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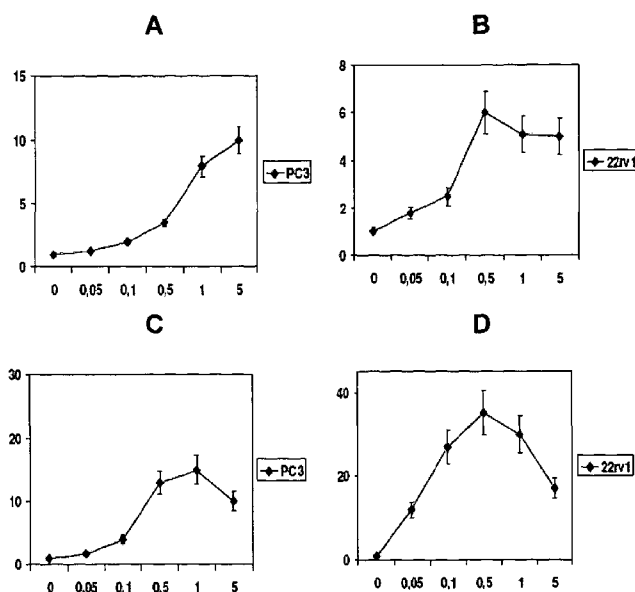
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(54) Title: COMBINATION TREATMENT EMPLOYING BELINOSTAT AND BICALUTAMIDE

FIGURE 1



(57) Abstract: The present invention relates generally to therapies for the treatment of diseases and disorders that are mediated by histone deacetylase (HDAC) (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.) which employ the synergistic combination of (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof.

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COMBINATION TREATMENT EMPLOYING
BELINOSTAT AND BICALUTAMIDE

RELATED APPLICATION

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This application is related to United States provisional patent application number 61/264,351 filed 25 November 2009, the contents of which are incorporated herein by reference in their entirety.

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TECHNICAL FIELD

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The present invention relates generally to therapies for the treatment of diseases and disorders that are mediated by histone deacetylase (HDAC) (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.) which employ the synergistic combination of (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof.

BACKGROUND

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A number of patents and publications are cited herein in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

25

Throughout this specification, including the claims which follow, unless the context requires otherwise, the word "comprise," and variations such as "comprises" and "comprising," will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

30

It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a pharmaceutical carrier" includes mixtures of two or more such carriers, and the like.

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Ranges are often expressed herein as from "about" one particular value, and/or to "about" another particular value. When such a range is expressed, another embodiment includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by the use of the antecedent "about," it will be understood that the particular value forms another embodiment.

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This disclosure includes information that may be useful in understanding the present invention. It is not an admission that any of the information provided herein is prior art or relevant to the presently claimed invention, or that any publication specifically or implicitly referenced is prior art.

Prostate Cancer

Prostate Cancer is a common cancer amongst males and a leading cause of cancer deaths beyond the age of 50. Prostate cancer begins as a tumour on the prostate gland. Tumours confined to the gland can often be treated successfully. If untreated, the cancer may spread to tissues near the prostate, to seminal vesicles, and to distant parts of the body, such as bones, liver and lungs.

It is known that androgen deprivation can slow the progression of cancers originating in the prostate. Androgen deprivation may be achieved by either surgical or chemical castration. The organ that is the primary source of male androgenic hormones is the testes. Surgical removal of the testes is known as orchiectomy: the majority of orchiectomy patients will experience diminished libido and erectile dysfunction. Other common side effects are weight gain, depression, fatigue, mood swings and hot flashes.

The benign prostatic epithelium as well as most prostatic adenocarcinomas (PCa) is dependent on androgens for the maintenance of proliferative potential as well as the inhibition of apoptosis. In fact, the dependence on androgens is the basis for androgen ablation therapy, the standard therapy for metastatic prostatic adenocarcinoma for the past 50 years. Unfortunately, the beneficial actions of existing endocrine measures are, in part, counteracted by the capacity of the tumour cells to eventually circumvent the use of steroid hormones, allowing them to continue to grow and progress despite such therapy. In fact, after a positive initial response, some tumours recur in an androgen-independent (AI) form. For these reasons, additional targets and therapies are needed in conjunction with androgen ablation.

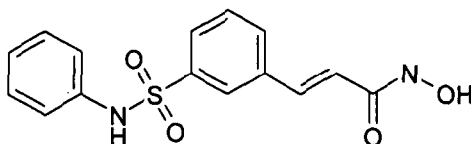
There is therefore a clear need for improved treatments for prostate cancer, and in particular, for androgen-independent prostate cancer and androgen receptor negative prostate cancer.

Belinostat

Belinostat (also known as (E)-N-hydroxy-3-(3-phenylsulfamoyl-phenyl)-acrylamide, PXD101, and PX 105684), shown below, is a well known histone deacetylase (HDAC) inhibitor. It was first described in Watkins et al., 2002. It is being developed for treatment

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of a range of disorders mediated by HDAC, and is the subject of a number of Phase I and Phase II trials for various cancers.



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Typically, liquid formulations of belinostat further comprise L-arginine, and are suitable for administration by injection, infusion, intravenous infusion, etc. See, for example, Bastin et al., 2006.

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Methods of treatment employing prolonged continuous infusion of belinostat are described, for example, in Sehested et al., 2009.

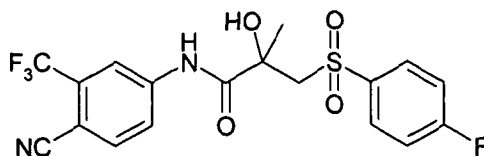
Bicalutamide

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Bicalutamide (also known as *N*-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide, and marketed as CasodexTM, CosudexTM, CalutideTM, and KalumidTM) is an oral non-steroidal anti-androgen used in the treatment of prostate cancer and hirsutism. It was first described in Tucker, 1984, and was first launched in 1995 as part of a combination treatment (with surgical or medical

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castration) for advanced prostate cancer. It was subsequently launched as a mono-therapy for the treatment of earlier stages of the disease.



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Bicalutamide has one chiral centre. The (R)-enantiomer is active, and the (S)-enantiomer is substantially inactive. Unless other specified, a reference herein to bicalutamide is to be understood to be a reference to (R)-bicalutamide, (S)-bicalutamide, as well as mixtures thereof (e.g., racemic bicalutamide).

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Bicalutamide (as the racemate) is marketed by AstraZeneca with the brand names CasodexTM and CosudexTM. The recommended dosage is 50 mg once daily in combination with a luteinizing hormone-releasing hormone analogue or surgical castration.

SUMMARY OF THE INVENTION

The present invention relates to the surprising and unexpected discovery that the combination of (a) belinostat, or a salt, hydrate, or solvate thereof and (b) bicalutamide, or a salt, hydrate, or solvate thereof, is synergistic in the treatment of diseases and disorders which are mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Thus, one aspect of the invention relates to a method of treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.) in a patient, comprising administering to said patient (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, in amounts such that the combination is therapeutically-effective.

Another aspect of the present invention relates to belinostat, or a salt, hydrate, or solvate thereof, for use, *in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention relates to belinostat, or a salt, hydrate, or solvate thereof, for use, *in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, in a method of treatment, for example, of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Another aspect of the present invention relates to bicalutamide, or a salt, hydrate, or solvate thereof, for use, *in combination with belinostat, or a salt, hydrate, or solvate thereof*, in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention relates to bicalutamide, or a salt, hydrate, or solvate thereof, for use, *in combination with belinostat, or a salt, hydrate, or solvate thereof*, in a method of treatment, for example, of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Another aspect of the present invention relates to use of belinostat, or a salt, hydrate, or solvate thereof, in the manufacture of a medicament, *for use in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, for the treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

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Another aspect of the present invention relates to use of bicalutamide, or a salt, hydrate, or solvate thereof, in the manufacture of a medicament, *for use in combination with belinostat, or a salt, hydrate, or solvate thereof*, for the treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g.,

5 androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

As will be appreciated by one of skill in the art, features and preferred embodiments of one aspect of the invention will also pertain to other aspects of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the dose-dependent effect of belinostat on histone acetylation measured at 24 hours in PC3 and 22rv1 cell lines. Panel A: H3/PC3. Panel B: H3/22rv1. Panel C: H4/PC3. Panel D: H4/22rv1. Each panel is a graph of degree of histone acetylation versus belinostat concentration (0, 0.05, 0.1, 0.5, 1, and 5 μ M).

Figure 2 illustrates the dose-dependent effect of belinostat on viable cells and mortality in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: Viable cells/PC3. Panel B: Dead cells/PC3. Panel C: Viable cells/22rv1. Panel D: Dead cells/22rv1. Each panel is a graph of viable cells ($\times 10^4$) (for A and C) or dead cells (% of total) (for B and D) versus days of culture for different belinostat concentrations (0, 0.1, 0.5, 1.0 and 5.0 μ M).

Figure 3 illustrates the dose-dependent effect of belinostat on cell cycle arrest, as shown by the G0/G1, G2/M, and S fractions, in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: PC3. Panel B: 22rv1. Each panel is pie chart showing the relative fractions of G0/G1, G2/M, and S fractions, for control, and three concentrations of belinostat (0, 0.1, 0.5, and 1.0 μ M).

Figure 4 illustrates the dose-dependent effect of belinostat on apoptosis in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: PC3. Panel B: 22rv1. Each panel is a graph of percentage of apoptotic cells versus belinostat concentration (0.0, 0.1, 0.5, and 1 μ M).

Figure 5 illustrates the dose-dependent effect of belinostat on a number of cellular proteins, for the 22rv1 cell line, measured at 24 hours. Each gel shows the levels for a particular protein (Cyclin A, Cyclin B1, Cdk1, p27, p21, p-P38MAPK, Bax, and BC12; β -actin is used as a loading control) versus belinostat concentration (0, 0.1, 0.5, 1.0, and 5.0 μ M).

Figure 6 illustrates the dose-dependent effect of belinostat on caspase-3 activity in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: PC3. Panel B: 22rv1. Each panel is a graph of caspase-3 activity (as compared to control) versus belinostat concentration (0.0, 0.1, 0.5, 1.0, and 5.0 μ M).

Figure 7 illustrates the dose-dependent effect of belinostat on a number of proteins, for the 22rv1 cell line, measured at 24 hours. Each gel shows the levels for a particular protein (active Caspase-3, active Caspase-8, active Caspase-9, PARP (and cleaved PARP); β -actin is used as a loading control) versus belinostat concentration (0, 0.1, 0.5, 1.0, and 5.0 μ M).

Figure 8 illustrates the dose-dependent anti-proliferative and apoptotic effects of belinostat on fetal bovine serum (FBS), charcoal-stripped fetal bovine serum (cFBS) and dihydrotestosterone (DHT) levels in 22rv1 (AR+, HRPC cell model) and LAPC-4 (AR+, hormone dependent) cell lines. Panel A: Proliferation/22rv1. Panel B: Proliferation/LAPC-4. Panel C: Apoptosis/22rv1. Panel D: Apoptosis/LAPC-4. Each panel shows a graph of percent versus control, for, from left to right, (a) FBS, (b) cFBS, and (c) DHT, as a function of belinostat concentration (0, 0.1, 0.5, and 1 μ M).

Figure 9 illustrates the effect of treatment with belinostat on the DNMT1, DNMT3a and DNMT3b expression in PC3 cells. Each gel shows the levels for a particular protein (DNMT1, DNMT3a and DNMT3b) versus days of treatment (0, 2, 8, and 15) with 0.5 μ M belinostat.

Figure 10 illustrates the effect of treatment with belinostat on the androgen receptor (AR) levels in PC3 cells. Each gel shows the level of androgen receptor (AR) (β -actin is used as a loading control) versus days of treatment (0, 2, 4, 6, 8, 12, 15, and 20) with 0.5 μ M belinostat.

