼、阿西替尼、舒尼替尼、索拉非尼、来妥替尼、司马沙尼、西地尼布、伊马替尼、尼洛替尼、达沙替尼、波舒替尼、来妥替尼、瓦他拉尼和 soratinib。

[0273] 在一些实施方案中，所述额外的药剂为 DNA 损伤抗癌剂和 / 或放射治疗。

[0274] DNA 损伤抗癌剂和 / 或放射治疗包括但不限于电离辐射、类放射药物、单官能烷化剂（如烷基磺酸酯、亚硝基脲、替莫唑胺）、双官能烷化剂（氮芥、丝裂霉素 C、顺铂）、抗代谢物（例如 5- 氟尿嘧啶、硫嘌呤、叶酸类似物）、拓扑异构酶抑制剂（例如喜树碱、依托泊苷、多柔比星）、复制抑制剂（例如阿非科林、羟基脲）、细胞毒性 / 细胞抑制剂、抗增生剂、异戊二烯基 - 蛋白质转移酶抑制剂、氮芥类、亚硝基脲、血管生成抑制剂、细胞增殖和存活信号途径抑制剂、细胞凋亡诱导剂、干扰细胞周期检查点的药剂、双膦酸盐，或者它们的任意组合。

[0275] 在一些实施方案中，所述额外的药剂为固有的多药抗性（MDR）的抑制剂，特别是与转运蛋白表达高水平相关的 MDR。这类 MDR 抑制剂包括 p- 糖蛋白（P-gp）的抑制剂，如 LY335979、XR9576、OC144-093、R101922、VX853 和 PSC833（伐司朴达）。

[0276] 在一些实施方案中，所述额外的药剂为止吐剂，以治疗恶心或呕吐，包括急性、迟发性、晚期和预期性呕吐，其可能是由于单独使用或与放射治疗联合使用 HDAC 抑制剂（例如 abexinostat）所导致的。止吐剂包括神经激肽 -1 受体拮抗剂、5HT3 受体拮抗剂（如昂丹司琼、格拉司琼、托烷司琼、帕洛诺司琼和 zatisetron）、$GABA_B$ 受体激动剂（如巴氯芬）、

皮质类固醇（如地塞米松、泼尼松、泼尼松龙或其它，如美国专利号 2,789,118 ;2,990,401 ; 3,048,581 ;3,126,375 ;3,929,768 ;3,996,359 ;3,928,326 和 3,749,712 所公开的）、多巴胺拮抗剂（如多潘立酮、氟哌利多、氟哌啶醇、氯丙嗪、异丙嗪、丙氯拉嗪、甲氧氯普胺）、抗组胺药（H1 组胺受体拮抗剂，如赛克利嗪、苯海拉明、茶苯海明、美克洛嗪、异丙嗪、羟嗪）、大麻素类（如大麻、屈大麻酚、卓那比醇）和其它（如曲美苄胺、生姜、癒吐宁锭（emetrol）、丙泊酚）。

[0277] 在一些实施方案中，所述额外的药剂是选自神经激肽 -1 受体拮抗剂、5HT3 受体拮抗剂和皮质类固醇的止吐剂。

[0278] 在一些实施方案中，所述额外的药剂是可用于治疗贫血的药剂。

该贫血治疗剂为，例如，连续的红细胞生成受体激活剂（如依泊汀 -α）。

[0279] 在一些实施方案中，所述额外的药剂是可用于治疗嗜中性粒细胞减少症的药剂。可用于治疗嗜中性粒细胞减少症的药剂的例子包括但不限于调节嗜中性粒细胞的产生和功能的造血生长因子，如人粒细胞集落刺激因子 (G-CSF)。G-CSF 的例子包括非格司亭。

[0280] 在一些实施方案中，所述额外的药剂为至少一种 CYP 酶的抑制剂。在其中 abexinostat（或其盐）或帕唑帕尼（或其盐）被一种或多种 CYP 酶代谢的情况下，与 CYP 抑制剂共同给药降低了体内代谢并改善了该药剂的药代动力学性质。

[0281] 其它联合治疗公开于 WO 08/082856 和 WO 07/109178，二者在此全文引入作为参考。

放射治疗

[0282] 在一些实施方案中，本文公开的方法进一步包含放射治疗。放射治疗，也称为放疗，是用电离辐射治疗癌症和其它疾病。电离辐射沉积能量，该能量通过损伤其遗传物质来伤害或摧毁被治疗区域（“目标组织”）中的细胞，使得这些细胞不能继续生长。虽然辐射同时破坏癌细胞和正常细胞，但是后者能更好地适当修复其自身和功能。放射治疗可用于治疗局部实体瘤，如皮肤、舌、喉、脑、乳房、前列腺、结肠、子宫和 / 或宫颈的癌症。其还可用于治疗白血病和淋巴瘤（分别为血液形成细胞和淋巴系统的癌症）。

[0283] 将辐射递送至癌症细胞的技术是将放射性植入物直接置于肿瘤或体腔内。这被称为内放射治疗（近距离放射治疗、组织间照射和腔内照射是内放射治疗的类型）。使用内放射治疗，辐射剂量集中于一个小区域内，患者需要住院数天。内放射治疗经常用于舌、子宫、前列腺、结肠和宫颈的癌症。

[0284] 术语“放射治疗”或“电离辐射”包括所有形式的辐射，包括但不限于 α、β 和 γ 辐射和紫外线。放射治疗联合或不联合同时或相继的化学治疗对于头颈、乳腺、皮肤、阴肛部癌症和某些非恶性疾病如瘢痕疙瘩、硬纤维瘤、血管瘤、动静脉畸形和组织细胞增生症 X 而言是有效的疗法。

[0285] 在一些实施方案中，本文公开的方法减少了由至少一种其它治疗性处理导致的副作用，如辐射诱导的正常组织纤维化或化学治疗诱导的组织坏死，本文提供的方法还与放射治疗和其它抗癌剂一起协同抑制肿瘤细胞生长。

RAD51

[0286] DNA 损伤导致染色体不稳定性、瘤形成、细胞死亡和严重的细胞功能障碍。DNA 修复系统对于活细胞的生存非常重要。参与双链 DNA 断裂的修复的两种主要 DNA 修复机制是

同源重组 (HR) 和非同源末端连接 (NHEJ)。真核生物 RAD51 基因是大肠杆菌 (Escherichia coli)RecA 的直向同源物，基因产物 RAD51 蛋白在同源重组中发挥核心作用。

[0287] 很多治疗性处理，如抗癌剂，通过其对细胞产生 DNA 损伤的能力来发挥其治疗效应。如果细胞如癌细胞具有活跃的 DNA 修复机制，则这类治疗的治疗效果可能会消弱，可能需要高剂量以获得期望的治疗效果。

