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(57) Abstract: Provided herein are methods of using (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and an androgen receptor signaling inhibitor for treating prostate cancer. Also provided are pharmaceutical compositions comprising (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and an androgen receptor signaling inhibitor.

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EZH2 AND ANDROGEN RECEPTOR SIGNALING INHIBITORS AS TOOLS FOR TARGETING PROSTATE CANCER

RELATED APPLICATIONS

[0001] This application claims the benefit of priority to international application PCT/US2018/067646, filed December 27, 2018, the entire contents of which are incorporated herein by reference.

BACKGROUND

[0002] According to the American Cancer Society (ACS), prostate cancer is the second most common type of cancer amongst men in the United States and is the second leading cause of cancer death in this population. The growth and survival of prostate cancer cells depend primarily on the androgen receptor signaling pathway. Cancer cells can use the binding of androgens to androgen receptors to trigger abnormal cell growth and tumor progression. The standard of care for the treatment of advanced prostate cancer is androgen deprivation therapy (ADT), which induces medical castration, or surgical castration to achieve reduced testosterone levels. Medical castration involves gonadotropin-releasing hormone antagonists, alone or in combination with first generation anti-androgen therapy. Most men with prostate cancer treated with ADT respond, as measured by tumor regression, relief of symptoms and reductions in serum prostate-specific antigen, or PSA, level and are considered to have hormone-sensitive prostate cancer.

[0003] However, almost all prostate cancer patients eventually experience a recurrence in tumor growth despite ADT. These patients are diagnosed with castration-resistant prostate cancer (CRPC), which refers to prostate cancer that progresses despite ADT and is characterized by low testosterone serum levels. The development of CRPC following ADT is due in part to tumor cells that adapt to the hormone-deprived environment of the prostate.

[0004] Castration-resistant prostate cancer that spreads, or metastasizes, to other parts of the body is diagnosed as mCRPC and may be characterized by increasing PSA levels, elevated circulating tumor cell (CTC) counts and soft tissue disease. Elevated CTC counts have been demonstrated to be a poor prognostic factor for overall survival in patients with mCRPC. See e.g., Int. J. Mol. Sci. 2016, 17(9), 1580. CTCs are cells that have shed from a primary tumor and are carried around the body in the blood and may lead to metastases. A 30% decline in CTC counts as early as four weeks after treatment initiation suggests that advanced prostate cancer patients may benefit from treatment.

[0005] Patients with mCRPC have an average survival of approximately 30 months and experience a deterioration in quality of life despite treatment with the available therapeutic options. The current standard of practice is to treat mCRPC with a second generation androgen receptor signaling (ARS) inhibitor, such as abiraterone acetate or enzalutamide. Such products are approved in the United States for first-line therapy in chemotherapy-naïve patients with mCRPC as well as for second-line treatment in patients who have received prior chemotherapy.

[0006] The problem with this treatment is that of those who have a PSA response, a large majority eventually develop resistance to ARS inhibitors. If patients with mCRPC have disease progression after treatment with a second-generation ARS inhibitor, they may be treated with either chemotherapy or a different second-generation ARS inhibitor. However, experts that treat mCRPC patients estimated that only 10-30% of patients will respond to the second-line treatment with a different ARS inhibitor and that the response achieved is typically less than half as durable, with three to six months of PSA progression-free survival, as compared to the response observed with first-line ARS inhibitor treatment. Beyond this, patients with mCRPC have very limited treatment options other than pain management and other palliative care options.

SUMMARY

[0007] We have now found that the addition of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide (Compound **1**) to patients with mCRPC who previously progressed on treatment with ARSIs such as enzalutamide and abiraterone acetate, led to significant benefits over the current standard of care, i.e., the use of an ARSI alone. For example, two (2) out of six (6) patients being dosed with Compound **1** and enzalutamide experienced over 80% reduction in PSA levels; two (2) out of four (4) evaluable patients being dosed with Compound **1** and enzalutamide experienced a reduction in CTC levels of more than 30% from baseline; and two (2) out of two (2) patients being dosed with Compound **1** and enzalutamide had resolution of metastatic disease. See e.g., **FIG. 5**, **FIG. 6**, and the Exemplification section below. In a compassionate-use patient who was treated with twelve (12) agents prior to treatment with Compound **1** and enzalutamide, including second generation ARSI, chemotherapy, PARP inhibitors, tyrosine kinase inhibitors, checkpoint inhibitors, radium 223, and radiotherapy, an 80% reduction in PSA and a reduction of tumor size in the neck was achieved. See e.g., **FIG. 7** and the Exemplification section below. In a

subject who had metastatic bone disease, an 83% reduction in PSA was seen after only one (1) month of therapy with Compound **1** and enzalutamide, and PET/CT scan revealed resolution of bone metastasis after two-post cycle therapies of Compound **1** alone. See **FIG. 8** and **FIG. 9**.

[0008] Provided herein, therefore, are methods of using Compound **1**, or a pharmaceutically acceptable salt thereof, and an ARSI such as enzalutamide, abiraterone, or abiraterone/prednisone for treating prostate cancer. Also provided herein are pharmaceutical compositions comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an ARSI such as enzalutamide, abiraterone, or abiraterone/prednisone. Other aspects of the disclosure are discussed below.

BRIEF DESCRIPTION OF THE FIGURES

[0009] **FIG. 1** illustrates the in vitro synergistic results on cell viability in the LNCaP prostate cancer cell line using Compound **1** and the ARSI enzalutamide. CPI-1205 is Compound **1**.

[0010] **FIG. 2** shows the in vitro effects of Compound **1** with enzalutamide or abiraterone in various prostate cancer cells lines. CPI-1205 is Compound **1**.

[0011] **FIG. 3** shows the in vivo efficacy of Compound **1** with enzalutamide in a mouse xenograft prostate tumor model. CPI-1205 is Compound **1**.

[0012] **FIG. 4** is an illustration of the human patient population in a clinical trial by treatment protocol and duration. CP-1205 and CPI-1205 are Compound **1**.

[0013] **FIG. 5** shows the evolution of PSA changes for each evaluable patient in a clinical trial treated with Compound **1** and enzalutamide or abiraterone, beginning with the pre-screening period (prior to treatment). CPI-1205 is Compound **1**.

[0014] **FIG. 6** depicts the change in CTC count in four patients in a clinical trial, using Compound **1** and enzalutamide or abiraterone, who had unfavorable CTC counts at baseline and have had at least one post-baseline CTC measurement.

[0015] **FIG. 7** shows the PSA reduction in a patient who was treated and refractory to numerous therapies prior to the administration of Compound **1** and enzalutamide. CPI-1205 is Compound **1**.

[0016] **FIG. 8** shows results from a PET/CT scan following 1 month treatment with Compound **1** and enzalutamide, followed by monotherapy with Compound **1**.

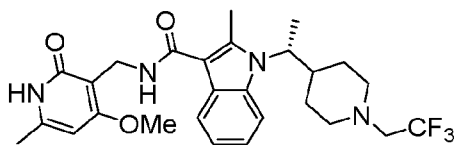
[0017] **FIG. 9.** shows results from a PET/CT scan following 1 month treatment with Compound **1** and enzalutamide, followed by monotherapy with Compound **1**.

DETAILED DESCRIPTION

[0018] Provided herein are methods of using Compound **1**, or a pharmaceutically acceptable salt thereof, and an ARSI such as enzalutamide, abiraterone, or abiraterone/prednisone for treating prostate cancer. Also provided are pharmaceutical compositions comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an ARSI such as enzalutamide, abiraterone, or abiraterone/prednisone.