Figure 11 illustrates the effect of treatment with belinostat on the androgen receptor (AR) levels. The gel shows the level of androgen receptor (AR) for each of four cell lines (LnCaP, LnCaP-104S, LnCaP-104R1, and LnCaP-C81) 48 hours after treatment with belinostat.

Figure 12 illustrates the time-dependent effect of treatment with belinostat on the androgen receptor (AR) levels. Each gel shows the level of androgen receptor (AR) for each of four cell lines (LnCaP, LnCaP-104S, LnCaP-104R1, and LnCaP-C81) after 0, 2, 8, and 15 days of treatment with 0.5 μ M belinostat.

Figure 13 illustrates the effects of belinostat pre-treatment on proliferation, in the presence or absence of the androgen DHT, in PC3 and (androgen independent) LnCaP-C81 cell lines. The bar-graph on the left is for PC3. The bar-graph on the right is for LnCaP-C81. Each bar-graph shows proliferation (percent of control) for, from left to right, (1) control, (2) FBS, (3) cFBS, and (4) DHT, where 0.5 μ M is present in each of (2), (3), and (4).

Figure 14 illustrates the dose-dependent effect of belinostat on a number of cellular proteins, for the 22rv1 cell line, measured at 24 hours. Each gel shows the levels for a particular protein (Acetyl-HSP90; HSP70, p-Akt, Akt, Her2, c-raf1, p-Erk, and Erk; β -actin is used as a loading control) versus belinostat concentration (0, 0.1, 0.5, 1.0, and 5.0 μ M).

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Figure 15 illustrates the dose-dependent effect of belinostat on tumour volume in PC3 and 22rv1 xenograft models. Panel A: 22rv1. Panel B: PC3. Each panel is a graph of tumour volume (mm^3) versus time (days) for control (vehicle), 20 mg/kg bid belinostat, and 40 mg/kg bid belinostat.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the surprising and unexpected discovery that the combination of (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, is synergistic in the treatment of diseases and disorders which are mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Thus, one aspect of the invention relates to a method of treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.) in a patient, comprising administering to said patient (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, in amounts such that the combination is therapeutically-effective.

Another aspect of the present invention relates to belinostat, or a salt, hydrate, or solvate thereof, for use, *in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention relates to belinostat, or a salt, hydrate, or solvate thereof, for use in combination with bicalutamide, or a salt, hydrate, or solvate thereof, in a method of treatment, for example, of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Another aspect of the present invention relates to bicalutamide, or a salt, hydrate, or solvate thereof, for use, *in combination with belinostat, or a salt, hydrate, or solvate thereof*, in a method of treatment of the human or animal body by therapy.

Another aspect of the present invention relates to bicalutamide, or a salt, hydrate, or solvate thereof, for use in combination with belinostat, or a salt, hydrate, or solvate thereof, in a method of treatment, for example, of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Another aspect of the present invention relates to use of belinostat, or a salt, hydrate, or solvate thereof, in the manufacture of a medicament, *for use in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, for the treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

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Another aspect of the present invention relates to use of bicaltamide, or a salt, hydrate, or solvate thereof, in the manufacture of a medicament, *for use in combination with belinostat, or a salt, hydrate, or solvate thereof*, for the treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g.,
5 androgen-insensitive prostate cancer, androgen receptor negative prostate cancer, etc.).

Treatment Order and Timing

Typically, the treatment is performed over one or more treatment cycles, wherein the
10 active agents, (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, are administered to the patient over the course of each of said treatment cycles.

Within a treatment cycle, the active agents, (a) belinostat, or a salt, hydrate, or solvate
15 thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, may be administered simultaneously, or sequentially.

The treatment may comprise one treatment cycle, or two or more treatment cycles, which may be the same or different. For example, if there are two treatment cycles, they may,
20 independently, have the same or different duration, the same or different treatment order, the same or different dosages, etc.

The number of treatment cycles may be, for example, from 2 to 6 (e.g., 2, 3, 4, 5, 6); for example, from 2 to 3 cycles; from 2 to 4 cycles; from 2 to 5 cycles; from 2 to 6 cycles;
25 from 3 to 4 cycles; from 3 to 5 cycles; from 3 to 6 cycles; from 4 to 5 cycles; from 4 to 6 cycles; etc.

Any or each treatment cycle may be, for example, from 3 to 49 days in length; for example, about 3 days in length; about 7 days in length; about 14 days in length; about
30 21 days in length, about 28 days in length; about 35 days in length, about 42 days in length, about 49 days in length, etc.

Dosage

It will be appreciated by one of skill in the art that appropriate dosages of the active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof), and compositions comprising the active agents, can vary from patient to patient.
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Determining the optimal dosages will generally involve the balancing of the level of therapeutic benefit against any risk or deleterious side effects. The selected dosage
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5 levels will depend on a variety of factors including, but not limited to, the activity of the agents, the route of administration, the time of administration, the rate of excretion of the agents, the duration of the treatment, other drugs, compounds, and/or materials used in combination, the severity of the condition, and the species, sex, age, weight, condition, general health, and prior medical history of the patient.

10 The amounts and routes of administration will ultimately be at the discretion of the physician, veterinarian, or clinician, although generally the dosages will be selected to achieve local concentrations at the site of action which achieve the desired effect without causing substantial harmful or deleterious side-effects.

Route of Administration

15 In one embodiment, one or both active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof) is administered parenterally.

20 In one embodiment, one or both active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof) is administered intravenously.

25 In one embodiment, one or both active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof) is administered by intravenous infusion.

In one embodiment, one or both active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof) is administered orally.

30 "Infusion" differs from "injection" in that the term "infusion" describes the passive introduction of a substance (e.g., a fluid, electrolyte, etc.) into a vein or tissues by gravitational force, whereas the term "injection" describes the active introduction of a substance into a vein or tissues by additional forces, e.g., the pressure in a syringe. Intravenous infusion is often referred to as "intravenous drip" or "i.v. drip".

Administration of Belinostat

In one embodiment, the belinostat, or a salt, hydrate, or solvate thereof, is administered parenterally.

40 In one embodiment, the belinostat, or a salt, hydrate, or solvate thereof, is administered intravenously.

In one embodiment, the belinostat, or a salt, hydrate, or solvate thereof, is administered by intravenous infusion.

- 5 In one embodiment, the belinostat, or a salt, hydrate, or solvate thereof, is administered by prolonged intravenous infusion.

In one embodiment, the belinostat, or a salt, hydrate, or solvate thereof, is administered by prolonged continuous intravenous infusion.

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By "prolonged", it is intended that the intravenous infusion is for a period of at least about 12 hours.

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By "continuous", it is intended that the intravenous infusion is substantially uninterrupted, that is, continuous except for the requirements of administration, for example, the need to change reservoirs, i.v. bags, etc.

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In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of about 12 hours; of about 16 hours; of about 24 hours; of about 36 hours; of about 48 hours; of about 60 hours; or about 78 hours.

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In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of at least about 12 hours, for example, a period of from 12 to 24 hours, a period of from 12 to 48 hours, a period of from 12 to 60 hours, a period of from 12 to 72 hours, a period of from 12 to 96 hours, etc.

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In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of at least about 16 hours, for example, a period of from 16 to 24 hours, a period of from 16 to 48 hours, a period of from 16 to 64 hours, a period of from 16 to 72 hours, a period of from 16 to 96 hours, etc.

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In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of at least about 24 hours, for example, a period of from 24 to 48 hours, a period of from 24 to 72 hours, a period of from 24 to 96 hours etc.

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In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of at least about 36 hours, for example, a period of from 36 to 48 hours, a period of from 36 to 72 hours, a period of from 36 to 96 hours etc.

In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of at least about 48 hours, for example, a period of from 48 to 72 hours, a period of from 48 to 96 hours etc.

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In one embodiment, the intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion) is for a period of at least 72 hours, for example, a period of from 72 to 96 hours etc.

10 Criteria for determining a suitable dosage of belinostat, or a salt, hydrate, or solvate thereof are discussed above under the heading "Dosage".

However, in general, a suitable dose of belinostat will be in the range of 100-2500 mg/m²/d, for example from 500-1500 mg/m²/d. Where the belinostat is provided as a salt, hydrate, or solvate, the amount administered is calculated on the basis of the parent compound and so the actual weight to be used is increased proportionately.

15 In one embodiment, for intravenous infusion (e.g., prolonged intravenous infusion, e.g., prolonged continuous intravenous infusion), the dosage during intravenous infusion is from 100 to 2500 mg/m²/d of belinostat. In one embodiment, the dosage during intravenous infusion is from 500 to 1500 mg/m²/d of belinostat.

In one embodiment, the invention employs belinostat or a salt, hydrate, or solvate thereof.

25 It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of belinostat, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts," *J. Pharm. Sci.*, Vol. 66, pp. 1-19.

30 Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na⁺ and K⁺, alkaline earth cations such as Ca²⁺ and Mg²⁺, and other cations such as Al³⁺. Examples of suitable organic cations include, but are not limited to, ammonium ion (i.e., NH₄⁺) and substituted ammonium ions (e.g., NH₃R⁺, NH₂R₂⁺, NHR₃⁺, NR₄⁺).

35 Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is N(CH₃)₄⁺.

Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

5 Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetyoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, 10 palmitic, pantoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

15 It may be convenient or desirable to prepare, purify, and/or handle a corresponding solvate of belinostat. The term "solvate" is used herein in the conventional sense to refer to a complex of solute (e.g., belinostat, salt of belinostat) and solvent. If the solvent is water, the solvate may be conveniently referred to as a hydrate, for example, a mono-hydrate, a di-hydrate, a tri-hydrate, etc.

20 In one preferred embodiment, the invention employs belinostat.

The belinostat may be provided in a formulation suitable for parenteral administration, for example, a formulation suitable for administration by intravenous administration, e.g., 25 intravenous infusion. Guidance for suitable parenteral formulations is provided, for example, in Avis et al., 1992.

The belinostat (or a salt, hydrate, or solvate thereof) may be presented as a pharmaceutical formulation (e.g., composition, preparation, medicament) suitable for 30 administration by intravenous administration, e.g., intravenous infusion, and comprising belinostat (or a salt, hydrate, or solvate thereof), together with one or more other pharmaceutically acceptable ingredients well known to those skilled in the art, including, but not limited to, pharmaceutically acceptable carriers, diluents, excipients, adjuvants, buffers, preservatives, anti-oxidants, stabilisers, solubilisers, surfactants (e.g., wetting 35 agents), etc. The formulation may further comprise other active agents, for example, other therapeutic or prophylactic agents.

The term "pharmaceutically acceptable," as used herein, pertains to compounds, ingredients, materials, compositions, dosage forms, etc., which are, within the scope of 40 sound medical judgment, suitable for use in contact with the tissues of the subject in question (e.g., mammal, human) without excessive toxicity, irritation, allergic response, or

other problem or complication, commensurate with a reasonable benefit/risk ratio. Each carrier, diluent, excipient, etc. must also be "acceptable" in the sense of being compatible with the other ingredients of the formulation.

5 Suitable carriers, diluents, excipients, etc. can be found in standard pharmaceutical texts, for example, Remington's Pharmaceutical Sciences, 18th edition, Mack Publishing Company, Easton, Pa., 1990; and Handbook of Pharmaceutical Excipients, 5th edition, 2005.

10 The formulation may be prepared by any methods well known in the art of pharmacy.

 The formulation may be prepared to provide for rapid or slow release; immediate, delayed, timed, or sustained release; or a combination thereof. The belinostat, or a formulation comprising the belinostat, may be presented in a liposome or other
15 microparticulate which is designed to target the belinostat, for example, to blood components or one or more organs.