[0288] 在一些实施方案中，本文公开的方法用于降低癌症病人中的细胞 DNA 修复活性。

[0289] 在一些实施方案中，本文公开的方法在联合治疗中降低细胞 DNA 修复活性。在一些实施方案中，本文公开的方法干扰涉及 RAD51 或 BRCA1 的 DNA 修复机制。

[0290] 在一些实施方案中，本文公开的方法治疗与 DNA 非同源末端连接缺陷有关的癌症。在一些实施方案中，本文公开的方法进一步包括施用能够损伤细胞 DNA 的治疗。

[0291] DNA 非同源末端连接缺陷包含选自下组的基因中的缺陷 :Ku70、Ku80、Ku86、Ku、PRKDC、LIG4、XRCC4、DCLRE1C 和 XLF。在一个方面，所述癌症选自伯基特淋巴瘤、慢性髓性白血病和 B 细胞淋巴瘤。在一个方面，所述癌症为本文已描述的。

[0292] 在一些实施方案中，本文公开的方法用于治疗人的端粒交替延长 (ATL) 阳性癌症。

[0293] 包括抑制 RAD51 活性 (例如 HDAC 抑制剂 (例如 abexinostat)) 的额外的联合治疗、治疗策略等等公开于美国专利公开号 20080153877 和 WO 08/082856(二者在此引入作为参考)。

药盒 / 制品

[0294] 为了在此处描述的使用治疗方法中使用，在此还描述了药盒和制品。这样的药盒包括载具、包装或容器，该容器被区室化为接纳一个或多个容器如小瓶、管等，每个容器包含将在此处描述的方法中使用的一个单独元件。合适的容器包括，例如，瓶子、小瓶、注射器和试管。在一个实施方案中，容器由多种材料如玻璃或塑料形成。

[0295] 在此提供的制品含有包装材料。用于包装药物产品的包装材料包括，例如，美国专利号 5,323,907、5,052,558 和 5,033,252。药物包装材料的例子包括但不限于泡罩包装、瓶子、管、泵、袋、容器、瓶子，和任何适于选定制剂和预期给药和治疗模式的包装材料。考虑了在此提供的化合物和组合物的大量制剂。

[0296] 这样的药盒任选地包含关于其在此处所述方法中的应用的标识性描述或标签或说明书。

[0297] 在一个实施方案中，标签处于容器上或与之相关联。在一个实施方案中，当构成标签的字母、数字或其它字符附加、模塑或铭刻在容器本身之内时，标签处于容器上 ；当标签例如作为包装插页存在于同样容纳容器的接受器 (receptacle) 或载具中时，标签与容器相关联。在一个实施方案中，标签用于表明内容物将用于特定治疗应用。标签还标明关于如在此处描述的方法中使用内容物的指导。

[0298] 在某些实施方案中，该药物组合物呈现于包装或分配装置中，该装置含有一个或多个含有在此提供的化合物的单位剂型。包装例如包含金属或塑料箔，如泡罩包装。在一个实施方案中，包装或分配装置伴随有给药说明。在一个实施方案中，包装或分配装置还伴随有监管药物生产、使用或销售的政府机构所规定的形式的、与容器相关联的通告，这样的通告反映了该机构对用于人类或兽医给药的药物形式的批准。例如，这样的通告是由美国

食品药品管理局对处方药批准的标签或批准的产品插页。

实施例

[0299] 这些实施例仅为说明性目的提供，而并非限制在此提供的权利要求的范围。

Abexinostat 的合成

[0300] Abexinostat 根据美国专利号 7,276,612 的实施例 7 所述制备，其内容在此全文引入作为参考。

实施例 1 :Abexinostat 盐酸盐的静脉内溶液

[0301] 将 Abexinostat 盐酸盐配制为静脉内 (IV) 溶液以用于人体初期临床试验。IV 溶液是用等渗盐水稀释后预期用于输注给药的水溶液制剂。每个一次性使用小瓶包含 abexinostat 盐酸盐在等渗盐水和 50mM 乳酸盐缓冲液 pH 4.0-4.5 中的 25mL 的 5mg/mL(0.5％) 溶液。临床制剂中的所有赋形剂都是药典规定的，并且常用于肠胃外剂型中。表 1 中给出了制剂的定量组成。推荐的存储条件是 2-8℃。

表 1. IV 溶液 (5mg/mL) 的定量组成

成分	百分比 (% w/w)	mg/g (w/w)	典型批次 (57.5 kg)
Abexinostat 盐酸盐	0.5	5.0	0.288 kg
乳酸	0.45	4.5	0.259 kg
氯化钠	0.665	6.65	0.382 kg
注射用水	-	-	适量，达到体积
1N 氢氧化钠*和/或 1N 盐酸盐*，适量加至 pH 4.0-4.5 ± 0.2	-	-	适量，达到 pH

实施例 2 :速释胶囊

[0302] 通过将 abexinostat 盐酸盐与微晶纤维素、乳糖和硬脂酸镁混合并继而将该混合物加入至明胶胶囊中来配制速释胶囊 (见表 2)。胶囊以两种强度制备。20mg 剂量强度包括在 4 号瑞典橙色硬明胶胶囊中的 20mg 的 abexinostat 盐酸盐。100mg 剂量强度包括在 2 号深绿色硬明胶胶囊中的 100mg abexinostat 盐酸盐。将胶囊装入 30cc HDPE 瓶中并用感应密封进行密封并用儿童保护螺旋顶盖加盖。20mg 剂量强度按照每瓶 50 个胶囊包装。100mg 剂量强度按照每瓶 30 个胶囊包装。将瓶存储在控制室温 20-25℃ (68-77° F) 下。

表 2. 速释胶囊

成分	质量标准	Mg/胶囊		功能
Abexinostat 盐酸盐	制造商说明书	20 mg[(a)]	100 mg[(a)]	活性药物成分
Avicel PH113 (微晶纤维素)	NF	68 mg	76 mg	崩解剂
乳糖，无水	NF	15.7 mg	17.6 mg	稀释剂
硬脂酸镁	NF	1.3 mg	1.5 mg	润滑剂

[(a)] 每个胶囊中 abexinostat 的量根据水含量和纯度进行调节。

实施例 3 :定时释放的多颗粒脉冲制剂

[0303] 将 80 克氯化钠和 24 克聚乙烯吡咯烷酮溶解于 1.2 千克水中，其中悬浮 400 克粉状的 abexinostat 盐酸盐。

[0304] 在流化床包衣器中，将 400 克淀粉 / 糖种子 (30/50 目) 悬浮于暖空气中并与 abexinostat 盐酸盐悬液一起喷雾包衣直至种子被期望的药物效价均匀涂覆。