1. Certain Definitions

[0019] (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, referred to herein as Compound **1**, has the following chemical structure:



[0020] The term “pharmaceutically acceptable carrier” refers to a non-toxic carrier, adjuvant, or vehicle that does not adversely affect the pharmacological activity of the compound with which it is formulated, and which is also safe for human use. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, magnesium stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances (e.g., microcrystalline cellulose, hydroxypropyl methylcellulose, lactose monohydrate, sodium lauryl sulfate, and crosscarmellose sodium), polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0021] Pharmaceutically acceptable salt forms of Compound **1** and/or the androgen receptor signaling inhibitor include pharmaceutically acceptable acidic/anionic or basic/cationic salts. Suitable pharmaceutically acceptable basic/cationic salts include e.g., the sodium, potassium, calcium, magnesium, diethanolamine, n-methyl-D-glucamine, L-lysine, L-arginine, ammonium, ethanolamine, piperazine and triethanolamine salts. Pharmaceutically acceptable acid addition salts include e.g., salts of inorganic acids (such as hydrochloric acid,

hydrobromic, phosphoric, nitric, and sulfuric acids) and of organic acids (such as, acetic acid, benzenesulfonic, benzoic, methanesulfonic, and p-toluenesulfonic acids).

[0022] As used herein, the terms “treatment,” “treat,” and “treating” refer to reversing, alleviating, or inhibiting the progress of prostate cancer, or one or more symptoms thereof.

[0023] The term “effective amount” or “therapeutically effective amount” refers to an amount of a compound described herein that will elicit a biological or medical response of a subject e.g., a dosage of between 0.001 - 100 mg/kg body weight/day.

[0024] The term “patient,” as used herein, means an animal, such as a mammal, and such as a human. The terms “subject” and “patient” may be used interchangeably.

[0025] Compositions and method of administration herein may be orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term “parenteral” as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. In one aspect, the compositions described herein are formulated for oral administration. Other forms of administration are as described in WO 2013/075083, WO 2013/075084, WO 2013/078320, WO 2013/120104, WO 2014/124418, WO 2014/151142, and WO 2015/023915, the contents of which are incorporated herein by reference.

[0026] A subject who is characterized as progressed or relapsed is one who at one time responded to a given treatment such as an androgen receptor signaling inhibitor, a steroid, a pharmacological inhibitor of the enzyme poly ADP ribose polymerase (PARP), a tyrosine kinase inhibitor, a checkpoint inhibitor, radium 223, radiotherapy, chemotherapy, a CYP17A inhibitor, a steroid, or a VEGF inhibitor, but who no longer responds. A subject who is characterized as refractory or resistant is one who is unresponsive or demonstrates worsening of disease while on a given treatment such as an androgen receptor signaling inhibitor, a steroid, a pharmacological inhibitor of the enzyme poly ADP ribose polymerase (PARP), a tyrosine kinase inhibitor, a checkpoint inhibitor, radium 223, radiotherapy, chemotherapy, a CYP17A inhibitor, a steroid, or a VEGF inhibitor.

2. Description of Certain Embodiments

[0027] In a first embodiment, provided herein are methods of treating prostate cancer in a subject comprising administering to the subject a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically

acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof.

[0028] In a second embodiment, provided herein is the use of a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating prostate cancer.

[0029] In a third embodiment, provided herein is a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof, for use in treating prostate cancer.

[0030] In a fourth embodiment, provided herein are pharmaceutical compositions comprising a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable carrier.

[0031] In a fifth embodiment, provided is a pharmaceutical composition comprising a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable carrier for treating prostate cancer.

[0032] In a sixth embodiment, in the present methods and uses (e.g., as described in any one of the first to third and fifth embodiments), a therapeutically effective amount of Compound **1** may be administered prior to, concurrently with, or after administration of the androgen receptor signaling inhibitor. Thus, simultaneous administration is not necessary for therapeutic purposes. In one aspect, however, Compound **1** (e.g., as described in any one of the first to third and fifth embodiments) is administered concurrently with the androgen receptor signaling inhibitor. In another aspect, the subject described herein (e.g., as described in any one of the first to third and fifth embodiments) is pre-treated with the androgen

receptor signaling inhibitor (i.e., Compound **1** is administered after the androgen receptor signaling inhibitor) for a period of time such as e.g., 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, or 6.0 hours or greater before Compound **1** is administered to the subject.

[0033] In a seventh embodiment, exemplary types of prostate cancer treated by the methods and uses described herein (e.g., as is any one of the first to third, fifth, and sixth embodiments) include e.g., acinar adenocarcinoma, ductal adenocarcinoma, transitional cell cancer, squamous cell cancer, small cell prostate cancer, and castration resistant prostate cancer (CRPC). In one aspect, the prostate cancer to be treated by the methods and uses described herein (e.g., as is any one of the first to third, fifth, and sixth embodiments) is mCRPC.

[0034] In one aspect, the therapeutically effective amount of Compound **1** and/or the androgen receptor signaling inhibitor that is administered to a subject, or the effective amount of Compound **1** and/or the androgen receptor signaling inhibitor that is formulated in a provided composition, is such that a dosage of between 0.01 - 100 mg/kg body weight/day can be administered to the subject. It will be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the cancer being treated.

[0035] In an eighth embodiment, the therapeutically effective amount of Compound **1** described in the methods and uses herein (e.g., as is any one of the first to third and fifth to seventh embodiments) ranges from 50 mg to 3.5 grams administered once, twice, or three times a day, e.g., from 100 mg to 3.5 grams, from 200 mg to 3.0 grams, from 200 mg to 2.5 grams, from 200 mg to 1.0 grams, from 200 mg to 1.5 grams, from 200 mg to 1 gram, from 300 mg to 800 mg, from 400 mg to 800 mg, or from 400 mg to 600 mg administered once, twice, or three times a day. Alternatively as an eighth embodiment, the therapeutically effective amount of Compound **1** described in the methods and uses herein (e.g., as is any one of the first to third and fifth to seventh embodiments) ranges from 100 mg to 3.5 grams, from 200 mg to 3.0 grams, from 200 mg to 2.5 grams, from 200 mg to 1.0 grams, from 200 mg to 1.5 grams, from 200 mg to 1 gram, from 300 mg to 800 mg, from 400 mg to 800 mg, from 400 mg to 600 mg, from 1.0 grams to 2.0 grams, from 1.4 grams to 1.7 grams, from 500 mg to 700 mg, from 550 mg to 650 mg, from 700 mg to 900 mg, from 750 mg to 850 mg, from 300 mg to 500 mg, or from 350 mg to 450 mg administered once, twice, or three times a day. Alternatively as an eighth embodiment, the therapeutically effective amount of Compound **1** described in the methods and uses herein (e.g., as is any one of the first to third and fifth to

seventh embodiments) is 3.5 grams, 3.4 grams, 3.3 grams, 3.2 grams, 3.1 grams, 3.0 grams, 2.9 grams, 2.8 grams, 2.7 grams, 2.6 grams, 2.5 grams, 2.4 grams, 2.3 grams, 2.2 grams, 2.1 grams, 2.0 grams, 1.9 grams, 1.8 grams, 1.7 grams, 1.6 grams, 1.5 grams, 1.4 grams, 1.3 grams, 1.2 grams, 1.1 grams, 1.0 grams, 900 mg, 800 mg, 700 mg, 600 mg, 500 mg, 400 mg, or 300 mg administered once, twice, or three times a day. Alternatively as an eighth embodiment, the therapeutically effective amount of Compound **1** described in the methods and uses herein (e.g., as is any one of the first to third and fifth to seventh embodiments) is 3.2 grams, 2.4 grams, 1.6 grams, 1.2 grams, 800 mg administered once, twice, or three times a day. Alternatively as an eighth embodiment, the therapeutically effective amount of Compound **1** described in the methods and uses herein (e.g., as is any one of the first to third and fifth to seventh embodiments) is 1.6 grams administered twice a day, 800 mg administered three times a day, 800 mg administered twice a day, 600 mg administered twice a day, or 400 mg administered twice a day. Alternatively as an eighth embodiment, the therapeutically effective amount of Compound **1** described in the methods and uses herein (e.g., as is any one of the first to third and fifth to seventh embodiments) is 800 mg administered three times a day. Compositions described herein (e.g., as in the fourth embodiment) may be formulated with an amount or range for Compound **1** as described in this eighth embodiment.