 The formulation may suitably be in the form of a liquid, a solution (e.g., aqueous, non-aqueous), a suspension (e.g., aqueous, non-aqueous), an emulsions (e.g., oil-in-water, water-in-oil), etc.
20

 Formulations suitable for parenteral administration (e.g., by injection), include aqueous or non-aqueous, isotonic, pyrogen-free, sterile liquids (e.g., solutions, suspensions), in which the belinostat is dissolved, suspended, or otherwise provided (e.g., in a liposome or
25 other microparticulate). Such liquids may additionally contain other pharmaceutically acceptable ingredients, such as anti-oxidants, buffers, preservatives, stabilisers, bacteriostats, suspending agents, thickening agents, and solutes which render the formulation isotonic with the blood (or other relevant bodily fluid) of the intended recipient. Examples of excipients include, for example, water, alcohols, polyols, glycerol, vegetable
30 oils, and the like. Examples of suitable isotonic carriers for use in such formulations include Sodium Chloride Injection, Ringer's Solution, or Lactated Ringer's Injection. The formulations may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately
35 prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets.

 The preferred active ingredient, belinostat, is sparingly soluble in water at physiological pH, and so must be administered in a pharmaceutical formulation where the belinostat is
40 freely soluble and the composition is well tolerated, for example, in combination with L-arginine, as described in Bastin et al., 2006.

In one embodiment, the belinostat (or a salt, hydrate, or solvate thereof) is provided in a formulation suitable for parenteral administration (e.g., intravenous infusion) further comprising L-arginine.

5

Typically, parenteral formulations (i.e., formulations suitable for parenteral administration, e.g., intravenous infusion) are typically packaged in plastic or glass large volume parenteral (LVP) containers to which is attached a suitable intravenous (i.v.) set at the time of infusion. Venous entry is typically by a metal needle or plastic catheter.

10

A continuous infusion system provides continuous regulated fluid flow at a pre-set rate. Once a prescribed flow rate (e.g., 125 mL/hr) has been established, the fluid should continue to flow accurately from the system until the reservoir container has emptied.

15

The infusion may be infused according to a continuous or intermittent dose schedule. A continuous schedule typically involves the non-stop infusion of a relatively large volume of fluid (e.g., 1 litre per 8 hour period for adults). Continuous therapy typically additionally provides fluid, electrolytes, agents to adjust acid-base balance, nutrients, and some other drugs. The total fluid intake must not exceed the patient's requirements (approximately 2400 mL per day for an adult).

20

Accordingly, the belinostat (or a salt, hydrate, or solvate thereof) may be formulated for parenteral administration, and may be presented, for example, in unit dose form in ampoules, pre-filled syringes, small volume infusion containers, or multi-dose containers optionally with an added preservative. The formulations may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulation agents such as suspending agents, stabilising agents, dispersing agents, etc.

25

For example, the belinostat may be provided as a concentrate for solution for infusion containing 50 mg/mL of belinostat and 100 mg/mL L-arginine, in water-for-injection, at a pH of 9.0-9.9. Immediately before administration, the concentrate is diluted, for example, with water-for-injection, glucose solution, or sodium chloride solution.

30

Alternatively, the belinostat may be formulated for oral administration, for example, at hard gelatin capsules (e.g., size 00) filled with belinostat (e.g., 250 mg).

35

Administration of Bicalutamide

Formulations of bicalutamide (or a salt, hydrate, or solvate thereof) which are suitable for administration (e.g., parenterally, orally) are well-known in the art.

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In one embodiment, the bicalutamide (or a salt, hydrate, or solvate thereof) is administered orally.

5 Criteria for determining a suitable dosage of bicalutamide (or a salt, hydrate, or solvate thereof) are discussed above under the heading "Dosage".

10 In addition, acceptable dosages of bicalutamide (or a salt, hydrate, or solvate thereof) are well-known in the art, both in the context of treatments using bicalutamide alone, and combination treatments using bicalutamide with other active agents or therapies.

In one embodiment, the dosage of bicalutamide corresponds to any of the well-known or standard dosages of bicalutamide known in the art.

15 In one embodiment, the dosage of bicalutamide is from 50 to 150 mg once daily, by oral administration.

In one embodiment, the dosage of bicalutamide is 50 mg once daily, by oral administration.

20 Conditions Treated

In one embodiment, the disease or disorder is a disease or disorder which is mediated by HDAC.

25 In one embodiment, the disease or disorder is a disease or disorder which is treatable or known to be treatable with an HDAC inhibitor.

In one embodiment, the disease or disorder is a proliferative condition.

30 In one embodiment, the disease or disorder is a tumour.

In one embodiment, the disease or disorder is a solid tumour.

In one embodiment, the disease or disorder is cancer.

35 In one embodiment, the disease or disorder is solid tumour cancer.

40 In one embodiment, the disease or disorder is lung cancer, prostate cancer, renal cancer, hepatoma, bladder cancer, colorectal cancer, pancreatic cancer, gastric cancer, breast cancer, ovarian cancer, soft tissue sarcoma, osteosarcoma, hepatocellular carcinoma, skin cancer, leukaemia, or lymphoma.

In one embodiment, the disease or disorder is prostate cancer.

In one embodiment, the disease or disorder is androgen-insensitive prostate cancer.

In one embodiment, the disease or disorder is androgen receptor negative prostate cancer.

The Patient

In one embodiment, the patient is a mammal, i.e., a living mammal. In one embodiment, the patient is a human, i.e., a living human, including a living human foetus, a living human child, and a living human adult.

Treatment

The term "treatment," as used herein in the context of treating a condition, pertains generally to treatment and therapy, whether of a human or an animal (e.g., in veterinary applications), in which some desired therapeutic effect is achieved, for example, the inhibition of the progress of the condition, and includes a reduction in the rate of progress, a halt in the rate of progress, amelioration of the condition, and cure of the condition. Treatment as a prophylactic measure (i.e., prophylaxis) is also included. For example, use with subjects who have not yet developed the condition, but who are at risk of developing the condition, is encompassed by the term "treatment."

For example, treatment of a tumour may indicated by tumour reduction.

For leukaemia, "tumour reduction" may be indicated by a reduction in blast cells (e.g., the number of blast cells, the percentage of blast cells) in the blood (e.g., peripheral blood) and/or the reduction of blast cells (e.g., the number of blast cells, the percentage of blast cells) in the bone marrow.

For solid tumours, "tumour reduction" may be indicated by a reduction of tumour mass, for example, as determined by radiographic examination (e.g., using PET and/or NMR methods) or by physical examination.

The term "therapeutically-effective amount," as used herein, pertains to the amounts of the active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof) that is effective for producing some desired therapeutic effect, commensurate with a reasonable benefit/risk ratio, when administered in accordance with a desired treatment regimen.

The term "treatment" includes combination treatments and therapies, in which two or more treatments or therapies are combined, for example, sequentially or simultaneously. For example, the active agents (belinostat, or a salt, hydrate, or solvate thereof; and bicalutamide, or a salt, hydrate, or solvate thereof) may also be used in further combination therapies, e.g., in conjunction with other agents, for example, other cytotoxic agents, etc. Examples of further treatments and therapies include, but are not limited to, chemotherapy (the administration of other active agents, including, e.g., other HDAC inhibitors, antibodies (e.g., as in immunotherapy), prodrugs (e.g., as in photodynamic therapy, GDEPT, ADEPT, etc.); surgery; radiation therapy; and gene therapy.

Kits

One aspect of the invention pertains to a kit comprising (a) belinostat (or a salt, hydrate, or solvate thereof), or a composition comprising belinostat (or a salt, hydrate, or solvate thereof), e.g., preferably provided in a suitable container and/or with suitable packaging; and (b) instructions for use, e.g., written instructions on how to administer the compound or composition in accordance with the present invention, for example, in combination with bicalutamide (or a salt, hydrate, or solvate thereof).

In one embodiment, the kit *further comprises*: (b) bicalutamide, or a salt, hydrate, or solvate thereof, or a composition comprising bicalutamide, or a salt, hydrate, or solvate thereof, e.g., preferably provided in a suitable container and/or with suitable packaging.

The written instructions may also include a list of indications for which the active ingredient(s) is/are a suitable treatment.

EXAMPLES

The following examples are provided solely to illustrate the present invention and are not intended to limit the scope of the invention, as described herein.

5

Study 1

In Vitro Studies using Belinostat

10

15

Seven (7) prostate cancer cell lines and three (3) androgen-deprived LnCaP cell derivatives (LnCaP-104S, LnCaP-104R1, and LnCaP-C81) were cultured in vitro in the presence of different concentrations of belinostat, alone or in combination with androgens or anti-androgens in order to evaluate: viability (using a trypan blue exclusion assay and/or extracellular LDH release), proliferation/cytotoxicity (using cell count, MTT assay and 3H-Thymidine uptake), senescence (using beta-galactosidase assay), apoptosis (using FACS, oligonucleosomal DNA fragmentation, enzymatic determination of caspases, and western blot analyses).

20

Belinostat was able to induce acetylation of histones H3 and H4 in a time and dose-dependent manner. With increasing belinostat exposure, an increased percentage of apoptotic cells was observed, which was preceded by an accumulation of cells in G2/M cell phase accompanied by comparative decreases in the G0/G1 and particularly S fractions. HDACi-induced G2/M arrest was associated with reduced expression of cyclins A and B as well as of Cdk1, key components for G2-M transition, and the increased expression of the Cdk inhibitors p21 and p27.

25

Belinostat triggered caspase-3 activity and PARP cleavage in a dose dependent manner both in PC3 and 22rv1. Increase in caspase-3 activity in PC3 and 22rv1 cells was associated with reduced Bcl2 and Bcl-XL expression, as well as with increased caspase-8 activity.

30

Figure 1 illustrates the dose-dependent effect of belinostat on histone acetylation measured at 24 hours in PC3 and 22rv1 cell lines. Panel A: H3/PC3. Panel B: H3/22rv1. Panel C: H4/PC3. Panel D: H4/22rv1. Each panel is a graph of degree of histone acetylation versus belinostat concentration (0, 0.05, 0.1, 0.5, 1, and 5 μ M).

35

Figure 2 illustrates the dose-dependent effect of belinostat on viable cells and mortality in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: Viable cells/PC3. Panel B: Dead cells/PC3. Panel C: Viable cells/22rv1. Panel D: Dead cells/22rv1. Each panel is a graph of viable cells ($\times 10^4$) (for A and C) or dead cells (% of total) (for B and D) versus days of culture for different belinostat concentrations (0, 0.1, 0.5, 1.0 and 5.0 μ M).

40

Figure 3 illustrates the dose-dependent effect of belinostat on cell cycle arrest, as shown by the G0/G1, G2/M, and S fractions, in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: PC3. Panel B: 22rv1. Each panel is pie chart showing the relative fractions of G0/G1, G2/M, and S fractions, for control, and three concentrations of belinostat (0.1, 0.5, and 1.0 μ M).

Figure 4 illustrates the dose-dependent effect of belinostat on apoptosis in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: PC3. Panel B: 22rv1. Each panel is a bar graph of percentage of apoptotic cells versus belinostat concentration (0.0, 0.1, 0.5, and 1 μ M).

Figure 5 illustrates the dose-dependent effect of belinostat on a number of cellular proteins, for the 22rv1 cell line, measured at 24 hours. Each gel shows the levels for a particular protein (Cyclin A, Cyclin B1, Cdk1, p27, p21, p-P38MAPK, Bax, and BC12; β -actin is used as a loading control) versus belinostat concentration (0, 0.1, 0.5, 1.0, and 5.0 μ M).

Figure 6 illustrates the dose-dependent effect of belinostat on caspase-3 activity in PC3 and 22rv1 cell lines, measured at 24 hours. Panel A: PC3. Panel B: 22rv1. Each panel is a graph of caspase-3 activity (as compared to control) versus belinostat concentration (0.0, 0.1, 0.5, 1.0, and 5.0 μ M).