[0305] 将硬脂酸镁的异丙醇溶液与 Eudragit NE30D(Rohm Pharma of Weiterstadt, Germany) 以 2:1(干燥的聚合物 :硬脂酸镁) 的比例混合。向活性核心上喷涂足量的聚合物悬液以提供特定薄膜包衣厚度，从而获得一组微丸的特定滞后时间和释放速率。最终包衣的微丸在 50℃干燥 2 小时以确保完全去除潮湿，从而稳定核心内容物。

[0306] 用不同包衣厚度重复该流程至少一批，以获得不同的滞后时间和释放速率。在本实施例中，制备了两组，一组包衣增重 10％，另一组增重 30％。通过以预定比例将两组混合在一起并用混合物填充凝胶制备单位剂量。

[0307] 在对人口服施用单位剂量后，第一组微丸没有开始释放 abexinostat，直到约 2-3 小时的初始滞后时间逝去之后。第二组微丸没有开始释放 abexinostat，直到约 6-7 小时的初始滞后时间逝去之后。每组微丸的平均释放时间 (一半药物被释放的时间) 应彼此间隔至少 3-4 小时。

[0308] 流化床包衣器是本领域熟知的，然而也可以使用本领域熟知的其它包衣设备和方法。

实施例 4 :备选的定时释放多颗粒脉冲制剂

[0309] 活性核心按实施例 3 所述制备。将硬脂酸镁和三醋精塑化剂与 Eudragit RS 30D 悬液以 1 :0.6 :2 的干重比混合。按照实施例 3 将聚合物悬液涂覆于核心上，从而制备多组，每组具有特定包衣厚度以在应用的水环境中提供药物的特定滞后时间和释放速率。

[0310] 如实施例 3 所述，混合不同组微丸，并用混合物填充胶囊。

实施例 5 :脉冲制剂—胶囊中的片剂

[0311] 用于施用 abexinostat 盐酸盐的脉冲释放剂型通过以下步骤制备 :(1) 配制两种单独的压制片剂，每种具有不同的释放谱，然后 (2) 将这两种片剂包封到明胶胶囊中，然后闭合并密封胶囊。这两种片剂的成分如下。

表 3. 片剂 1(无包衣)

成分	功能	每片的量
abexinostat 盐酸盐	活性剂	20.0mg
二水合磷酸二钙	稀释剂	38.5mg
微晶纤维素	稀释剂	38.5mg
羟基乙酸淀粉钠	崩解剂	2.4mg
硬脂酸镁	润滑剂	0.6mg

[0312] 通过对单独的药物颗粒和其它核心成分进行湿法造粒来制备片剂，如可通过流化床造粒机进行，或通过对组分混合物直接压片进行制备。片剂 1 是速释剂型，其在给药后 1-2 小时内完全释放活性剂。

[0313] 将一半的速释片剂用 1 号延迟包衣进行包衣，以提供片剂 2。片剂 2 将

abexinostat 盐酸盐在给药后的释放延迟约 3-5 小时。将一半的速释片剂用 2 号延迟包衣进行包衣，以提供片剂 3。片剂 3 将 abexinostat 盐酸盐在给药后的释放延迟约 4-9 小时。使用常规包衣技术如喷雾 - 包衣等进行包衣。

表 4. 片剂 2（有包衣）

成分	功能	重量
片剂 1	包含活性剂的“核心”	100.0mg
Eudragit RS30D	延迟释放包衣材料	8.0mg
滑石	包衣成分	6.0mg
柠檬酸三乙酯	包衣成分	2.0mg

表 5. 片剂 3（有包衣）

成分	功能	重量
片剂 1	包含活性剂的“核心”	100.0mg
Eudragit RS30D	延迟释放包衣材料	12mg
滑石	包衣成分	7mg
柠檬酸三乙酯	包衣成分	3.0mg

[0314] 胶囊对患者的口服给药应导致具有两个脉冲的释放谱，abexinostat 盐酸盐的初始释放发生在给药后约 3-5 小时，abexinostat 盐酸盐从第二片剂的释放发生在给药后约 7-9 小时。

实施例 6 :脉冲制剂—胶囊或片剂中的珠粒

[0315] 重复实施例 5 的方法，不同之处是使用含药物的珠粒代替片剂。速释珠粒通过用惰性支撑材料如乳糖对药物进行包衣来制备。速释珠粒用一定量的肠溶衣材料进行包衣，其足以提供约 3-5 小时的无药物释放期。第二部分的珠粒通过用更大量的肠溶衣材料对速释珠粒进行包衣来制备，其足以提供约 7-9 小时的无药物释放期。按照实施例 5 所述对两组包衣珠粒进行胶囊化，或者在缓冲剂的存在下将其压片形成单一的脉冲释放片剂。

实施例 7 :持续释放片剂

[0316] abexinostat 的持续释放片剂如下制备 :首先制备持续释放赋形剂。通过在高速混合器 / 造粒机中干混所需量的黄原胶、刺槐豆胶、药学上可接受的疏水聚合物和惰性稀释剂 2 分钟来制备持续释放赋形剂。在运行粉碎机 / 叶轮的同时加入水，对混合物进行另外 2 分钟的造粒。然后在流化床干燥器上干燥颗粒至干重失重（“LOD”）为 4-7％。然后用 20 目筛磨碎这些颗粒。持续释放赋形剂的成分如以下表 6 所示 :

表 6. 持续释放斌形剂混合物

成分	％重量

黄原胶	10
刺槐豆胶	10
羧甲基纤维素	30
葡萄糖	50
水	23*

* 在加工过程中去除

[0317] 接下来，将如上所述制备的持续释放赋形剂与所需量的 abexinostat 在 V 型搅拌机中干混 10 分钟。对于下述实施例加入适量的制片润滑剂 Pruv® （硬脂酰富马酸钠，NF），并将混合物再混合 5 分钟。将该最终混合物压制为片剂，每片含有 10％重量的 abexinostat。产生的片剂重 500mg（直径为 3/8 英寸；硬度为 2.6Kp）。片剂的比例如以下表 7 所示。

表 7. 持续释放片剂

成分	％重量
表 6 的持续释放赋形剂混合物	88.5
abexinostat	10
硬脂酰富马酸钠	1.5

[0318] 然后对片剂进行溶出实验。该溶出实验在自动化 USP 溶出设备（II 型桨叶，pH 7.5 缓冲液，50rpm，500mL）上进行。片剂到 2 小时时应释放出约 30％的 abexinostat，然后持续释放，从而约 98％的 abexinostat 在 12 小时结束时得到释放。

实施例 8：包衣的持续释放片剂

[0319] 如上所述通过干混所需量的黄原胶、刺槐豆胶和惰性稀释剂制备持续释放赋形剂。在添加成分后再进行 2 分钟的造粒（添加后造粒共 4 分钟）。用乙基纤维素水分散体替换上述方法中的水。持续释放赋形剂的成分描述于表 8。