[0036] In a ninth embodiment, the androgen receptor signaling inhibitor in the methods, uses, and compositions herein (e.g., as in any one of the first to eighth embodiments) is selected from enzalutamide, abiraterone acetate, bicalutamide, apalutamide, darolutamide, or a pharmaceutically acceptable salt thereof.

[0037] In a tenth embodiment, the therapeutically effective amount of the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to ninth embodiments) ranges from 10 mg to 4.0 grams, e.g., from 50 mg to 3.0 grams, from 100 mg to 3.0 grams, from 500 mg to 2.5 grams, from 500 mg to 2.0 grams, from 500 mg to 1.5 grams, from 750 mg to 1.5 grams, from 50 mg to 1.0 gram, from 50 mg to 500 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, or from 100 mg to 200 mg. Compositions described herein (e.g., as in the fourth and eighth embodiment) may be formulated with an amount or range for an androgen receptor signaling inhibitor as described in this tenth embodiment.

[0038] In an eleventh embodiment, the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to tenth embodiments) is enzalutamide, or a pharmaceutically acceptable salt thereof.

[0039] In a twelfth embodiment, the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to tenth embodiments) is enzalutamide, or a pharmaceutically acceptable salt thereof in an amount ranging from 50 mg to 1.0 gram, from 50 mg to 500 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, or from 100 mg to 200 mg. Alternatively, as an twelfth embodiment, the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to tenth embodiments) is enzalutamide, or a pharmaceutically acceptable salt thereof in an amount ranging from 150 mg to 170 mg. Compositions described herein (e.g., as in the fourth and eighth embodiment) may be formulated with an amount or range for enzalutamide as described in this twelfth embodiment.

[0040] In a thirteenth embodiment, the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to tenth embodiments) is abiraterone acetate.

[0041] In a fourteenth embodiment, the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to tenth embodiments) is abiraterone acetate in an amount ranging from 100 mg to 3.0 grams, from 500 mg to 2.5 grams, from 500 mg to 2.0 grams, from 500 mg to 1.5 grams, or from 750 mg to 1.5 grams. Alternatively, in a fourteenth embodiment, the androgen receptor signaling inhibitor in the methods and uses herein (e.g., as in any one of the first to tenth embodiments) is abiraterone acetate ranging in amount from 900 mg to 1.1 grams. Compositions described herein (e.g., as in the fourth and eighth embodiment) may be formulated with an amount or range for abiraterone acetate as described in this fourteenth embodiment.

[0042] In a fifteenth embodiment, the androgen receptor signaling inhibitor abiraterone acetate (e.g., as described in the fourteenth embodiment) is combined with a therapeutically effective amount of prednisone, or a pharmaceutically acceptable salt thereof. Thus, the disclosed methods and compositions (e.g., as in any one of the first to fourteenth embodiments) include Compound **1** and the androgen receptor signaling inhibitor abiraterone acetate and prednisone. In such aspects, the therapeutically effective amount of prednisone, or pharmaceutically acceptable salt thereof, ranges from 1 mg to 10 mg, from 1 mg to 8 mg, from 2 mg to 8 mg, from 3 mg to 7 mg, or from 4 mg to 6 mg.

[0043] In a sixteenth embodiment, a subject treated by the methods and uses described herein (e.g., as in any one of the first to fifteenth embodiments) are characterized as progressed or relapsed to a disclosed androgen receptor signaling inhibitor, a steroid, a pharmacological inhibitor of the enzyme poly ADP ribose polymerase (PARP), a tyrosine

kinase inhibitor, a checkpoint inhibitor, radium 223, radiotherapy, chemotherapy, a CYP17A inhibitor, a steroid, or a VEGF inhibitor. In one aspect, a subject treated by the methods and uses described herein (e.g., as in any one of the first to fifteenth embodiments) are characterized as progressed or relapsed to chemotherapy, PARP inhibitors, tyrosine kinase inhibitors, checkpoint inhibitors, radium 223, or radiotherapy. In one aspect, a subject treated by the methods and uses described herein (e.g., as in any one of the first to fifteenth embodiments) are characterized as progressed or relapsed to a disclosed androgen receptor signaling inhibitor (e.g., enzalutamide, abiraterone acetate, and abiraterone acetate/prednisone).

[0044] In a seventeenth embodiment, a subject treated by the methods and uses described herein (e.g., as in any one of the first to fifteenth embodiments) is characterized as refractory or resistant to a disclosed androgen receptor signaling inhibitor, a steroid, a pharmacological inhibitor of the enzyme poly ADP ribose polymerase (PARP), a tyrosine kinase inhibitor, a checkpoint inhibitor, radium 223, radiotherapy, chemotherapy, a CYP17A inhibitor, a steroid, or a VEGF inhibitor. In one aspect, a subject treated by the methods and uses described herein (e.g., as in any one of the first to fifteenth embodiments) is characterized as refractory or resistant to chemotherapy, PARP inhibitors, tyrosine kinase inhibitors, checkpoint inhibitors, radium 223, or radiotherapy. In one aspect, a subject treated by the methods and uses described herein (e.g., as in any one of the first to fifteenth embodiments) is characterized as refractory or resistant to a disclosed androgen receptor signaling inhibitor (e.g., enzalutamide, abiraterone acetate, and abiraterone acetate/prednisone).

[0045] In an eighteenth embodiment, the methods, uses, and compositions described herein further comprise the addition of a therapeutically effective amount of cobicistat, or a pharmaceutically acceptable salt thereof.

EXEMPLIFICATION

[0046] (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide can be made according to the procedure set forth in U.S. Patent No. 9,085,583, the contents of which are incorporated herein by reference.

Effects on Cell Viability Using Compound 1 and ARSIs

[0047] The synergistic relationship between Compound 1 and ARSIs was examined. Prostate cancer cell lines were seeded in 96 well microtiter dishes in triplicate at cellular densities determined to maintain cells in log-phase growth for the duration of the treatment

period. Cells were treated with a titration of Compound 1, ARSI, or the combination of both, or a DMSO control in cell growth medium for seven days. After 7 days, cells were washed, enzymatically removed from the microtiter dish, and a fraction of the cells were evaluated for viability by following the manufacturer's instructions of a commercial kit that measures ATP levels (Promega Cell Titer Glo), with relative luminescence units (RLU) determined by a luminescence reader (Perkin-Elmer Envision). The remaining cells were reseeded in a new microtiter dish, with the DMSO-treated cells seeded at the same cellular density used at the outset of the experiment, and the remainder of the wells seeded using the same volume determined for the DMSO-treated cells. Well volumes were normalized with growth medium containing the same titration of drugs used at the outset of the experiment. The procedure was repeated every 7 days for up to 28 days. Relative cell viability percentage at each time point was calculated by dividing the RLU of each experimental condition by the RLU of the DMSO-treated control on the same plate, then multiplied by 100. The mean value plus or minus the standard error of the mean from triplicate plates were plotted versus concentration of either drug, and non-linear regression used to generate curve and extrapolate the 50% growth inhibition value (GI50). For combination plots, at each time point, the titration of one drug was represented on the x-axis with the titration of the other drug represented as different colored curves. To display a visual representation of synergy between the drugs used in combination, the relative cell viability for a titration of Compound 1 in the presence of varying concentrations of the ARSI was normalized to the relative cell viability of the ARSI used as a single agent. Additive effects on cellular viability result in curves that overlay, whereas synergistic effects on cellular viability result in a shift of the curve to the left. Representative results are shown by **FIG. 1**. As shown, LNCaP cell viability was impacted by either Compound 1 or the ARSI enzalutamide, with co-treatment of Compound 1 and the ARSI enzalutamide resulting in synergistic inhibition of cell viability.