Figure 7 illustrates the dose-dependent effect of belinostat on a number of proteins, for the 22rv1 cell line, measured at 24 hours. Each gel shows the levels for a particular protein (active Caspase-3, active Caspase-8, active Caspase-9, PARP (and cleaved PARP); β -actin is used as a loading control) versus belinostat concentration (0, 0.1, 0.5, 1.0, and 5.0 μ M).

Data regarding the effect of belinostat in various prostate cancer cell lines and LnCaP cells lines is summarised in Table 1 below. The values of IC20 and IC50 (Inhibition Concentration at 20% and 50%, respectively) and the values of EC20 and EC50 (Effective Dose at 20% and 50%, respectively) were obtained by the software Grafit (Erithacus Corp., UK) and expressed as mean $\pm$ standard deviation.

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Table 1								
The effects of belinostat in prostate cancer cell lines and LnCaP cell lines								
Cell Line	Proliferation		Vitality		Apoptosis		Senescence	
	IC20 (μ M)	IC50 (μ M)	ED20 (μ M)	ED50 (μ M)	ED20 (μ M)	ED50 (μ M)	ED20 (μ M)	ED50 (μ M)
PC3	0.31 $\pm$ 0.07	1.35 $\pm$ 0.32	0.97 $\pm$ 0.15	N.D.	3.16 $\pm$ 0.92	N.D.	0.62 $\pm$ 0.15	2.79 $\pm$ 0.52
LnCaP	0.17 $\pm$ 0.02	0.84 $\pm$ 0.16	0.48 $\pm$ 0.06	2.66 $\pm$ 0.48	1.25 $\pm$ 0.33	N.D.	0.23 $\pm$ 0.06	1.05 $\pm$ 0.64
LnCaP-104S	0.42 $\pm$ 0.06	1.05 $\pm$ 0.46	0.55 $\pm$ 0.06	3.16 $\pm$ 0.62	1.84 $\pm$ 0.65	N.D.	0.28 $\pm$ 0.08	0.95 $\pm$ 0.24
LnCaP-104R-1	0.66 $\pm$ 0.21	1.84 $\pm$ 0.54	0.59 $\pm$ 0.12	3.44 $\pm$ 1.03	2.54 $\pm$ 0.48	N.D.	0.32 $\pm$ 0.04	0.78 $\pm$ 0.12
LnCaP-C81	0.44 $\pm$ 0.17	1.65 $\pm$ 0.48	0.93 $\pm$ 0.23	2.95 $\pm$ 0.82	2.72 $\pm$ 0.24	N.D.	0.35 $\pm$ 0.05	1.26 $\pm$ 0.44
22rv1	0.54 $\pm$ 0.11	3.23 $\pm$ 0.28	0.87 $\pm$ 0.26	N.D.	2.14 $\pm$ 0.47	N.D.	0.84 $\pm$ 0.07	3.88 $\pm$ 0.65
LAPC-4	0.28 $\pm$ 0.09	0.68 $\pm$ 0.15	0.35 $\pm$ 0.11	2.84 $\pm$ 0.62	1.84 $\pm$ 0.57	N.D.	0.52 $\pm$ 0.11	1.57 $\pm$ 0.44
DU145	0.58 $\pm$ 0.22	1.37 $\pm$ 0.37	1.17 $\pm$ 0.44	N.D.	2.04 $\pm$ 0.55	N.D.	0.28 $\pm$ 0.08	1.87 $\pm$ 0.57
DuCaP	0.18 $\pm$ 0.03	0.62 $\pm$ 0.17	0.92 $\pm$ 0.25	1.65 $\pm$ 0.46	1.05 $\pm$ 0.26	N.D.	0.37 $\pm$ 0.04	1.36 $\pm$ 0.43
VCaP	0.33 $\pm$ 0.06	1.94 $\pm$ 0.53	1.35 $\pm$ 0.24	3.94 $\pm$ 0.72	3.24 $\pm$ 0.78	N.D.	1.25 $\pm$ 0.34	3.66 $\pm$ 0.78

N.D. = not detectable.

Study 2

5

In Vitro Studies of Belinostat in Combination with Hormone Manipulation

The effects of belinostat in combination with hormone manipulation were also examined.

10

Antiproliferative and pro-apoptotic effects of belinostat were higher in charcoal-stripped serum (cFBS, which mimics androgen deprivation therapy) when compared to culture in presence of FBS. Physiological concentration of 5 α -dihydrotestosterone (DHT) (1 nM) increased the proliferation of 22rv1 and LAPC-4, decreasing the efficacy of belinostat.

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Figure 8 illustrates the dose-dependent anti-proliferative and apoptotic effects of belinostat on fetal bovine serum (FBS), charcoal-stripped fetal bovine serum (cFBS) and dihydrotestosterone (DHT) levels in 22rv1 (AR+, HRPC cell model) and LAPC-4 (AR+, hormone dependent) cell lines. Panel A: Proliferation/22rv1. Panel B: Proliferation/LAPC-4. Panel C: Apoptosis/22rv1. Panel D: Apoptosis/LAPC-4. Each panel shows a graph of percent versus control, for, from left to right, (a) FBS, (b) cFBS, and (c) DHT, as a function of belinostat concentration (0, 0.1, 0.5, and 1 μ M).

Study 3

In Vitro Studies using Belinostat in combination with Bicalutamide

Belinostat combined with the specific androgen receptor antagonist bicalutamide (5 μ M) caused synergistic suppression of cell growth and induction of cell death according to the isobole method (i.e., CI < 1) in androgen-independent prostate cancer cells. The data summarised in Table 2 illustrate the effects of combined treatment in the androgen-independent LnCaP-C81 cell line.

Table 2						
Comparison of single and combination treatment in LaCaP-C81 cell line						
Treatment A (bicalutamide)		Treatment B (belinostat)		Combination Treatment (bicalutamide and belinostat)		
Dose (μ M)	GI	Dose (μ M)	GI	Expected GI	Observed GI	Increment (CI)
0.5	0.95	0.1	0.90	0.85	0.44	1.93 (0.52)
		0.2	0.75	0.70	0.30	2.33 (0.43)
1.0	0.90	0.1	0.90	0.80	0.31	2.58 (0.39)
		0.2	0.75	0.65	0.20	3.25 (0.31)
10.0	0.70	0.1	0.90	0.60	0.15	4.00 (0.25)
		0.2	0.75	0.45	0.10	4.50 (0.22)

GI = Growth Inhibition. CI = Combination Index.

Study 4

In Vitro Studies using Belinostat in combination with Bicalutamide

This study examined the chronic effects of belinostat, specifically, sensitization of androgen receptor negative PC3 cells to the DHT proliferative effects after restoration of the expression of the androgen receptor.

Although apoptotic machinery was induced at higher doses, a significant phenomenon associated with the use of HDAC inhibitors is the therapeutic effect of low doses

administered as a chronic treatment regimen. It was observed that treatment with belinostat at IC20 doses for 10-15 days was able to sustain an important apoptosis which followed the increment of beta galactosidase activity (senescence index) and the re-expression of some silenced gene products due to the down-modulation of the expression of DNMT1 and DNMT3b. The down-modulation of DNMT activity by 5-azacitidine restored the expression of the androgen receptor in PC3 cells (see, e.g., Gravina et al., 2008).

Figure 9 illustrates the effect of treatment with belinostat on the DNMT1, DNMT3a and DNMT3b expression in PC3 cells. Each gel shows the levels for a particular protein (DNMT1, DNMT3a and DNMT3b) versus days of treatment (0, 2, 8, and 15) with 0.5 μ M belinostat.

Western blotting analyses revealed that androgen receptor re-expression were observed also after pre-treatment with belinostat in PC3 cells.

Figure 10 illustrates the effect of treatment with belinostat on the androgen receptor (AR) levels in PC3 cells. Each gel shows the level of androgen receptor (AR) (β -actin is used as a loading control) versus days of treatment (0, 2, 4, 6, 8, 12, 15, and 20) with 0.5 μ M belinostat.

Hormone refractory disease is associated with increased expression and activity of androgen receptor as demonstrated in LnCaP after androgen deprivation therapy in androgen independent cell derivatives (LnCaP-104S, LnCaP-104R1, and LnCaP-C81).

Figure 11 illustrates the effect of treatment with belinostat on the androgen receptor (AR) levels. The gel shows the level of androgen receptor (AR) for each of four cell lines (LnCaP, LnCaP-104S, LnCaP-104R1, and LnCaP-C81) 48 hours after treatment with belinostat.

Belinostat was able to reduce the expression of androgen receptor in androgen receptor positive hormone sensitive or refractory cells including 22rv1 and androgen depleted LnCaP cell derivatives.

Figure 12 illustrates the time-dependent effect of treatment with belinostat on the androgen receptor (AR) levels. Each gel shows the level of androgen receptor (AR) for each of four cell lines (LnCaP, LnCaP-104S, LnCaP-104R1, and LnCaP-C81) after 0, 2, 8, and 15 days of treatment with 0.5 μ M belinostat.

Nevertheless, DHT increased the proliferative rate in PC3, 22rv1 and androgen depleted LnCaP cell derivatives pre-treated for 15 days with 0.5 μ M belinostat.

Figure 13 illustrates the effects of belinostat pre-treatment on proliferation, in the presence or absence of the androgen DHT, in PC3 and (androgen independent) LnCaP-C81 cell lines. The bar-graph on the left is for PC3. The bar-graph on the right is for LnCaP-C81. Each bar-graph shows proliferation (percent of control) for, from left to right, (1) control, (2) FBS, (3) cFBS, and (4) DHT, where 0.5 μ M is present in each of (2), (3), and (4).

This suggests that belinostat could effectively act synergistically to sensitize cells to hormone manipulation. To this end, cells were pre-treated for 10 days with 0.5 μ M belinostat, and then bicalutamide was added to cultures. Effectively, pre-treatment with belinostat synergistically sensitized the cells to bicalutamide effects. The results are summarized in Table 3 for PC3 and LnCaP-C81 cell lines.

Table 3						
Pharmacological parameters of in vitro pre-treatment with 0.5 μ M belinostat (BST) and sensitivity to bicalutamide (BCLT) in PC3 and LnCaP-C81 cell lines						
	Proliferation (Growth Inhibition, GI)			Apoptosis (% apoptotic cells)		
	0.5 μ M BCLT	1.0 μ M BCLT	10.0 μ M BCLT	0.5 μ M BCLT	1.0 μ M BCLT	10.0 μ M BCLT
<i>PC3</i>						
Without BST pre-treatment	0.95	1.05	1.00	< 2	< 2	< 2
With BST pre-treatment	0.65	0.40	0.40	5 $\pm$ 1	20 $\pm$ 4	35 $\pm$ 4
<i>LaCaP-C81</i>						
Without BST pre-treatment	1.05	1.0	1.0	< 2	< 2	< 2
With BST pre-treatment	0.70	0.45	0.30	25 $\pm$ 5	37 $\pm$ 4	39 $\pm$ 6

In addition, belinostat was able to reduce the expression of different growth factor receptors involved in the ligand-independent (androgen-independent) trans-activation including Her2. This effect may be mediated by increased ubiquitination linked to increased HSP-90 acetylation as demonstrated in 22rv1.

Figure 14 illustrates the dose-dependent effect of belinostat on a number of cellular proteins, for the 22rv1 cell line, measured at 24 hours. Each gel shows the levels for a particular protein (Acetyl-HSP90; HSP70, p-Akt, Akt, Her2, c-raf1, p-Erk, and Erk; β -actin is used as a loading control) versus belinostat concentration (0, 0.1, 0.5, 1.0, and 5.0 μ M).