表 8. 持续释放斌形剂

成分	％重量
黄原胶	12
刺槐豆胶	18
葡萄糖	65
乙基纤维素水分散体	5*

* 乙基纤维素水分散体包含约 25％重量的固体。加至制剂的量（即 5％）仅为固体。

[0320] 在 V 型搅拌机中干混黄原胶和刺槐豆胶 10 分钟，加入葡萄糖，将混合物继续混合 5 分钟。然后加入乙基纤维素水分散体，然后进行额外 5 分钟的混合。然后用硬脂酰富马酸钠作为制片润滑剂将得到的颗粒压制为片剂。然后用另外的乙基纤维素水分散体对片剂进行包衣。为实现这一点，将乙基纤维素（Surelease®，400g）与水（100g）混合形成水悬液。然后，在 Keith Machinery 包衣锅（直径 350mm；锅转速 20rpm；喷枪喷嘴 0.8mm；片剂床温 40° -50℃；每批加载 1kg；干空气 -Conair Prostyle1250，60° -70℃）中对片剂进行包衣。片剂被包衣至增重约 5%。片剂应重约 500mg。片剂的比例如以下表 9 所示：

表 9. 包衣的持续释放片剂

成分	%重量
表 8 的持续释放赋形剂混合物	83.5
abexinostat	10
乙基纤维素	5
硬脂酰富马酸钠	1.5

[0321] 在自动化 USP 溶出设备上以模拟通过胃肠道的方式进行溶出实验。在前 1-2 小时中包衣的片剂不应释放多于 10%的 abexinostat，然后应当以稳定速率释放 abexinostat，使得约 90%到 100%的 abexinostat 在 12 小时后得到释放。

实施例 9：体外释放谱

[0322] 使用美国药典设备 I 在 37℃和 100RPM 下得到溶出谱。溶出介质随时间变化，开始 0-2 小时使用 0.1N HCl。在 2-4 小时，介质为 pH 6.5 的磷酸盐缓冲液，在 4-24 小时，介质为 pH 7.5 的磷酸盐缓冲液。

[0323] 或者，使用 USP III 型 (VanKel Bio-Dis II) 设备获得溶出谱。

实施例 10：体外进食 / 禁食溶出方案

[0324] 在多种溶出条件下对测试制剂进行评估，以确定 pH、介质、搅拌和设备的影响。溶出实验使用 USP III 型 (VanKel Bio-Dis II) 设备进行。为了确定对于系列剂型在进食状态和禁食状态之间可能存在的差异，在含有 30%花生油的溶液中进行体外溶出实验（“进食”），以模拟具有典型膳食脂肪负载的胃肠道。对照测定了在不含脂肪负载的溶液中的溶出速率（“禁食”）。pH- 时间方案（范围从酸至碱以模拟消化过程）如以下表 10 所示。搅拌为 15cpm。测试的样品体积为 250mL。

表 10. 进食 / 禁食溶出方案

设备介质			
“进食”	“禁食”	时间	pH
30%花生油	无花生油	0-1 小时	1.5
30%花生油	无花生油	1-2 小时	3.5
30%花生油	无花生油	2-4 小时	5.5
30%花生油	无花生油	4-12 小时	7.5

[0325] 预期片剂上的肠溶衣能提供具有在禁食和进食状态下无显著不同的溶出速率的

片剂。

实施例 11 :I 期试验

研究目的

[0326] 确定帕唑帕尼盐酸盐与 abexinostat 盐酸盐联合在晚期实体瘤患者中的安全性、耐受性以及最大耐受剂量 (MTD)。

[0327] 表征 abexinostat 盐酸盐、帕唑帕尼盐酸盐以及二者组合的药代动力学。

[0328] 利用临床受益率 (Clinical Benefit Rate) = CR+PR+SD、客观响应比例和无进展生存期 (Progression-free survival) 来评估初步疗效。

[0329] 在响应者和非响应者中探索在血液和活检肿瘤中的组蛋白乙酰化的表达水平变化与血浆中包括 VEGF、VEGFR、HIF 和 RAD51 在内的生物标志物的表达之间的关系。

[0330] 探索单核苷酸多态性 (SNP) 变化与潜在毒性的关系。

[0331] 使用 FLT PET(3’ 脱氧 -3’ -18F- 氟胸苷正电子发射断层扫描) 评估功能成像,以测量细胞分裂速率的变化和与肿瘤响应的相关性。

研究设计的概述

[0332] 建立开放标签、非随机、剂量递增和扩展 I 期试验,以评价 abexinostat 与帕唑帕尼组合的安全性并确定该组合的推荐的 II 期剂量。

[0333] 第 1-28 天,每日一次给予帕唑帕尼盐酸盐,并应该至少在餐前 1 小时或餐后 2 小时在不进食的情况下口服。在第 1-5 天、第 8-12 天、第 15-19 天期间,每日两次口服 abexinostat 盐酸盐。各个周期将持续 28 天。一个周期的持续时间是 28 天。病情进展前持续对患者进行治疗。

入选标准

[0334] Ia 期 :患者必须患有经组织学或细胞学证明的转移性实体瘤的恶性肿瘤。

[0335] Ib 期 :患者必须患有经组织学或细胞学证实的局部晚期的、不可切除的或转移性的肉瘤或肾细胞癌。

[0336] 根据 RECIST 1.1 可测量的疾病。

[0337] 尽管经过多次前期治疗,患者仍可能患有新生的或进展的转移性疾病。

[0338] 美国东部肿瘤协作组 (ECOG) 表现状态为 0-1。

[0339] 除脱发外,全部与化疗或放疗相关的毒性减退至 1 级或更低的严重程度。

[0340] 患者必须距上一次标准或实验治疗 (包括放射治疗) 至少 2 周或 5 个半衰期 (以较长者为准)。

[0341] 先前已经接受帕唑帕尼盐酸盐的患者具有资格,但必须在过去两周内未接受。

排除标准

[0342] 除宫颈原位癌或者非黑色素瘤的皮肤癌外,患有其它未治疗的、当前的原发恶性肿瘤的患者。

[0343] 除患有先前治疗的中枢神经系统 (CNS) 转移瘤的个体外,中枢神经系统 (CNS) 转移瘤或脑膜癌病的病史或临床证据是无症状,并且不要求在首剂研究药物之前施用 4 周的类固醇或抗惊厥药物。