[0048] Various cell lines treated with combination of Compound 1 and the ARSIs enzalutamide or abiraterone for up to 28 days. Cells were split, re-seeded, and fed fresh drug every 7 days. Combinatorial activity was determined using both Bliss and Loewe models of synergy, with Bliss synergy scores or Chou-Talalay combination index (CI) values determined for the GI50 effect level for all combinations when applicable. The results are shown in **FIG. 2**.

Efficacy in Prostate Tumor Models

[0049] Intact male CB17/SCID mice inoculated with LNCaP cell line in Matrigel. Mice were randomized into treatment groups once mean tumor volume reached 150 cubic mm.

Combination treatment with Compound **1** and enzalutamide resulted in enhanced tumor growth inhibition (TGI) with 2 out of 7 animals showing tumor regression. Results are shown in **FIG. 3** and **Table 1**.

[0050] Table 1

Treatment Group	TGI	Regressions/total
Vehicle	0%	0/8
Compound 1	35%	0/7
enzalutamide	40%	0/8
Compound 1 + enzalutamide	65%	2/7

Human Clinical Data

[0051] Ten patients in a Phase 1b trial were treated with Compound **1**, consisting of four patients treated with the combination of Compound **1** and abiraterone acetate and six patients treated with the combination of Compound **1** and enzalutamide. Eight patients had unfavorable CTC counts (greater than five cells per 7.5 mL of blood) at baseline determined by the Veridex CellSearch assay, which is a poor prognostic factor for overall survival in patients with mCRPC. Four patients had soft tissue metastases at baseline. Three patients were ARV7 positive at baseline based on at least one of two assays that we use to measure ARV7. ARV7 is a marker for more aggressive mCRPC. Of the ten patients, seven patients were treated for longer than one month, and of those seven patients, three patients have been treated for more than two months and two patients have been treated for longer than four months. **FIG. 4** presents the duration of treatment for each of the ten patients treated in the trial.

[0052] One patient, treated with the combination of Compound **1** and abiraterone acetate, discontinued treatment prior to completing one cycle (28 days) due to elevated liver enzymes, or transaminases. The elevated transaminases were asymptomatic and reversible. This patient also had clinical disease progression. No other dose-limiting toxicities have been observed and each combination was generally well tolerated. No treatment-related serious adverse events in this trial were observed. One patient treated with the combination of Compound **1**, abiraterone acetate and the co-medication had evidence of progression and died due to complications of pneumonia after two cycles of treatment in the trial. The clinical investigator concluded that the fatal event was not related to treatment with the trial combination.

[0053] Both of the patients who have been on therapy for more than four months have been treated in the combination of Compound **1** and enzalutamide arm. One of these patients experienced an 85% reduction in PSA level after one cycle of therapy. This patient had measurable soft tissue disease and an unfavorable CTC count. This patient experienced a complete response after two months of treatment as assessed by CT scan and converted to favorable CTC status (defined as less than five cells per 7.5 mL of blood). The other patient experienced an 83% reduction in PSA levels after one cycle of therapy. This patient chose to discontinue treatment with enzalutamide after the first cycle of combination therapy and continued to be treated with Compound **1** as a monotherapy. Prior to entering the trial, this patient had metastatic bone disease, and after three cycles of therapy, the PET/CT scan showed resolution of bone metastasis. See **FIG. 8** and **FIG. 9**. **FIG. 5** shows the evolution of PSA changes for each evaluable patient treated in the trial beginning with the pre-screening period (prior to treatment). One patient did not have a PSA measurement at baseline and is not included in the figure below. **FIG. 6** depicts the change in CTC counts in the four patients in the trial who had unfavorable CTC counts at baseline and had at least one post-baseline CTC measurement. Each of these patients have been treated in the enzalutamide arm. As in **FIG. 6**, two of these patients have experienced a reduction in CTC count of more than 30% from baseline.

[0054] Two patients were treated with a combination of Compound **1** and enzalutamide under a compassionate use protocol based on preliminary anti-tumor activity. The first patient's cancer previously progressed on treatment with both abiraterone acetate and enzalutamide as well as multiple chemotherapy treatments, treatment with immune checkpoint inhibitors, treatment with a tyrosine kinase enzyme inhibitor and radium regimens. Shortly after first dosing with Compound **1** and enzalutamide, treatment was interrupted for approximately four days due to non-treatment associated pneumonia. Based on an assessment taken two weeks after initiation of therapy, this patient was observed to have an 80% reduction in PSA levels and showed evidence of tumor size reduction in the neck by palpation. See **FIG. 7**. Subsequently, the patient was found to have progressive disease in the liver, stopped therapy, and died shortly thereafter due to disease progression. The second patient was heavily pretreated with abiraterone acetate, enzalutamide and docetaxel. This patient stopped chemotherapy without evidence of progressive disease and began treatment with Compound **1** and enzalutamide, rendering us unable to evaluate the results of treatment. This patient discontinued the experimental combination due to disease progression.

[0055] The contents of all references (including literature references, issued patents, published patent applications, and co-pending patent applications) cited throughout this application are hereby expressly incorporated herein in their entireties by reference. Unless otherwise defined, all technical and scientific terms used herein are accorded the meaning commonly known to one with ordinary skill in the art.

Listing of Claims:

1. A method of treating prostate cancer in a subject comprising administering to the subject a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof.
2. The method of Claim 1, wherein the prostate cancer is selected from acinar adenocarcinoma, ductal adenocarcinoma, transitional cell cancer, squamous cell cancer, small cell prostate cancer, and castration resistant prostate cancer (CRPC).
3. The method of Claim 1 or 2, wherein the prostate cancer is metastatic castration resistant prostate cancer (mCRPC).
4. The method of any one of Claims 1 to 3, wherein the androgen receptor signaling inhibitor is selected from enzalutamide, abiraterone acetate, bicalutamide, apalutamide, and darolutamide, or a pharmaceutically acceptable salt thereof.
5. The method of any one of Claims 1 to 4, wherein the androgen receptor signaling inhibitor is enzalutamide, or a pharmaceutically acceptable salt thereof.
6. The method of Claim 5, wherein the therapeutically effective amount of enzalutamide, or pharmaceutically acceptable salt thereof, ranges from 50 mg to 1.0 gram, from 50 mg to 500 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, or from 100 mg to 200 mg.
7. The method of Claim 5 or 6, wherein the therapeutically effective amount of enzalutamide, or pharmaceutically acceptable salt thereof, ranges from 150 mg to 170 mg.
8. The method of any one of Claims 1 to 4, wherein the androgen receptor signaling inhibitor is abiraterone acetate.