Study 5In Vivo Studies of Belinostat in 22rv1 and PC3 Prostate Xenograft Models

- 5 Male CD1 nude mice received sub-cutaneous flank injections of 1×10^6 PC3 or 22rv1 cells. Tumour growth was assessed by measurement of tumour diameters with a Vernier calliper (length x width). Treatments were started when tumour volumes reached about 80 mm^3 (Day 0).
- 10 Figure 15 illustrates the dose-dependent effect of belinostat on tumour volume in PC3 and 22rv1 xenograft models. Panel A: 22rv1. Panel B: PC3. Each panel is a graph of tumour volume (mm^3) versus time (days) for control (vehicle), 20 mg/kg bid belinostat, and 40 mg/kg bid belinostat.
- 15 Additional data are summarised in the Table 4 below.

Table 4								
Anti-tumour activity of belinostat in 22rv1 and PC3 xenografts								
	PC3 Xenograft				22rv1 Xenograft			
	Saline	Belinostat			Saline	Belinostat		
Dose (mg/kg bid)	-	20	40	Stat.	-	20	40	Stat.
Weight of Mice (g)	25.0 ± 2.1	24.4 ± 1.7	23.0 ± 2.3	P= 0.100	25.3 $\pm$ 1.8	24.1 ± 2.0	24.0 ± 1.4	P= 0.200
Tumour weight (mg)	585 ± 235	388 ± 180	314 ± 117	P= 0.008	652 $\pm$ 200	365 ± 133	218 ± 125	P< 0.001
TGD (days)	-	7.5	14.4	-	-	11.6	16.0	-
PI (Ki67, %)	37.3 ± 4.5	24.4 ± 2.7	14.7 ± 1.3	P< 0.001	45.5 $\pm$ 6.5	18.8 ± 0.7	11.7 ± 0.5	P< 0.001
Apoptosis (%)	< 2	12.4 ± 2.6	25.6 ± 3.1	P< 0.001	< 2	15.4 ± 3.0	28.4 ± 3.0	P< 0.001
Vessels	30.0 ± 4.3	20.4 ± 2.7	10.4 ± 2.3	P< 0.001	38.5 $\pm$ 5.0	11.4 ± 0.8	7.5 ± 0.8	P< 0.001
Tumour-free mice	0/10	0/10	0/10	P= 1.000	0/10	1/10	3/10	P= 0.133

TGD = Tumor Growth Delay.

PI = Proliferation Index (= percent of cells with positive immunostaining for Ki67).

- 20 Bi-daily administration of belinostat caused a significant dose-dependent suppression of the growth of established PC3 and 22rv1 xenografts. In PC3 xenografts, the effects of belinostat were less marked though still significant.

Study 6In Vivo Studies of Belinostat and Bicalutamide in 22rv1 and PC3 ProstateXenograft Models

5

Male CD1 nude mice received sub-cutaneous flank injections of 1×10^6 PC3 or 22rv1 cells. Tumour growth was assessed by bi-weekly measurement of tumour diameters with a Vernier calliper (length x width). Treatments were started when tumour volumes reached about 80 mm^3 (Day 0) and were stopped after 28 days.

10

Mice were randomly assigned as follows:

Group A: 10 intact nude mice received intraperitoneal (i.p.) injections of 100 μL phosphate buffered saline (PBS).

15

Group B: 10 intact nude mice received i.p. injections of 100 μL of belinostat (BST) (40 mg/kg bid) for consecutive three weeks (5 days/week).

Group C: 10 castrated nude mice received intraperitoneal (i.p.) injections of 100 μL phosphate buffered saline (PBS).

20

Group D: 10 castrated nude mice received i.p. injections of 100 μL of belinostat (BST) (40 mg/kg bid) for consecutive three weeks (5 days/week).

25

Group E: 10 intact nude mice received 50 mg/kg/day bicalutamide (BCLT), by oral gavage, for consecutive 18 days.

Group F: 10 intact nude mice received 50 mg/kg/day bicalutamide (BCLT), by oral gavage, for 18 consecutive days, in combination with i.p. injections of 100 μL of belinostat (BST) (40 mg/kg bid) for three consecutive weeks (5 days/week).

30

The data are summarised in the Table 5A, Table 5B, Table 6A, and Table 6B, below.

Table 5A						
Antitumour activity of belinostat (BST) and bicalutamide (BCLT) in 22rv1 xenografts						
Group	A	B	C	D	E	F
Drug	Saline	BST	Castration	BST & Castration	BCLT	BST & BCLT
Dose	-	40 mg/kg bid	-	40 mg/kg bid	50 mg/kg	40 mg/kg bid & 50 mg/kg
Weight of mice (g)	25.3 ± 1.8	24.0 ± 1.4	26.8 ± 1.2	25.8 ± 2.0	26.4 ± 1.7	23.4 ± 2.2
Tumour weight (mg)	652 ± 200	218 ± 125	587 ± 121	185 ± 118	415 ± 44	108 ± 65
TGD (days)	-	16.0	2.7	21.0	5.4	23.4
PI (Ki67, %)	45.5 ± 6.5	11.7 ± 0.5	33.4 ± 5.6	8.5 ± 1.4	35.0 ± 5.0	7.0 ± 1.5
Apoptosis (%)	< 2	28.4 ± 3.0	< 2	18.2 ± 2.5	< 2	18.8 ± 2.1
Vessels	38.5 ± 5.0	7.5 ± 0.8	27.5 ± 3.0	7.0 ± 1.5	13.8 ± 2.4	7.3 ± 2.4
Tumour-free mice	0/10	3/10	0/10	4/10	0/10	6/10

Table 5B								
Antitumour activity of belinostat (BST) and bicalutamide (BCLT) in 22rv1 xenografts:								
Related statistics - P values								
Group	A vs B	A vs C	A vs E	C vs D	B vs D	E vs F	B vs F	D vs F
Weight of mice	0.088	0.042	0.177	0.192	0.032	0.003	0.476	0.020
Tumour weight	< 0.001	0.391	0.002	<0.001	0.551	<0.001	0.024	0.087
PI	<0.001	0.014	0.021	<0.001	0.001	<0.001	<0.001	0.085
Apoptosis	<0.001	1.000	<0.001	<0.001	<0.001	<0.001	<0.001	0.692
Vessels	<0.001	0.003	<0.001	<0.001	0.024	0.003	0.071	0.819
Tumour-free mice	0.210	1.000	0.094	0.094	0.302	0.015	1.000	0.655

Table 6A						
Antitumour activity of belinostat (BST) and bicalutamide (BCLT) in PC3 xenografts						
Group	A	B	C	D	E	F
Drug	Saline	BST	Castration	BST & Castration	BCLT	BST & BCLT
Dose	-	40 mg/kg bid	-	40 mg/kg bid	50 mg/kg	40 mg/kg bid & 50 mg/kg
Weight of mice (g)	25.0 ± 2.1	23.0 ± 2.3	26.1 ± 1.4	23.8 ± 2.8	25.1 ± 1.5	23.0 ± 2.0
Tumour weight (mg)	585 ± 235	314 ± 117	600 ± 205	244 ± 58	570 ± 121	174 ± 102
TGD (days)	-	14.4	0	16.7	0.8	28.0
PI (Ki67, %)	37.3 ± 4.5	14.7 ± 1.3	38.5 ± 3.1	6.9 ± 0.6	35.5 ± 3.1	4.0 ± 0.4
Apoptosis (%)	< 2	25.6 ± 3.1	< 2	28.3 ± 2.4	< 2	38.3 ± 2.7
Vessels	30.0 ± 4.3	10.4 ± 2.3	28.9 ± 3.8	7.0 ± 2.2	28.9 ± 3.0	5.5 ± 0.5
Tumour-free mice	0/10	0/10	0/10	2/10	0/10	5/10

Table 6B								
Antitumour activity of belinostat (BST) and bicalutamide (BCLT) in PC3 xenografts:								
Related statistics - P values								
Group	A vs B	A vs C	A vs E	C vs D	B vs D	E vs F	B vs F	D vs F
Weight of mice	0.057	0.185	0.904	0.032	0.494	0.016	1.000	0.472
Tumour weight	0.004	0.881	0.860	<0.001	0.107	<0.001	0.011	0.075
PI	<0.001	0.014	0.637	<0.001	<0.001	<0.001	<0.001	<0.001
Apoptosis	<0.001	1.000	1.000	<0.001	0.162	<0.001	<0.001	<0.001
Vessels	<0.001	0.680	0.651	<0.001	0.044	<0.001	0.002	0.175
Tumour-free mice	1.000	1.000	1.000	0.456	0.456	0.039	0.039	0.348

- 30 -

Significant differences in the distribution of Ki67 positive cells, apoptotic cells and vessels were observed in combined treatments when compared to those observed in single treatments. In contrast to castration, bicalutamide induced more marked differences in tumour growth when compared to control.

5

Belinostat plus bicalutamide efficacy was significantly synergistic when compared with the efficacy observed with each of belinostat and bicalutamide alone.

10

Belinostat (40 mg/kg bid) alone induced a 67% of reduction of tumour mass after 21 days of treatment in intact nude mice bearing 22rv1. The tumour mass reduction reached 69% in combination with castration, and 74% in combination with bicalutamide. Castration alone reduced tumour mass by 10%, when compared to intact nude mice used as controls. Bicalutamide alone reduced tumour mass by 36%, when compared to intact nude mice used as controls.

15

As expected bicalutamide and castration, alone, did not show anti-tumour effects in androgen receptor negative PC3 cells. Belinostat alone induced a 46% of inhibition of tumour mass in intact nude mice. This reduction increased to 59% in combination with castration, and to 69% in combination with bicalutamide.

20

The differences in Ki67 positive cell percentage, apoptosis, and vessel number were more significant in the combination of bicalutamide and belinostat when compared to those observed in single treatments.

25

In both xenografts, the combination of bicalutamide and belinostat showed higher efficacy when compared to combination of castration and belinostat.

30

The synergy of the HDAC inhibitor belinostat with the anti-androgen bicalutamide in androgen-insensitive prostate cancer cells and in androgen receptor negative prostate cancer cells is unexpected and surprising. Indeed, a previous study (see, e., Marrocco et al., 2007) showed no synergy between the HDAC inhibitor SAHA (Zolinza®) and bicalutamide in androgen-independent and androgen receptor negative prostate cancer cells (see Figures 8A and 8B and discussion, therein).

35

* * *

The foregoing has described the principles, preferred embodiments, and modes of operation of the present invention. However, the invention should not be construed as limited to the particular embodiments discussed. Instead, the above-described
embodiments should be regarded as illustrative rather than restrictive, and it should be
5 appreciated that variations may be made in those embodiments by workers skilled in the art without departing from the scope of the present invention.

REFERENCES

10 A number of patents and publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure, to the same
15 extent as if each individual reference was specifically and individually indicated to be incorporated by reference.

Avis, K.E. et al. (editors), 1992, "Pharmaceutical Dosage Forms: Parenteral Medications, Volume 1", second edition, pp. 514-518.

20 Bastin et al., 2006, "Pharmaceutical formulations of HDAC inhibitors", international patent application publication number WO/2006/120456 published 16 November 2007.

Gravina et al., 2008, "Chronic azacitidine treatment results in differentiating effects, sensitizes against bicalutamide in androgen-independent prostate cancer cells", The Prostate, Vol. 68, No. 7, pp. 793-801.

25 Marrocco et al., 2007, "Suberoylanilide hydroxamic acid (vorinostat) represses androgen receptor expression and acts synergistically with an androgen receptor antagonist to inhibit prostate cancer cell proliferation", Mol. Cancer Ther., Vol. 6, No. 1, pp. 51-60.

Sehested et al., 2009, "Methods of treatment employing prolonged continuous infusion of belinostat", international patent application publication number WO 2009/109861
30 published 11 September 2009.