[0344] 可能增加胃肠道出血风险的临床显著的胃肠道异常。

[0345] 使用 Friedrichs 公式的校正的 QT 间期 (QTc)>480 毫秒。

[0346] 使用已知会导致 QT 延长的药物。

[0347] 在过去的 6 个月内，具有任何一个或多个下列心血管状况的病史：

a. 心脏血管成形术或支架术

b. 心肌梗死

c. 不稳定型心绞痛

d. 冠状动脉旁路移植术

e. 有症状的外周血管疾病

[0348] 控制不佳的高血压 [定义为收缩压 (SBP) ≥ 140mmHg 或舒张压 (DBP) ≥ 90mmHg]。

[0349] 在过去的 6 个月内，具有包括短暂性脑缺血发作 (TIA) 在内的脑血管意外、肺栓塞或未经治疗的深部静脉血栓形成 (DVT) 的病史。

a. 注：用治疗性抗凝治疗至少 6 周的患有近期 DVT 的患者是合格的。

[0350] 任何严重的和 / 或不稳定的预先存在的医疗、精神或其它状况，所述状况可干扰受试者的安全、知情同意书的提供或对研究程序的遵守

[0351] 在首剂研究药物之前和研究的持续期间内，无法或不愿意停止使用所禁止的药物至少 14 天或 5 个半衰期 (以较长者为准)

患者组群和剂量递增原则

[0352] 本试验提出了使用 abexinostat 盐酸盐增加疗效并且可能逆转血管生成抑制剂 (在本研究中是帕唑帕尼盐酸盐) 抗性的机制。为了适应最佳给药并达到 abexinostat 盐酸盐的稳定水平，在 28 天中的第 1-5 天、第 8-9 天、第 15-19 天每日口服 abexinostat 盐酸盐两次。在 28 天中的第 1-28 天每日服用帕唑帕尼。周期将每 28 天进行重复。

[0353] 患者将接受 abexinostat 盐酸盐和帕唑帕尼盐酸盐的交替递增剂量。根据下表进行剂量递增。设计下列剂量组群，然而，若在任何组群中观察到 >2 例 DLT 而在前一组群中未观察到 DLT，则将探查中间剂量水平 (例如：在 45mg 时观察到了 2 例 DLT 而在 30mg 时未出现 DLT，我们将探查 35mg)。

[0354] 如果在第一组群中观察到了可能与帕唑帕尼盐酸盐相关的 DLT，则首先降低帕唑帕尼盐酸盐的剂量。如果有证据表明毒性可能由 abexinostat 盐酸盐导致，则将 abexinostat 盐酸盐剂量降至 30mg(组群 -1)。

[0355] 在 Ia 期内，为使 DLT 可评估，在第一周期期间，患者必须接受 20 天的帕唑帕尼盐酸盐 (≥ 75％) 和 10 天的 abexinostat 盐酸盐 (≥ 75％)。若由于研究药物而导致第一周期内的治疗延迟 >14 天，其被视为 DLT 且患者将不会被替换。若治疗是由于其它原因而延迟的，则患者将会被替换。

组群	患者人数	帕唑帕尼盐酸盐	Abexinostat 盐酸盐
-1	(6)	400 mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，30 mg/m^2 PO BID
1*	1 (+2)	400 mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，45 mg/m^2 PO BID
2	1 (+2)	600 mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，45 mg/m^2 PO BID
3	3	600 mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，60 mg/m^2 PO BID
4	3	800 mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，60 mg/m^2 PO BID
5	6	800 mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，60 mg/m2 PO BID 75 mg/m^2 PO BID
MTD	**肉瘤、RCC 和其它各 20 人**	xxx mg po qd	第 1-5 天、第 8-12 天、第 15-19 天，xxx mg/m^2 PO BID

* 起始剂量

[0356] 从剂量水平 1 开始，若 1 名患者经历 DLT（如第 4.5 节所定义），则该剂量水平将扩展以包括 2 名另外的患者。若该另外的患者未出现 DLT，则该剂量将扩展至下一水平。若 3 名患者中有 2 名患者出现 DLT，该剂量将会递减至剂量 -1。在剂量水平 3 时，扩展部分 I 将在标准 3+3 设计中出现。3 名患者将在剂量水平 3 和 4 下进行治疗。若 3 名患者中 0 名患者经历 DLT，则 3 名患者将在下一剂量水平下进行治疗。若在 3 名患者中 1 名患者经历由治疗而导致的 DLT，则另外 3 名患者（总共 6 名患者）将在该剂量水平下进行治疗。若在该扩展的剂量水平下未发现另外的 DLT（即 6 名中有 1 名出现 DLT），则该剂量将进行递增。在给定剂量水平下只要有 2 名或更多名患者经历任何由研究药物引起的 DLT，那么递增将终止。若达到剂量水平 5，则将加入 6 名患者。一旦定义了 MTD，那么将进行剂量扩展部分 II。

[0357] 将禁止组群内剂量递增。剂量递增将根据列出的递增步骤进行 :abexinostat 盐酸盐应在第 1 天上午开始并在 28 天周期的第 2-5 天继续。仅在周期 1 中的 abexinostat 盐酸盐的上午剂量后，在第 2 天给予帕唑帕尼，然后每日给予，共 28 天。4 周的治疗被定义为一个周期。2 个周期后将对响应进行评估。各个周期后将对患者的用药日记进行评估。

[0358] 如果在任何剂量下，观察到 DLT 而在前一剂量水平下未观察到 DLT，则在与 CHR、PI 和赞助者讨论后我们可以探查中间剂量。

[0359] 在同一周内将有不超过 2 名患者进行第一次给药，并且在较低组群的最后一名患者已完成 DLT 期之前在下一更高组群中不加入患者。

预计的患者人数

[0360] 本研究要招募的患者总数将在 46 名和 90 名之间。

干预和评估的持续时间

[0361] 在如 RECIST 1.1 所定义的病情进展、出现无法耐受的毒性、请求退出或按照首席研究者的要求退出之前，患者将在本研究中。

[0362] 患者将继续定期（大约每 6 个月）通过医疗记录进行追踪，并更新随后的癌症治疗、癌症进展和存活结果。将进行随访直到死亡或至少十年。

剂量限制性毒性

[0363] 这是一项组合试验，该试验可具有由帕唑帕尼盐酸盐和 abexinostat 盐酸盐剂量递增导致的不同毒性或由所述组合导致的不同毒性。特别应考虑由剂量递增引起的毒性。本试验的原理是通过联合治疗增加各种药物的疗效和逆转血管生成抑制剂的抗性机制。应尽最大努力以不延迟药物给药。延迟给药需要由首席研究者提前批准。如果毒性可以明确地只与一种药物相关联，则应只对抵触性药剂进行剂量修改。

[0364] 根据 NCI 不良事件常用术语标准 4.03 版 (NCI，CTC 网址 http://ctep.info.nih.gov)，对不良事件和其它症状进行评级。