9. The method of Claim 8, wherein the therapeutically effective amount of abiraterone acetate ranges from 100 mg to 3.0 grams, from 500 mg to 2.5 grams, from 500 mg to 2.0 grams, from 500 mg to 1.5 grams, or from 750 mg to 1.5 grams.
10. The method of Claim 8 or 9, wherein the therapeutically effective amount of abiraterone acetate ranges from 900 mg to 1.1 grams.
11. The method of any one of Claims 1 to 4 and 8 to 10, further comprising administering a therapeutically effective amount of prednisone, of a pharmaceutically acceptable salt thereof.
12. The method of Claim 11, wherein the therapeutically effective amount of prednisone, or pharmaceutically acceptable salt thereof, ranges from 1 mg to 10 mg, from 1 mg to 8 mg, from 2 mg to 8 mg, or from 3 mg to 7 mg.
13. The method of Claim 8 or 9, wherein the therapeutically effective amount of prednisone, or pharmaceutically acceptable salt thereof, ranges from 4 mg to 6 mg.
14. The method of any one of Claims 1 to 13, wherein the therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or pharmaceutically acceptable salt thereof, ranges from 100 mg to 3.5 grams, from 200 mg to 3.0 grams, from 200 mg to 2.5 grams, from 200 mg to 1.0 grams, from 200 mg to 1.5 grams, from 200 mg to 1 gram, from 300 mg to 800 mg, from 400 mg to 800 mg, from 400 mg to 600 mg, from 1.0 grams to 2.0 grams, from 1.4 grams to 1.7 grams, from 500 mg to 700 mg, from 550 mg to 650 mg, from 700 mg to 900 mg, from 750 mg to 850 mg, from 300 mg to 500 mg, or from 350 mg to 450 mg.
15. The method of any one of Claims 1 to 14, wherein the subject is refractory to treatment with an androgen receptor signaling inhibitor, a steroid, a pharmacological inhibitor of the enzyme poly ADP ribose polymerase (PARP), a CYP17A inhibitor, a steroid, or a VEGF inhibitor.

16. The method of any one of Claims 1 to 14, wherein the subject is progressed to treatment with an androgen receptor signaling inhibitor, a steroid, a pharmacological inhibitor of the enzyme poly ADP ribose polymerase (PARP), a CYP17A inhibitor, a steroid, or a VEGF inhibitor .

17. A pharmaceutical composition comprising a therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of an androgen receptor signaling inhibitor, or a pharmaceutically acceptable salt thereof.

18. The pharmaceutical composition of Claim 17, wherein the androgen receptor signaling inhibitor is selected from enzalutamide, abiraterone acetate, bicalutamide, apalutamide, and darolutamide, or a pharmaceutically acceptable salt thereof.

19. The pharmaceutical composition of Claim 17 or 18, wherein the androgen receptor signaling inhibitor is enzalutamide, or a pharmaceutically acceptable salt thereof.

20. The pharmaceutical composition of Claim 19, wherein the therapeutically effective amount of enzalutamide, or pharmaceutically acceptable salt thereof, ranges from 50 mg to 1.0 gram, from 50 mg to 500 mg, from 50 mg to 300 mg, from 50 mg to 200 mg, or from 100 mg to 200 mg.

21. The pharmaceutical composition of Claim 19 or 20, wherein the therapeutically effective amount of enzalutamide, or pharmaceutically acceptable salt thereof, ranges from 150 mg to 170 mg enzalutamide.

22. The pharmaceutical composition of Claim 17 or 18, wherein the androgen receptor signaling inhibitor is abiraterone acetate.

23. The pharmaceutical composition of Claim 22, wherein the therapeutically effective amount of abiraterone acetate ranges from 100 mg to 3.0 grams, from 500 mg to 2.5 grams, from 500 mg to 2.0 grams, from 500 mg to 1.5 grams, or from 750 mg to 1.5 grams.

24. The pharmaceutical composition of Claim 22 or 23, wherein the therapeutically effective amount of abiraterone acetate ranges from 900 mg to 1.1 grams.
25. The pharmaceutical composition of any one of Claims 17, 18, and 22 to 24, wherein the pharmaceutical composition further comprises prednisone, or a pharmaceutically acceptable salt thereof.
26. The pharmaceutical composition of Claim 25, wherein the therapeutically effective amount of prednisone, or pharmaceutically acceptable salt thereof, ranges from 1 mg to 10 mg, from 1 mg to 8 mg, from 2 mg to 8 mg, or from 3 mg to 7 mg.
27. The pharmaceutical composition of Claim 25 or 26, wherein the therapeutically effective amount of prednisone, or pharmaceutically acceptable salt thereof, ranges from 4 mg to 6 mg.
28. The pharmaceutical composition of any one of Claims 17 to 27, wherein the therapeutically effective amount of (R)-N-((4-methoxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)-2-methyl-1-(1-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)ethyl)-1H-indole-3-carboxamide, or pharmaceutically acceptable salt thereof, ranges from 100 mg to 3.5 grams, from 200 mg to 3.0 grams, from 200 mg to 2.5 grams, from 200 mg to 1.0 grams, from 200 mg to 1.5 grams, from 200 mg to 1 gram, from 300 mg to 800 mg, from 400 mg to 800 mg, from 400 mg to 600 mg, from 1.0 grams to 2.0 grams, from 1.4 grams to 1.7 grams, from 500 mg to 700 mg, from 550 mg to 650 mg, from 700 mg to 900 mg, from 750 mg to 850 mg, from 300 mg to 500 mg, or from 350 mg to 450 mg.
29. The pharmaceutical composition of any one of Claims 17 to 28, wherein the pharmaceutical composition is formulated for oral administration.