Tucker, 1984, "Amide derivatives", US Patent No. 4,636,505, granted 13 January 1987.

Watkins et al., 2002, "Carbamic acid compounds comprising a sulfonamide linkage as HDAC inhibitors", international patent application publication number
35 WO 02/30879 A2 published 18 April 2002.

CLAIMS

1. A method of treatment of a disease or disorder which is mediated by HDAC in a patient, comprising administering to said patient (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, in amounts such that the combination is therapeutically-effective.
2. A method according to claim 1, wherein said disease or disorder which is mediated by HDAC is cancer.
3. A method according to claim 1, wherein said disease or disorder which is mediated by HDAC is prostate cancer
4. A method according to claim 1, wherein said disease or disorder which is mediated by HDAC is androgen-independent prostate cancer
5. A method according to claim 1, wherein said disease or disorder which is mediated by HDAC is androgen receptor negative prostate cancer.
6. A method according to any one of claims 1 to 4, wherein said treatment comprises one or more treatment cycles, where said (a) belinostat, or a salt, hydrate, or solvate thereof, and (b) bicalutamide, or a salt, hydrate, or solvate thereof, are administered to said patient over the course of each of said treatment cycles.
7. A method according to claim 6, wherein said treatment comprises from 2 to 6 treatment cycles.
8. A method according to claim 6 or 7, wherein said treatment cycle or each of said treatment cycles is from 3 to 49 days in length.
9. A method according to claim 6 or 7, wherein said treatment cycle or each of said treatment cycles is about 21 days in length.
10. A method according to any one of claims 1 to 9, wherein said belinostat, or a salt, hydrate, or solvate thereof, is administered intravenously.
11. A method according to any one of claims 1 to 9, wherein said belinostat, or a salt, hydrate, or solvate thereof, is administered by intravenous infusion.

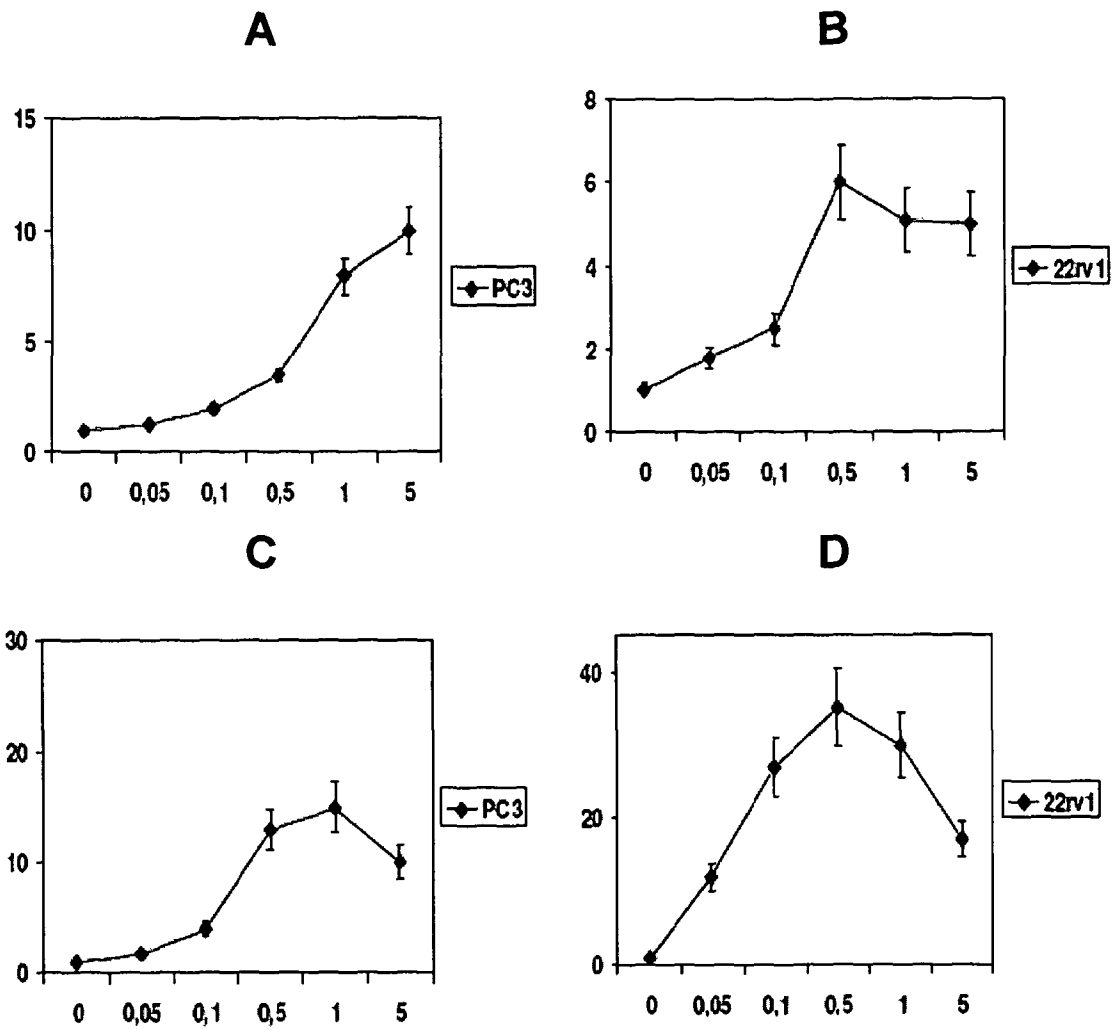
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12. A method according to any one of claims 1 to 11, wherein said belinostat, or a salt, hydrate, or solvate thereof, is administered by prolonged continuous intravenous infusion.
- 5 13. A method according to any one of claims 1 to 11, wherein said belinostat, or a salt, hydrate, or solvate thereof, is administered by intravenous infusion for a period of from 12 to 72 hours.
- 10 14. A method according to any one of claims 1 to 11, wherein said belinostat, or a salt, hydrate, or solvate thereof, is administered by intravenous infusion for a period of about 48 hours.
- 15 15. A method according to any one of claims 11 to 14, wherein the dosage of said belinostat, or a salt, hydrate, or solvate thereof, during said intravenous infusion is from 100 to 2500 mg/m²/d of belinostat.
- 20 16. A method according to any one of claims 11 to 14, wherein the dosage of said belinostat, or a salt, hydrate, or solvate thereof, during said intravenous infusion is from 500 to 1500 mg/m²/d of belinostat.
- 25 17. A method according to any one of claims 1 to 8, wherein said belinostat, or a salt, hydrate, or solvate thereof is administered orally.
- 30 18. A method according to any one of claims 1 to 17, wherein said bicalutamide, or a salt, hydrate, or solvate thereof, is administered orally.
- 35 19. A method according to claim 18, wherein the dosage of said bicalutamide, or a salt, hydrate, or solvate thereof, is 50 mg, once daily.
20. Belinostat, or a salt, hydrate, or solvate thereof, for use, *in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, in a method of treatment of the human or animal body by therapy.
21. Belinostat, or a salt, hydrate, or solvate thereof, for use, *in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, in a method of treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer).

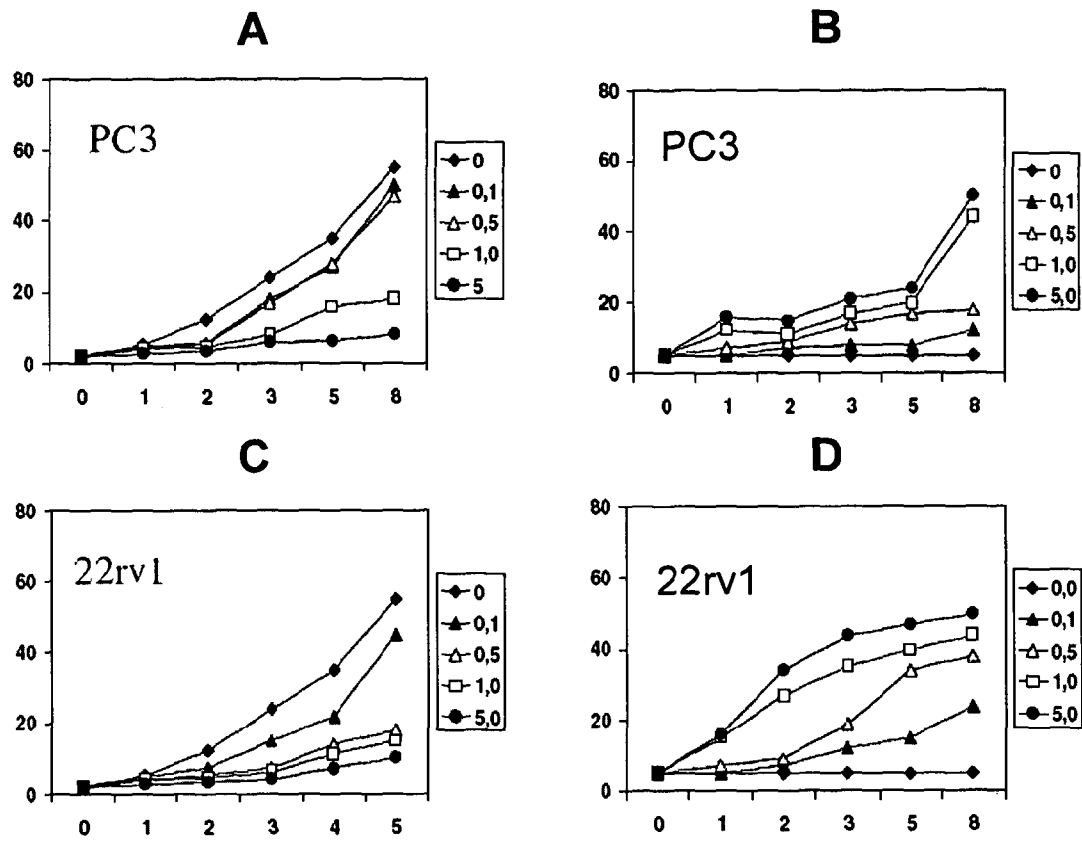
- 34 -

22. Bicalutamide, or a salt, hydrate, or solvate thereof, for use, *in combination with belinostat, or a salt, hydrate, or solvate thereof*, in a method of treatment of the human or animal body by therapy.
- 5 23. Bicalutamide, or a salt, hydrate, or solvate thereof, for use, *in combination with belinostat, or a salt, hydrate, or solvate thereof*, in a method of treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer).
- 10 24. Use of belinostat, or a salt, hydrate, or solvate thereof, in the manufacture of a medicament, *for use in combination with bicalutamide, or a salt, hydrate, or solvate thereof*, for the treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer).
- 15 25. Use of bicalutamide, or a salt, hydrate, or solvate thereof, in the manufacture of a medicament, *for use in combination with belinostat, or a salt, hydrate, or solvate thereof*, for the treatment of a disease or disorder which is mediated by HDAC (e.g., cancer, e.g., prostate cancer, e.g., androgen-insensitive prostate cancer, androgen receptor negative prostate cancer).
- 20