[0365] 剂量限制性毒性 (DLT) 将被定义为当与作为本研究的一部分的治疗相关或可能相关时，在第 1 周期内发生的下列 31 项不良事件中的任一项：

[0366] 血液剂量限制性毒性

a. 尽管有生长因子支持，4 级嗜中性粒细胞减少症持续≥ 7 天时间。第一周期的第 7 天后可施用 GCSF（非格司亭）或聚乙二醇化 -GCSF（培非格司亭）以处理 ANC ≤ 1000，并且在第一周期后根据主治医生的判断预防性给药。当给药时，这不构成 DLT。

b. 4 级嗜中性粒细胞减少症伴发烧 >38.5℃和需要抗生素或抗真菌治疗的感染。

c. 4 级血小板减少症（≤ 25.0x10^9/L）。

d. 因出血而复杂化的和 / 或需要输注血小板或输血的 3 级血小板减少症。

[0367] 非血液剂量限制性毒性—其将被定义为任何≥ 3 级的非血液学毒性，特殊情况例外。

[0368] 以下也将被认为是 DLT：

a. 有症状的心动过缓

b. QTc 间期的持续增加 (> 自基线 60ms 和 / 或 >500ms)

c. 大于 14 天的治疗延迟

d. 由于≥ 2 级与治疗相关的毒性，在第一周期内未能施用≥ 75％的计划中的研究药物

e. 因除毒性以外的原因而未完成第一周期的受试者将被归类为毒性不可评估并且将被替换。在 DLT 窗口内不能进行剂量减少。

最大耐受剂量

[0369] 最大耐受剂量 (MTD) 将被定义为最高测试剂量水平，在该剂量水平下少于 33％的患者在第一周期经历 DLT。

访视时间表和评估

测试/研究	研究前	第一周期的第 1-28 天				第二周期的第 1-28 天				每 8 周，直到研究 6 个月	研究 6 个月后每 8 周	各个周期的第一天之前	治疗结束
		第一周	第二周	第三周	第四周	第一周	第二周	第三周	第四周				
病史和药物日志	X[1]	X[1]				X 错误！未定义书签						X 错误！未定义书签	X
身体检查[3]	X[1]	X[1]				X 错误！未定义标签						X 错误！未定义标签	X
毒性评估[4]	X[1]	X	X	X	X	X						X	X
CBC，差异[5]	X[1]	X[1]				X						X	X
化学[6]	X[1]	X[1]	X 错误！未定义书签			X						X	X
TSH 和 T4[7]	X					X				X	X		X
INR/PT[8]	X[1]												
尿蛋白[9]	X[1]											X	
超声检查/MUGA[10]	X								X		?		X
EKG[11,12]	X	X 错误！未定义书签	X 错误！未定义书签	X 错误！未定义书签	X 错误！未定义书签	X 错误！未定义书签						X 错误！未定义书签	X
妊娠检查[13]	X					X						X	X
分期研究[14]	X								X	X	X		
帕唑帕尼 PK[15]		X			X								
Abexinostat PK[16]		X											
PD 标志物[17]	X[18]	X[18,19,]	X[18]			X 错误！未定义标签						X 错误！未定义标签	X
FLT/PET[21]		X							X				
肿瘤活检[22]	X	X											

[1] 若在 2 周内并且无显著变化发生，可在第一天检查进行研究前检查、病史和身体检查。

[2] 下一周期前 7 天内可进行后续周期的第一天身体检查和病史

[3] 身体检查包括 ECOG 状态和生命体征

[4] 毒性将根据 CTCAE v4.03 进行评估

[5] 血红蛋白、血细胞比容、血小板、总白细胞计数 (WBC) 和分类

[6]BUN、肌酸酐、钠、钾、氯化物、CO_2(HCO_3)、葡萄糖、钙、白蛋白、总蛋白、总胆红素、碱性磷酸酶、LDH(仅黑色素瘤)、AST/SGOT、ALT/SGPT、磷、镁。如果总胆红素大于正常值上限，则应

该进行直接和间接胆红素检验。如果可能，应在患者空腹后进行生物化学检验。在第一周期的第 2 周内还应获得 LFT，其包括总胆红素、碱性磷酸酶、LDH（仅黑色素瘤）、AST/SGOT、ALT/SGPT

[7] 甲状腺功能试验：每 8 周检测 TSH、FT4

[8] 对于服用华法林的患者，血凝谱包括凝血酶原时间或国际标准化比值 (INR)

[9] 尿蛋白应该通过尿分析中的蛋白质定量来测定

[10]MUGA 或超声检查 (ECHO) 应在基线时和第二周期结束时（±1 周）进行，并且仅在 EF 变化 ±10％时，在后续周期中重复

[11] 在第一周期，每周在以下两个时间点重复进行三次 EKG：abexinostat 盐酸盐给药之前和 abexinostat 盐酸盐给药之后 3 小时（±15min.）

[12] 周期≥ 2：如果给药前第一天 EKG 未显示心脏问题，则只进行一次 EKG

[13] 对于具有生育能力的女性。如果临床上指示，则每 2 个周期后将重复妊娠检查

[14] 应在治疗开始前不超过 30 天进行基线评估

[15] 帕唑帕尼 PK：最终时间表 TBD，仅 Ia 期

第 3 天：给药前、给药后：30 分钟、2 小时、4 小时、8 小时、24 小时

第 8 天：给药前（和 abexinostat 盐酸盐一起），给药后：30 分钟、1 小时、2 小时、4 小时、8 小时

第 22 天：给药前、给药后：30 分钟、2 小时、4 小时、8 小时、24 小时

[16]abexinostat 盐酸盐 PK：最终时间表 TBD，仅 Ia 期

第 1 天：给药前、给药后：30 分钟、1 小时、2 小时、4 小时、6 小时、8 小时、24 小时

第 8 天：见 #15

[17]PD 标志物将包括组蛋白乙酰化，VEGF、VEGFR、HIF 和 RAD51 的表达，药物基因组学

[18]abexinostat 盐酸盐的 PD 生物标志物：

治疗前：至多 10 天前

第 1 天：abexinostat 盐酸盐给药后 2 小时 (+15min)

第 8 天：abexinostat 盐酸盐给药前和给药后 2 小时 (+15min)

[19] 帕唑帕尼盐酸盐的 PD 标志物：每个周期采集血浆

[20] 药物基因组学：第一周期第一天采集全血

[21] 肿瘤 FNA：

第 1 天（至多 10 天前）和第 5 天在 abexinostat 盐酸盐给药后 120 分钟 (+30 分钟)。

＊肿瘤 FNA 或肿瘤活检对剂量递增是任选的，对剂量扩展是强制的＊

[22]FLT PET(3’脱氧 -3’-18F- 氟胸苷正电子发射断层扫描）可用基线成像进行，然后在第二周期前进行后续成像。

PK 时间表	给药	第一周期(第 1-28 天)				
		第 1 天	第 2 天	第 3 天	第 22 天	第 23 天
帕唑帕尼 (po)	一日一次			X	X	X
PCI-24781 (po)	一日两次	X	X	X		