FIG. 1

Day 14 co-treatment

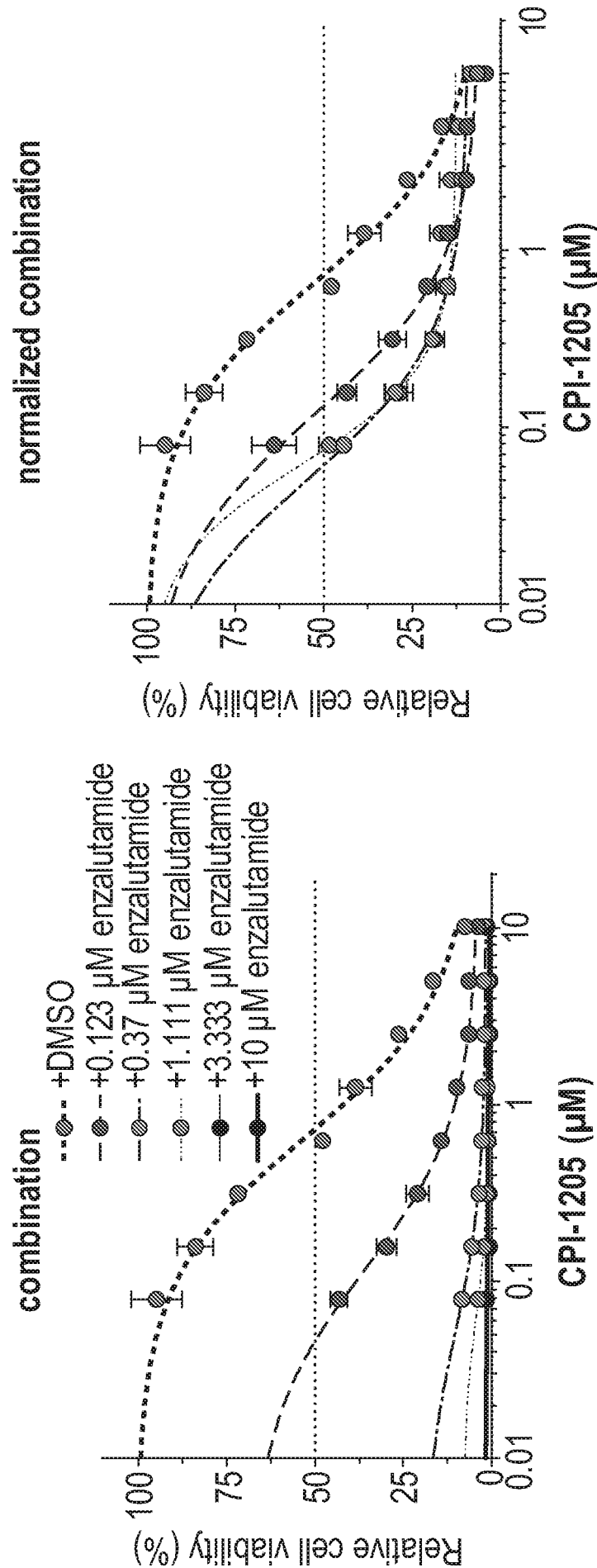


FIG. 2

Cell Line	Treatment	GI50 (µM)				Bliss synergy score combo w/CPI-1205				Combination index combo w/CPI-1205			
		D7	D14	D21	D28	D7	D14	D21	D28	D7	D14	D21	D28
DU145	CPI-1205	>10	>10	>10	>10								
	enzalutamide	>10	>10	>10	>10	0.00	0.24	0.32	0.50	na	na	na	na
	abiraterone	>10	>10	>10	>10	0.00	0.09	0.15	0.05	na	na	na	na
PC3	CPI-1205	>10	>10	>10	>10								
	enzalutamide	>10	>10	>10	>10	0.00	0.08	0.19	0.23	na	na	na	na
	abiraterone	>10	8.37	7.87	8.33	0.04	0.16	0.34	0.10	na	na	na	na
VCaP	CPI-1205	>10	4.09	0.52	0.26								
	enzalutamide	>10	4.52	0.92	1.01	0.69	3.36	2.80	2.17	na	0.21	0.34	0.51
	abiraterone	>10	>10	>10	>10	0.25	3.69	3.28	3.36	na	na	0.28	0.31
22Rv1	CPI-1205	>10	0.52	0.31	0.23								
	enzalutamide	>10	7.33	6.15	2.53	0.69	0.51	0.76	1.71	na	0.40	0.60	0.43
	abiraterone	>10	3.54	3.95	4.00	0.32	0.34	0.26	0.67	na	0.42	0.72	0.58
LNCaP	CPI-1205	>10	0.95	0.42	0.20								
	enzalutamide	1.04	0.18	0.15	0.14	2.93	1.34	0.91	0.71	na	0.38	0.57	0.61
	abiraterone	>10	5.10	2.06	1.79	1.81	3.05	1.67	1.59	na	0.30	0.61	0.68
LNCaP +1 nM R1881	CPI-1205	>10	>10	0.20	0.07								
	enzalutamide	>10	>10	3.88	3.86	0.47	3.46	5.25	2.76	na	na	na	na
	abiraterone	>10	>10	>10	9.73	0.06	0.59	1.01	0.84	na	na	na	na
LNCaP +60 pM R1881	CPI-1205	>10	>10	0.65	0.32								
	enzalutamide	0.95	0.20	0.16	0.17	0.06	0.27	0.42	0.53	na	na	0.44	0.56
	abiraterone	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd

FIG. 3

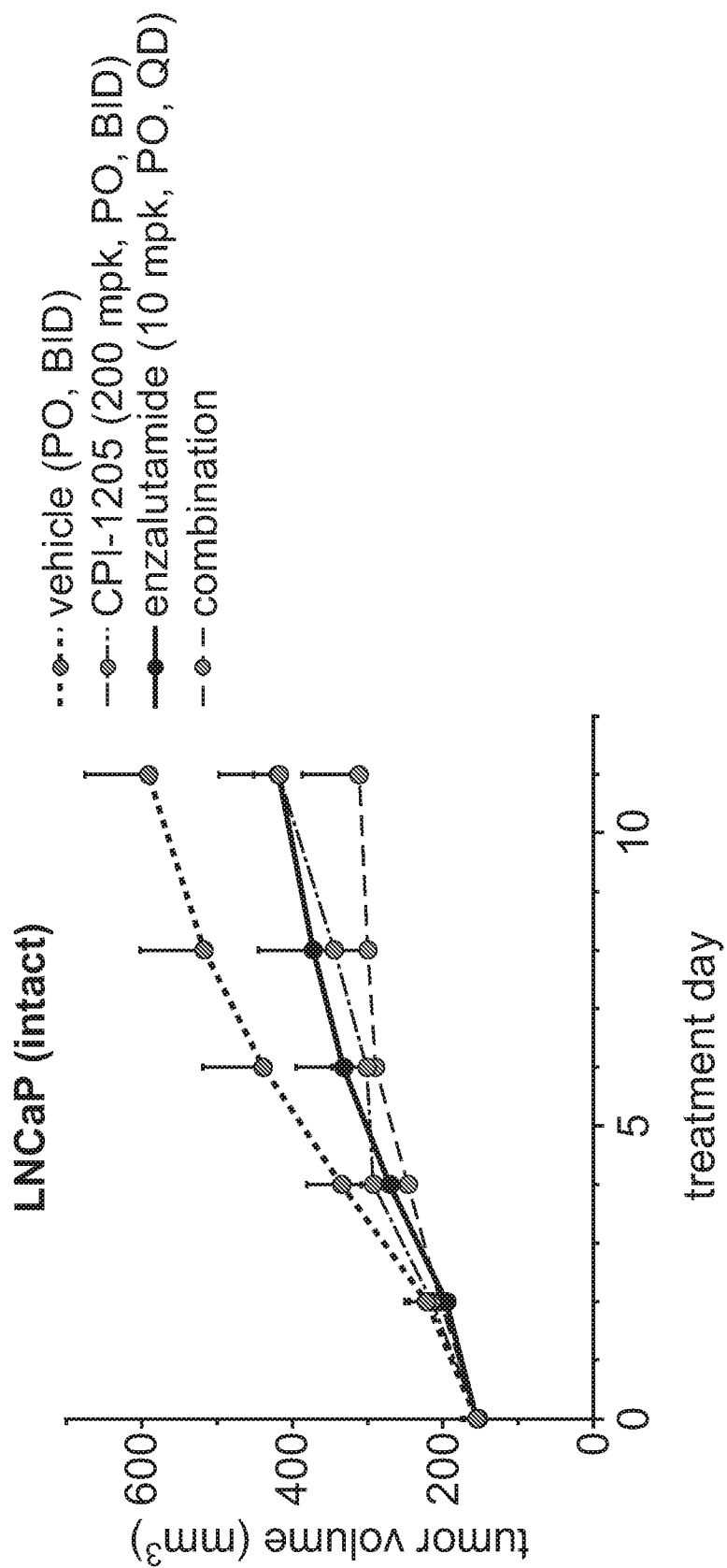


FIG. 4

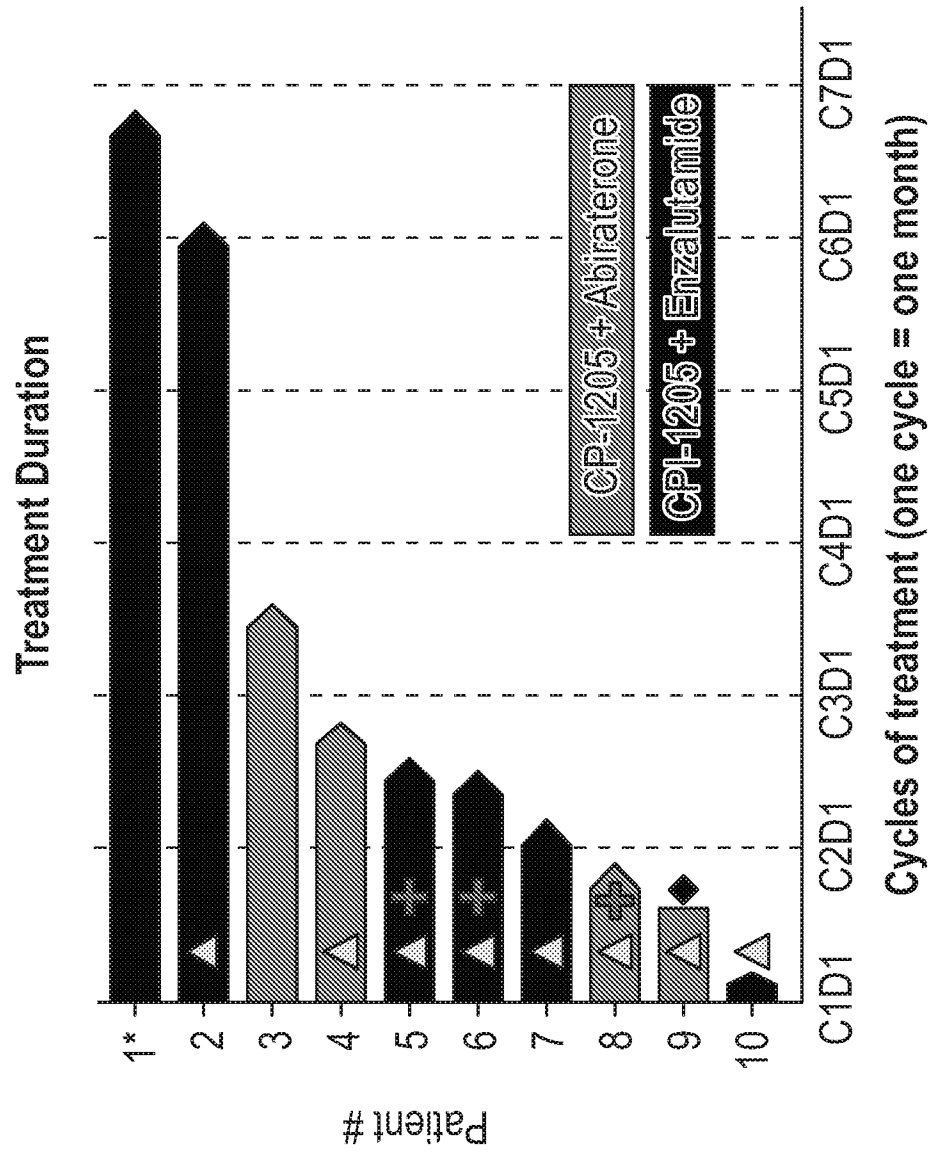


FIG. 6

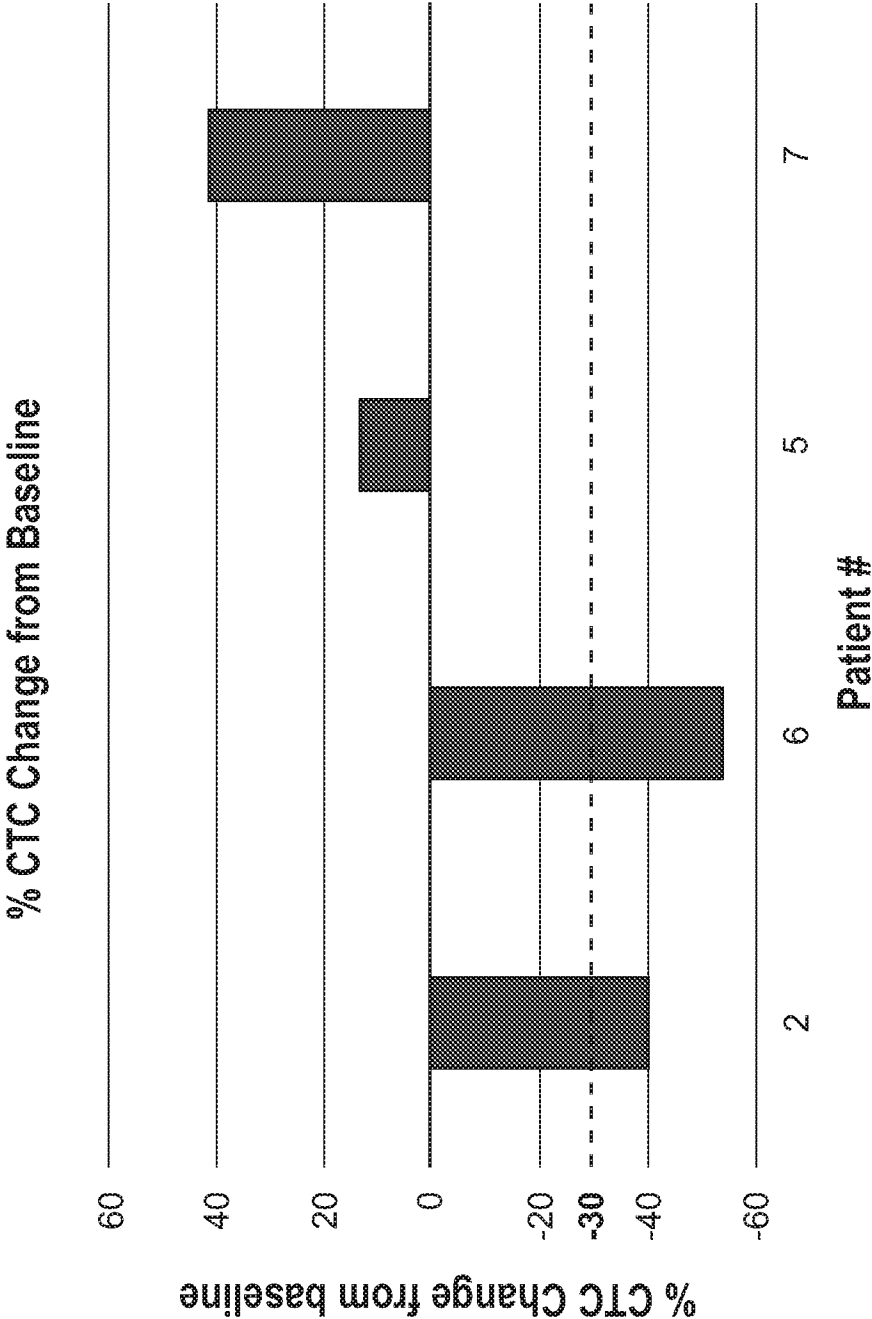


FIG. 7

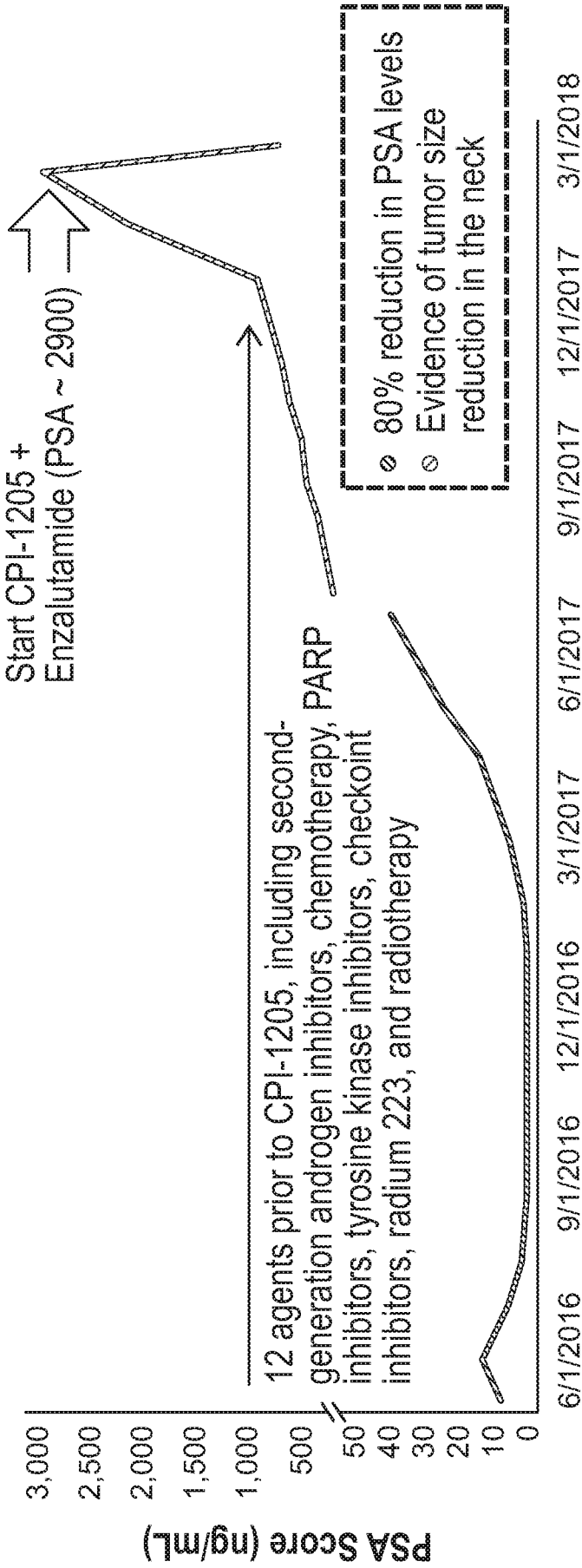


FIG. 8

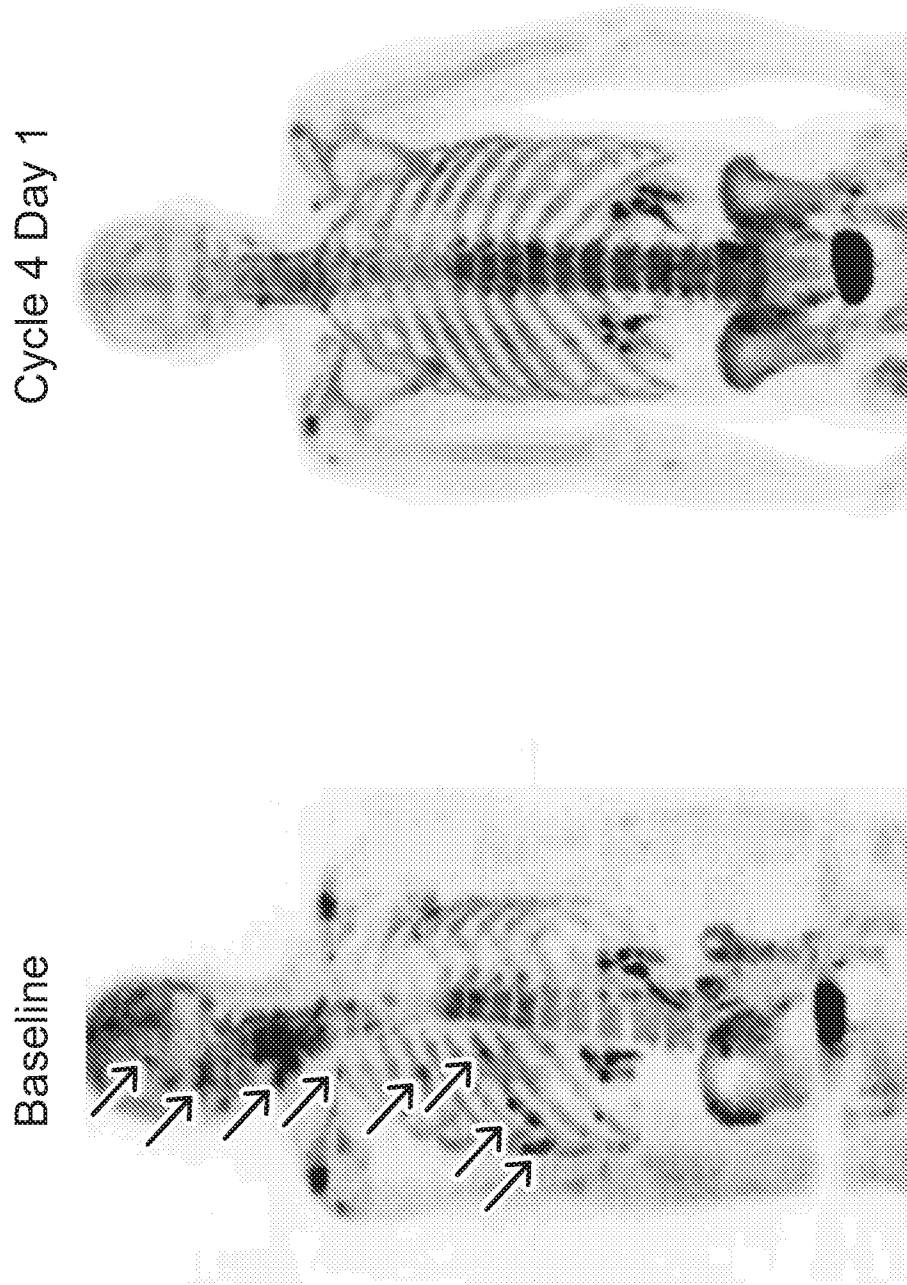
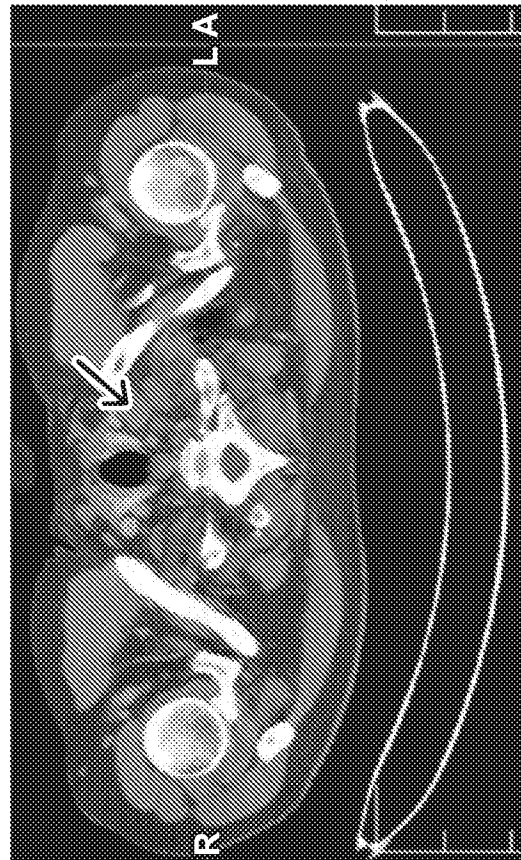


FIG. 9

February 2018



Baseline: December 2017



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/068575

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K31/4166 A61K31/4545 A61K31/58 A61P35/00 A61K31/573 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, SCISEARCH, 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	TAPLIN M-E ET AL: "A phase 1b/2 study of CPI-1205, a small molecule inhibitor of EZH2, combined with enzalutamide (E) or abiraterone/prednisone (A/P) in patients with metastatic castration resistant prostate cancer (mCRPC)", EMBASE, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, 1 February 2018 (2018-02-01), XP002788198, the whole document	1-13, 17-27,29
Y	----- WO 2018/136596 A1 (CONSTELLATION PHARMACEUTICALS INC [US]) 26 July 2018 (2018-07-26) claims ----- -/--	1-29
☒ 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 "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "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 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 6 April 2020		Date of mailing of the international search report 17/04/2020
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Venturini, Francesca

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/068575

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	XIAO LANBO ET AL: "Epigenetic Reprogramming with Antisense Oligonucleotides Enhances the Effectiveness of Androgen Receptor Inhibition in Castration-Resistant Prostate Cancer", CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, AACR ANNUAL MEETING 2018; APRIL 14-18, 2018; CHICAGO, IL, vol. 78, no. 20, 15 October 2018 (2018-10-15), pages 5731-5740, XP002788199, ISSN: 1538-7445, DOI: 10.1158/0008-5472.CAN-18-0941 results, discussion; figures -----	1-29
Y	US 2018/296574 A1 (SNYDER LINDA ANNE [US] ET AL) 18 October 2018 (2018-10-18) claims; examples -----	1-29

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2019/068575

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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