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FIGURE 1



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FIGURE 2



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FIGURE 3

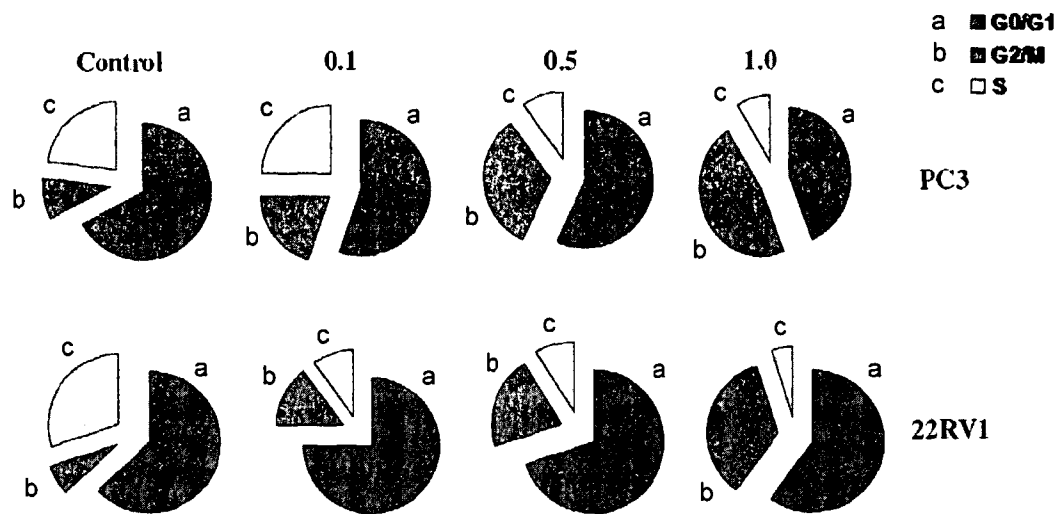
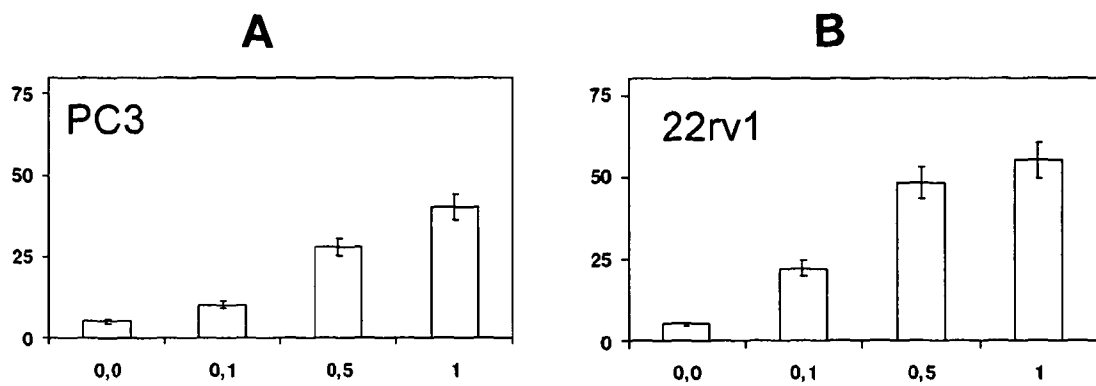
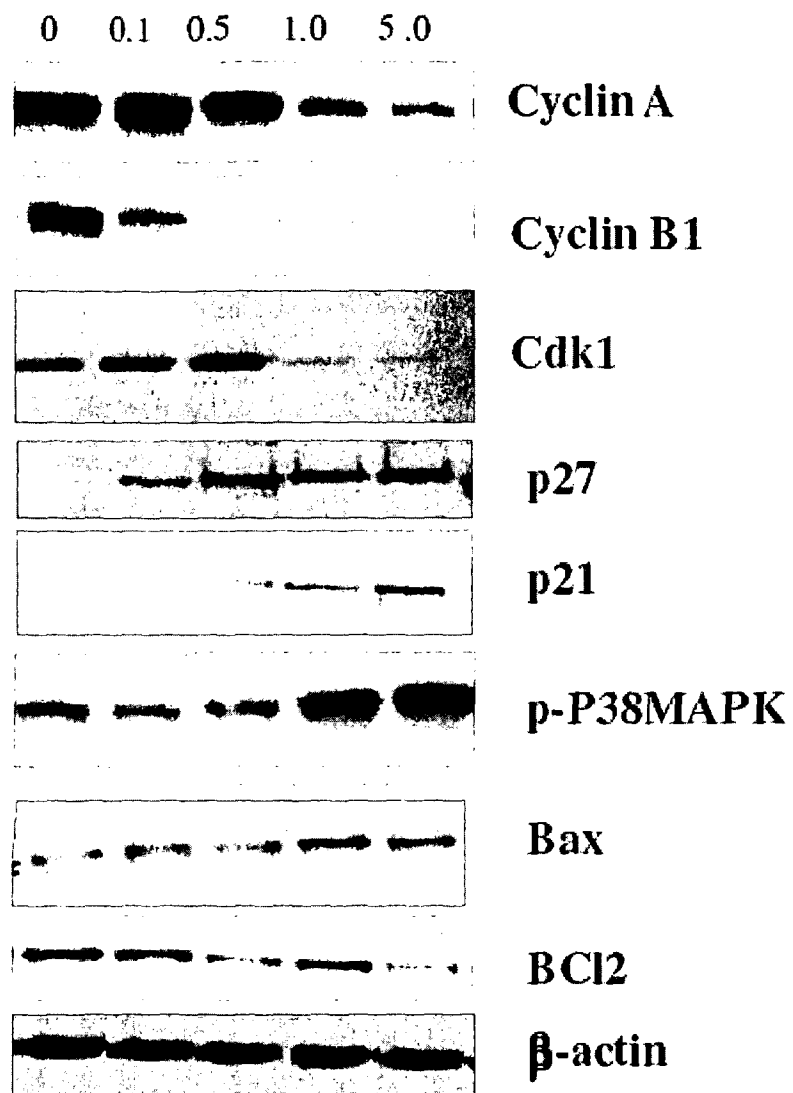


FIGURE 4



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FIGURE 5

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FIGURE 6

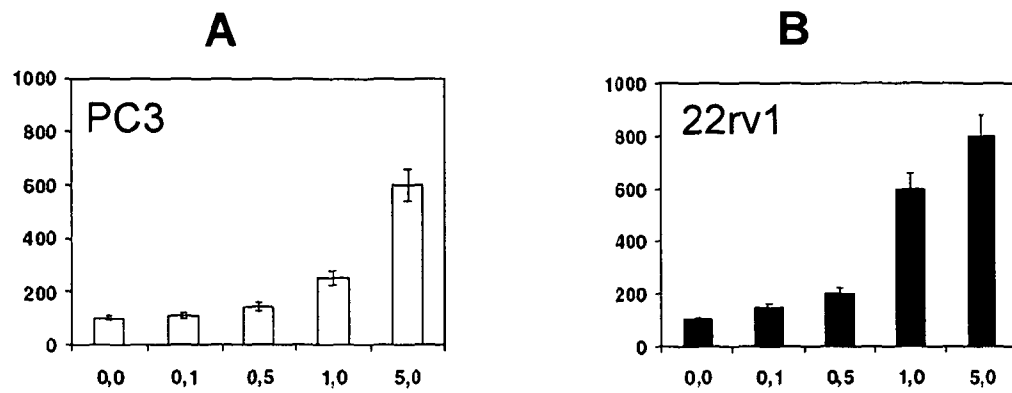
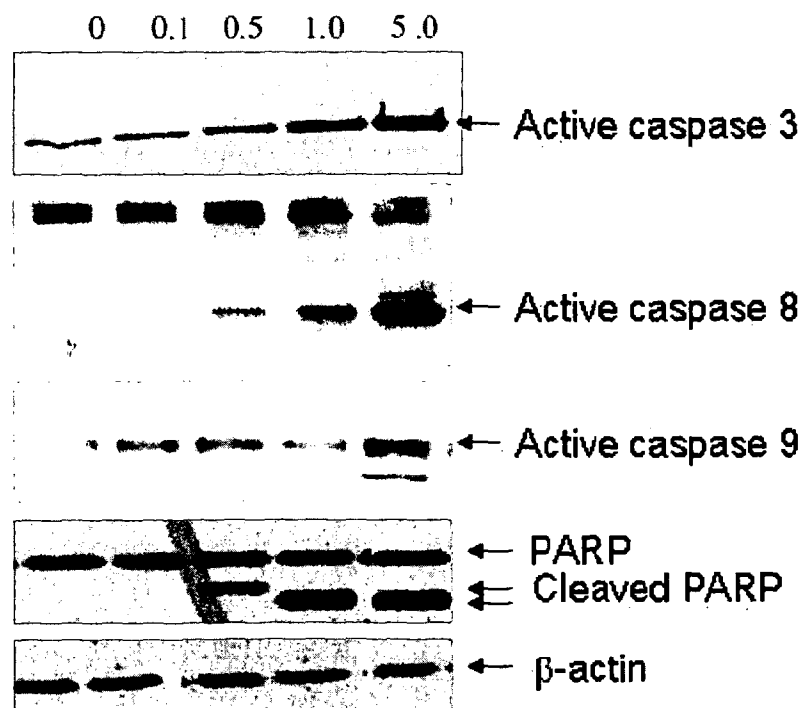
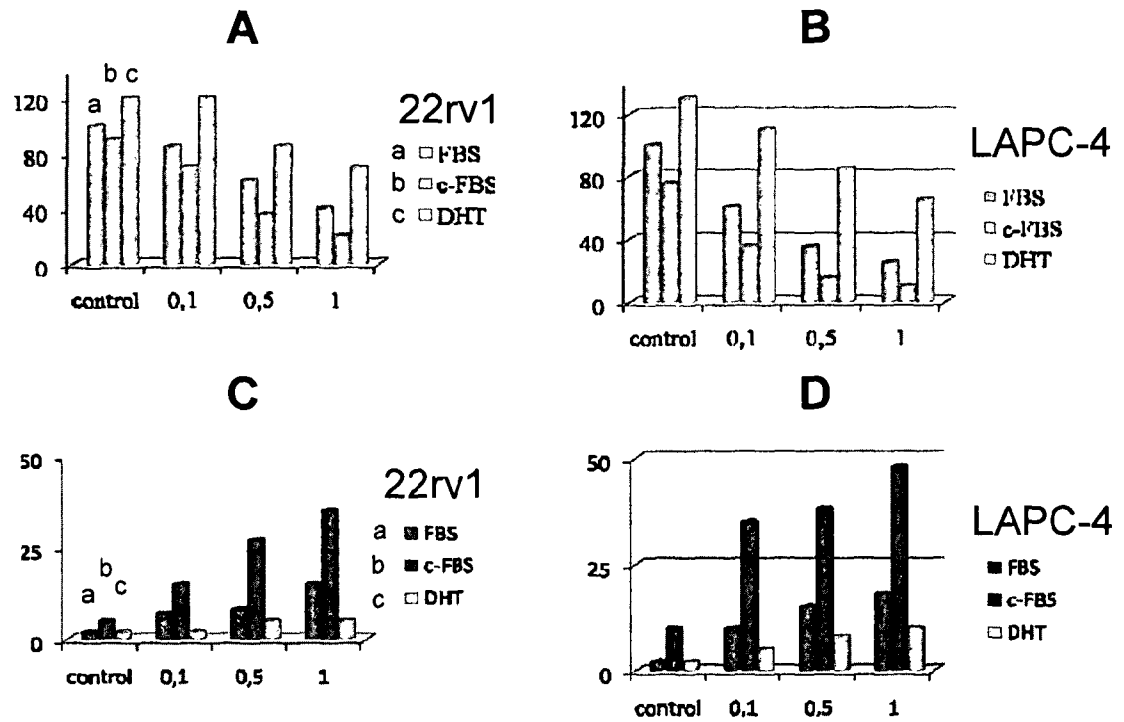