帕唑帕尼时间表：给药前，30 分钟、2 小时、4 小时、8 小时、24 小时

Abexinostat 盐酸盐时间表：给药前，30 分钟、2 小时、4 小时、8 小时、24 小时

疗效评估

响应、进展和复发的标准

[0370] 在本研究中使用由实体瘤响应评价标准 (RECIST) 委员会 33 提出的新国际标准对响应和进展进行评估。仅肿瘤病变的最大直径（一维测量）的变化在 RECIST 1.1 中使用。注：使用以下提供的标准，病变是可测量的或不可测量的。涉及可测量性的术语“可评估的”因其不能提供附加的含义和准确性而将不再使用。

[0371] 对于本研究的目的，在第一周期后的奇数周期开始之前，每 8 周应对患者的响应进行评估。除基线扫描外，还应在首次证明客观响应后≥ 4 周获取验证扫描。

目标病变的评估

[0372] 完全响应 (CR)：所有目标病变消失。

[0373] 部分响应 (PR)：以基线总 LD 作为参考，目标病变的最长直径 (LD) 的总和至少减少 30％。

[0374] 病情进展 (PD)：以自治疗开始起记录的最低总 LD 作为参考，目标病变的 LD 总和至少增加 20％，或出现一个或多个新病变。

[0375] 病情稳定 (SD)：以自治疗开始起的最低总 LD 作为参考，既未充分收缩以达到 PR，也未充分增加以达到 PD。

肿瘤样品和 PBMC

[0376] 通过细针抽吸 (FNA) 取得的肿瘤样品由研究细胞病理学家根据 abexinostat 盐酸盐给药后评估时间表获得。在抽吸时研究细胞病理学家将使用 Diff-Quick 风干法 (FNA) 以确保在标本中存在肿瘤细胞。用于本研究目的的可及的病变被定义为对于在对患者具有低风险的 CT 指导下的 FNA（包括对颈部、腋下、腹股沟中的淋巴结和胸部、肝脏或肾上腺中的肿瘤块的 CT/ 超声引导的 FNA) 而言可及的皮下小结或淋巴结或病变。根据主治医生的判断经与首席研究者磋商作出本决定。如果没有肿瘤小结是可见的和 / 或可触及的或如上定义的可及的，则不进行活检。

[0377] 将针对 PCI24781 对肿瘤和 PBMC 组蛋白乙酰化的影响对组织进行评估。在 UCSF 的 Pamela Munster 实验室中，使用免疫荧光法和 Western 印迹分析 (IF) 法处理 PBMC 和肿瘤吸出物。细胞也将针对 HDAC 酶的表达进行染色。

[0378] 其它相关研究方法将在随后添加。

安全性评价

[0379] 安全性评价将由以下组成：监测和记录全部不良事件和严重不良事件，定期监测血液学、血液化学和尿液值，生命体征，ECOG 表现状态，以及定期的身体检查和 ECG 评估。

[0380] 根据不良事件常用毒性标准 (CTCAE)4.03 版对不良事件进行评估。

[0381] 严重的不良事件是在任何剂量下发生的任何不良药物体验，其：

a. 导致死亡；

b. 是危及生命的；

c. 导致患者住院或现有的住院治疗延长（为进行选择性外科手术或操作而入院不符合该条件）；

d. 导致永久的或显著的伤残 / 失能 ;或

e. 导致先天性异常 / 出生缺陷。

[0382] 不良事件是在开始研究药物后发生的任何不期望的指征、症状或医学状况的出现或恶化,即使不认为该事件与研究药物相关。在开始研究药物前存在的医学状况 / 疾病只有它们在开始研究药物后恶化时才被认为是不良事件。异常的实验室值或检验结果只有当它们引起临床指征或症状、被认为在临床上具有意义或需要治疗时才构成不良事件。

[0383] 应在研究期间的每次访视时通过对患者的非定向问询发现不良事件的发生。当患者在访视期间或之间主动提出时或通过身体检查、实验室检查或其它评估,也可检测到不良事件。尽可能的对各个不良事件进行评估以确定 :严重性等级 (轻度、中度、重度) 或 (1-4 级) ;它与研究药物的关系 (疑似 / 非疑似) ;其持续时间 (开始和结束日期,或者如果研究未结束则计为最后检查时) ;采取的措施 (未采取措施、调节 / 暂时中止研究药物剂量、由于该不良事件而永久停用研究药物、采用伴随用药、给予非药物治疗、住院治疗 / 延长住院治疗) ;以及其是否构成严重不良事件 (SAE)。

[0384] 所有不良事件应该适当地进行治疗。这样的治疗可包括研究药物治疗的变化 (包括可能的中断或终止)、开始或停止伴随治疗、评估频率或性质的改变、住院治疗或任何其它在医疗上需要的干预。一旦检测到不良事件,就应该对其进行追踪直到其消退,并应在每次访视时 (或必要时更频繁地) 就严重程度的任何变化、与研究药物的疑似关系、其治疗所需的干预及结果进行评估。

[0385] 关于所有严重不良事件的信息将被收集并记录下来。

终点

[0386] 将通过监测不良事件、安排的实验室评估、生命体征测量、ECG 和身体检查对 DLT 进行评估。毒性的严重程度将根据 2010 年 6 月 14 日公布的 NCI CTCAE v4.03 进行分级。各个治疗组用最大强度和与研究药物的关系来总结不良事件和具有临床意义的实验异常 (根据 CTCAE 满足 3 级、4 级或 5 级标准)。前 4 周每周进行安全性评价,然后每 4 周进行。简单的描述性统计将用于展示由帕唑帕尼盐酸盐和 abexinostat 盐酸盐的组合所看到的毒性数据。

[0387] Abexinostat 盐酸盐、帕唑帕尼盐酸盐和其组合的非房室药代动力学将通过测量和计算分布体积 (Vd)、生物利用度 (F)、清除率 (CL)、半衰期 (t1/2) 和曲线下面积 (AUC) 来进行评估。

[0388] 临床受益率 = CR+PR+SD。通过成像标准 RECIST 1.1 进行评估。

[0389] 客观响应率 (Objective response rate)。将计算为最佳响应患者 (具有临床益处的患者) 的数目除以研究的患者总数的比例。

[0390] 无进展生存期。到疾病进展的时间将被计算为从加入研究到由任何原因引起疾病复发、进展或死亡时的时间,或者如果未发生复发、进展或死亡,则到最后一次接触的时间。

[0391] 总生存期 (Overall survival)。OS 时间将被计算为从加入研究到由任何原因引起死亡时的时间,或者如果患者未死亡,则到最后一次接触的时间。