FIGURE 7



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FIGURE 8



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FIGURE 9

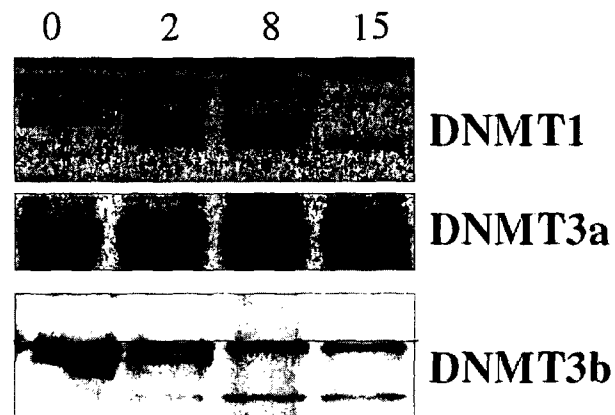


FIGURE 10

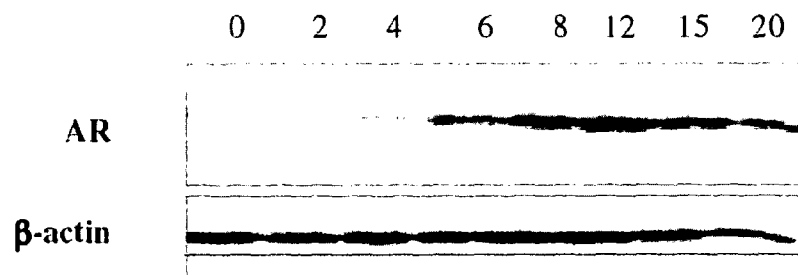
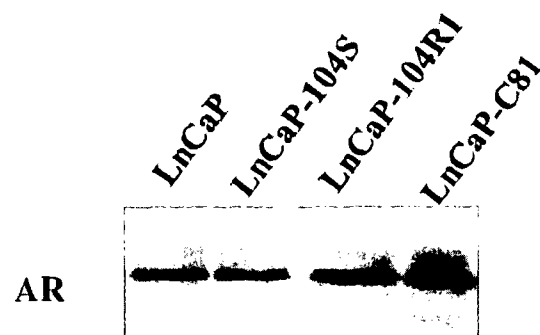


FIGURE 11



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FIGURE 12

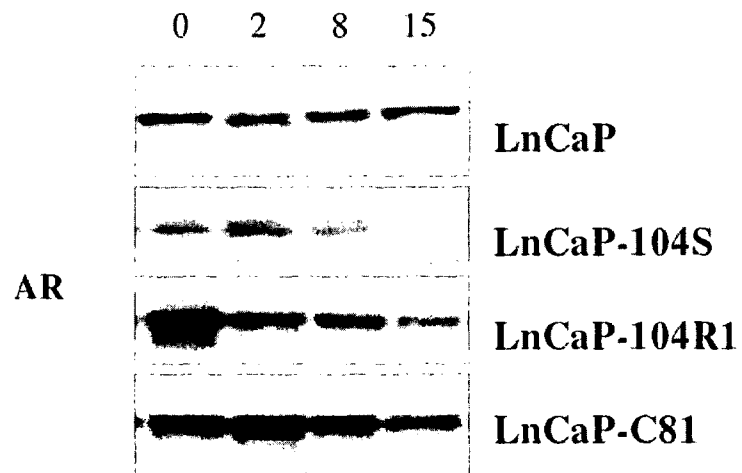
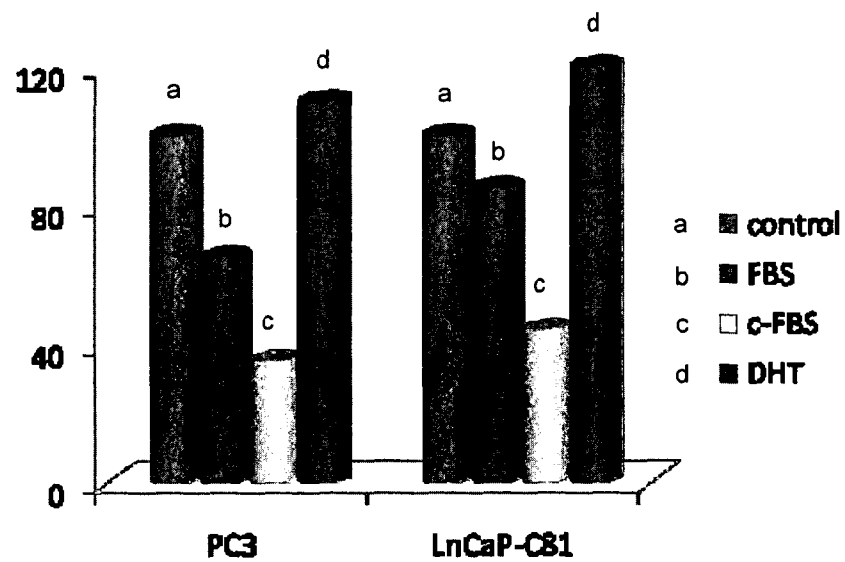
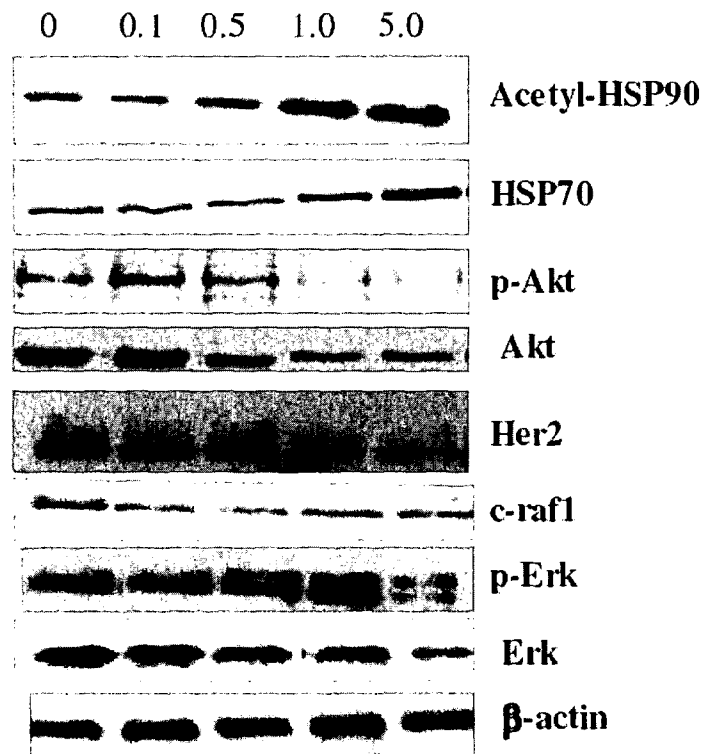


FIGURE 13

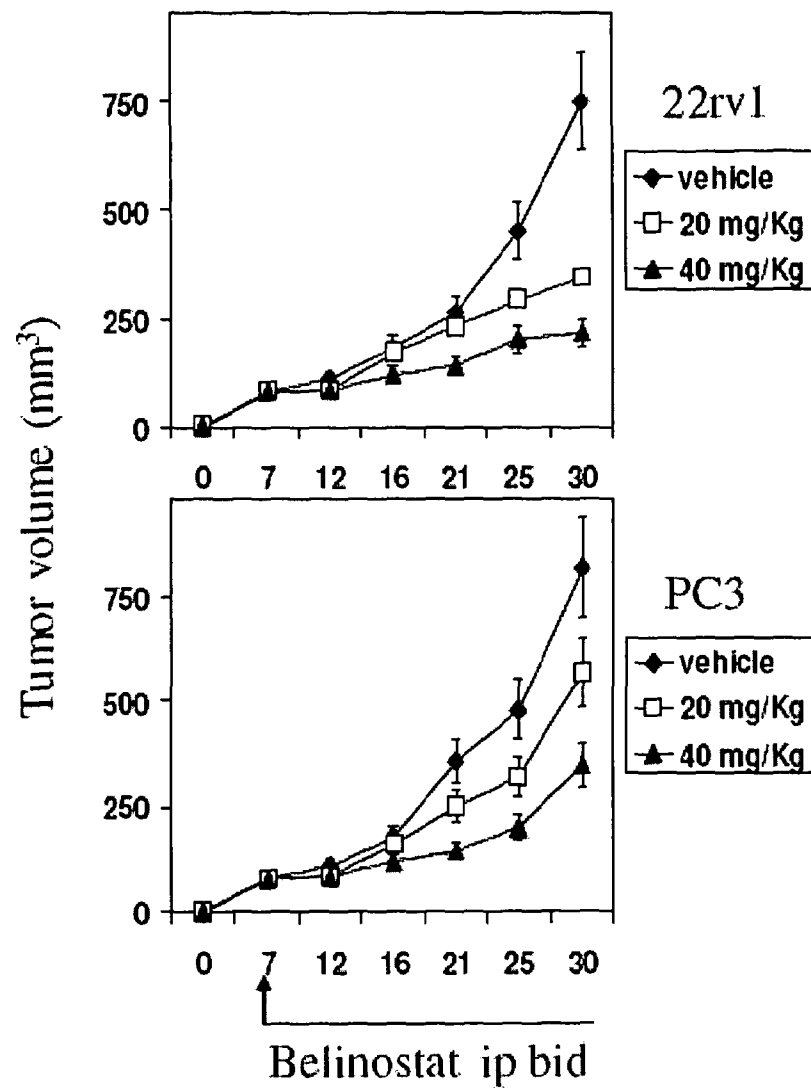


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FIGURE 14



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FIGURE 15



INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/003145

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/277 A61K47/18 A61P35/00
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/154402 A2 (UNIV MARYLAND [US]; BRODIE ANGELA [US]; NJAR VINCENT C O [US]; SABNIS) 18 December 2008 (2008-12-18) claims 36, 37,39,40 paragraphs [0125], [0160] ----- -/--	1-25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search

17 February 2011

Date of mailing of the international search report

24/02/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Loher, Florian

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2010/003145

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JEFFERS M ET AL: "351 POSTER Activity of the histone deacetylase (HDAC) inhibitor PXD101 in preclinical prostate cancer studies", EUROPEAN JOURNAL OF CANCER. SUPPLEMENT, PERGAMON, OXFORD, GB, vol. 4, no. 12, 1 November 2006 (2006-11-01), page 109, XP025026726, ISSN: 1359-6349, DOI: DOI:10.1016/S1359-6349(06)70356-1 [retrieved on 2006-11-01] the whole document -----	1-25
Y	ON BEHALF OF THE SCANDINAVIAN PROSTATIC CANCER GROUP IVERSEN ET AL: "BICALUTAMIDE (150 MG) VERSUS PLACEBO AS IMMEDIATE THERAPY ALONE OR AS ADJUVANT TO THERAPY WITH CURATIVE INTENT FOR EARLY NONMETASTATIC PROSTATE CANCER: 5.3-YEAR MEDIAN FOLLOWUP FROM THE SCANDINAVIAN PROSTATE CANCER GROUP STUDY NUMBER 6", JOURNAL OF UROLOGY, LIPPINCOTT WILLIAMS & WILKINS, BALTIMORE, MD, US, vol. 172, no. 5, 1 November 2004 (2004-11-01), pages 1871-1876, XP005530267, ISSN: 0022-5347, DOI: DOI:10.1097/01.JU.0000139719.99825.54 the whole document -----	1-25
X,P	FESTUCCIA C ET AL: "184 Histone deacetylase inhibitor Belinostat (PXD-101) represses androgen receptor expression and acts synergistically with castration and bicalutamide treatment to inhibit prostate cancer growth hormone refractory models", EUROPEAN JOURNAL OF CANCER. SUPPLEMENT, PERGAMON, OXFORD, GB, vol. 8, no. 7, 1 November 2010 (2010-11-01), pages 62-63, XP027497872, ISSN: 1359-6349 [retrieved on 2010-11-01] the whole document -----	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2010/003145

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008154402 A2	18-12-2008	CA 2726734 A1	18-12-2008
		EP 2167090 A2	31-03-2010
		GB 2454118 A	29-04-2009
		US 2009048156 A1	19-02-2009