[0392] 组蛋白乙酰化根据 PBMC 和肿瘤活检物中的 HDAC1、HDAC2、HDAC3 和 HDAC6 表达的变化来测量。

[0393] 其它 PD 生物标志物 :等离子体,针对 VEGF、VEGFR、HIF 和 RAD51 表达。

[0394] 药物基因组学：一次采集血液以用于评估 SNP 变异及与毒性的相关性。

[0395] FLT PET(3’脱氧 -3’-18F- 氟胸苷正电子发射断层扫描）的变化

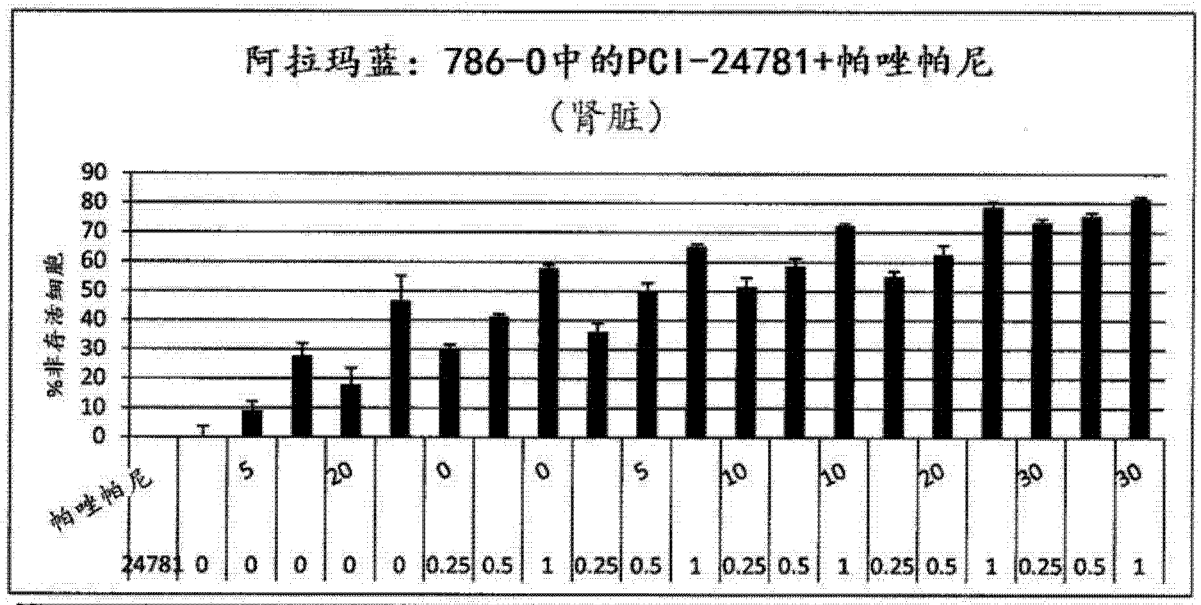
实施例 11：帕唑帕尼 +Abexinostat 的效果的体外分析

[0396] 帕唑帕尼 +abexinostat(PCI-24781) 组合的效果在 786-0 人肾癌细胞中进行分析。结果显示于图 1 中。连续三天向细胞施用该组合，之后测量阿拉玛蓝水平。

实施例 12：帕唑帕尼 +Abexinostat 的效果的体外分析

[0397] 帕唑帕尼 +abexinostat(PCI-24781) 组合的效果在 U2-OS 骨肉瘤细胞中进行分析。结果显示于图 2 中。连续三天向细胞施用该组合，之后测量阿拉玛蓝水平。

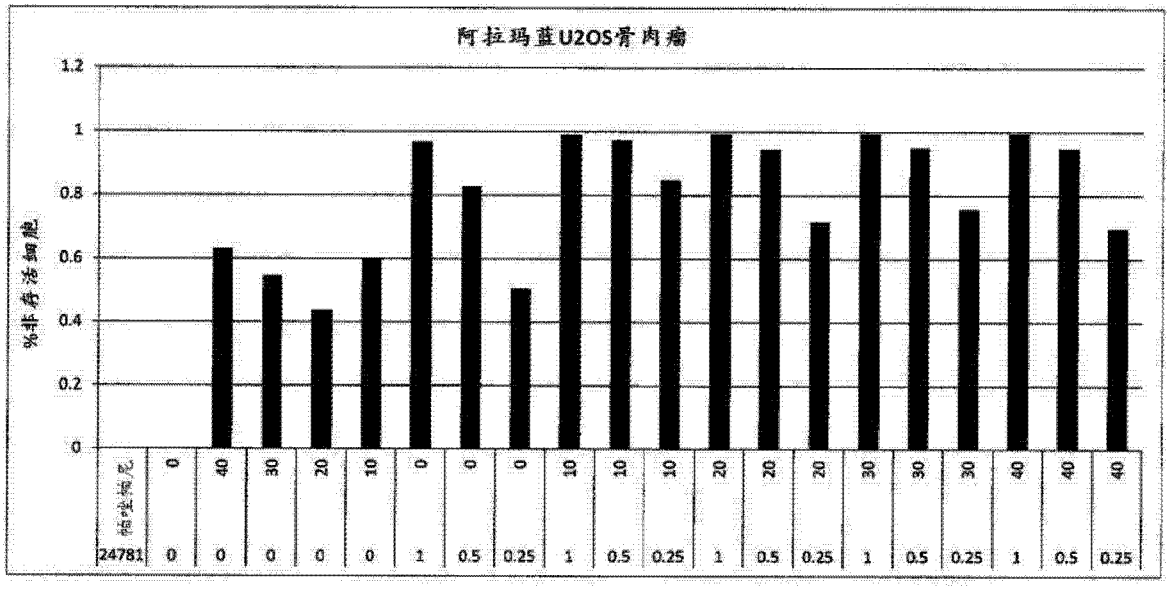
[0398] 在此描述的实施例和实施方案仅用于说明性目的，对本领域技术人员建议的各种修改或改变将包括在公开内容的精神和范围以及所附权利要求的范围内。本领域技术人员将会理解，上述实施例中列出的具体成分可以被替换为功能上等价的其它成分，例如，稀释剂、粘合剂、润滑剂、填充剂、包衣等等。



24781	帕唑帕尼	CI	24781	帕唑帕尼	CI	24781	帕唑帕尼	CI
0.25	5	0.883	0.5	5	0.817	1	5	0.719
0.25	10	0.516	0.5	10	0.604	1	10	0.526
0.25	20	0.608	0.5	20	0.623	1	20	0.406
0.25	30	0.315	0.5	30	0.37	1	30	0.373

3天连续处理，浓度单位为微摩尔

图 1



24781	帕唑帕尼	CI	24781	帕唑帕尼	CI	24781	帕唑帕尼	CI
0.25	10	0.489	0.5	10	0.446	1	10	#######
0.25	20	0.675	0.5	20	0.621	1	20	0.478
0.25	30	0.621	0.5	30	0.598	1	30	0.469
0.25	40	0.704	0.5	40	0.605	1	40	0.476

3天连续处理，浓度单位为微摩尔

图 2

Abstract

Dosing regimens, methods of treatment, controlled release formulations, and combination therapies that include an HDAC inhibitor, or a pharmaceutically acceptable salt thereof, and pazopanib (or a salt thereof; e.g., pazopanib HCl) are described.