ANTI-ANDROGENS FOR THE TREATMENT OF NON-METASTATIC CASTRATE-RESISTANT PROSTATE CANCER

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Patent Application Ser. No. 61/705,900, filed September 26, 2012, the contents of which are incorporated by reference herein in its entirety for all putrposes

FIELD OF THE INVENTION

[0002] Described herein are methods of treating non-metastatic castrate-resistant prostate cancer with anti-androgens, including but not limited to, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.

BACKGROUND OF THE INVENTION

[0003] Prostate cancer is the second most frequently diagnosed cancer and the second leading cause of cancer death in males. The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states based on the extent of disease, hormonal status, and absence or presence of detectable metastases: localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate state.

SUMMARY OF THE INVENTION

[0004] In one aspect, described herein is a method of treating non-metastatic castration-resistant prostate cancer in a male human comprising administering a therapeutically effective amount of an anti-androgen to a male human with non-metastatic castration-resistant prostate cancer. In some embodiments, wherein the non-metastatic castration-resistant prostate

cancer is high risk non-metastatic castration-resistant prostate cancer. In some embodiments, the male human with high risk non-metastatic castration-resistant prostate cancer has a prostate-specific antigen doubling time (PSADT) that is less than or equal to 10 months. In some embodiments, administration of the anti-androgen provides an increase in the metastasis-free survival of the male human.

[0005] In another aspect, described herein is a method of providing an increase in the metastasis-free survival of a male human with prostate cancer comprising administering a therapeutically effective amount of an anti-androgen to the male human with prostate cancer. In some embodiments, the prostate cancer is non-metastatic castration-resistant prostate cancer. In some embodiments, the prostate cancer is high risk non-metastatic castration-resistant prostate cancer. In some embodiments, the male human with high risk non-metastatic castration-resistant prostate cancer has a prostate-specific antigen doubling time (PSADT) that is less than or equal to 10 months.

[0006] In some embodiments, the anti-androgen is a non-steroidal anti-androgen.

[0007] In some embodiments, the anti-androgen binds directly to the ligand-binding domain of the androgen receptor.

[0008] In some embodiments, the anti-androgen is a second-generation anti-androgen.

[0009] In some embodiments, the anti-androgen is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide; 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide (enzalutamide); or 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (RD162).

[0010] In some embodiments, the anti-androgen is administered orally to the male human. In some embodiments, the anti-androgen is administered to the male human in the form of a tablet, a pill, a capsule, a solution, a suspension, or a dispersion. In some embodiments, the anti-androgen is administered to the male human on a continuous daily dosing schedule.

[0011] In some embodiments, the anti-androgen is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-

6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered daily to the male human. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30mg per day to about 480mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 180mg per day to about 480mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30mg per day, about 60mg per day, about 90mg per day, about 120mg per day, about 180mg per day, about 240mg per day, about 300mg per day, about 390mg per day, or about 480mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 240mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human on a continuous daily dosing schedule.

[0012] In any of the embodiments described herein, the methods of treatment further comprises administering a gonadotropin-releasing hormone (GnRH) agonist. In some embodiments, the GnRH agonist is leuprolide, buserelin, nafarelin, histrelin, goserelin, or deslorelin.

[0013] In any of the aforementioned aspects the effective amount of the anti-androgen is: (a) systemically administered to the male human; and/or (b) administered orally to the male human; and/or (c) intravenously administered to the male human; and/or (d) administered by injection to the male human.

[0014] In any of the aforementioned aspects, the effective amount of the anti-androgen is administered (i) once a day; or (ii) multiple times over the span of one day. In some embodiments, the effective amount of the anti-androgen is administered once a day, twice a day, three times a day or four times a day.

[0015] In any of the aforementioned aspects the effective amount of the anti-androgen is administered continuously or intermittently. In some embodiments, the effective amount of the anti-androgen is administered continuously. In some embodiments, the effective amount of the anti-androgen is administered daily.

[0016] In some embodiments, compounds provided herein are orally administered.

[0017] Other objects, features and advantages of the methods, uses and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description

DETAILED DESCRIPTION OF THE INVENTION

[0018] It is to be appreciated that certain features of the invention which are, for clarity, described herein in the context of separate embodiments, may also be provided in combination in a single embodiment. That is, unless obviously incompatible or specifically excluded, each individual embodiment is deemed to be combinable with any other embodiment(s) and such a combination is considered to be another embodiment. Conversely, various features of the invention that are, for brevity, described in the context of a single embodiment, may also be provided separately or in any sub-combination. Finally, while an embodiment may be described as part of a series of steps or part of a more general structure, each said step may also be considered an independent embodiment in itself, combinable with others.

[0019] The transitional terms "comprising," "consisting essentially of," and "consisting" are intended to connote their generally in accepted meanings in the patent vernacular; that is, (i) "comprising," which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps; (ii) "consisting of" excludes any element, step, or ingredient not specified in the claim; and (iii) "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel

characteristic(s)" of the claimed invention. Embodiments described in terms of the phrase "comprising" (or its equivalents), also provide, as embodiments, those which are independently described in terms of "consisting of" and "consisting essentially of."

[0020] When a list is presented, unless stated otherwise, it is to be understood that each individual element of that list, and every combination of that list, is a separate embodiment. For example, a list of embodiments presented as "A, B, or C" is to be interpreted as including the embodiments, "A," "B," "C," "A or B," "A or C," "B or C," or "A, B, or C."

[0021] Androgen receptor (AR) is a member of the steroid and nuclear receptor superfamily. Among this large family of proteins, only five vertebrate steroid receptors are known and include the androgen receptor, estrogen receptor, progesterone receptor, glucocorticoid receptor, and mineralocorticoid receptor. AR is a soluble protein that functions as an intracellular transcriptional factor. AR function is regulated by the binding of androgens, which initiates sequential conformational changes of the receptor that affect receptor–protein interactions and receptor–DNA interactions.

[0022] AR is mainly expressed in androgen target tissues, such as the prostate, skeletal muscle, liver, and central nervous system (CNS), with the highest expression level observed in the prostate, adrenal gland, and epididymis. AR can be activated by the binding of endogenous androgens, including testosterone and 5α-dihydrotestosterone (5α-DHT).

[0023] The androgen receptor (AR), located on Xq11-12, is a 110 kD nuclear receptor that, upon activation by androgens, mediates transcription of target genes that modulate growth and differentiation of prostate epithelial cells. Similar to the other steroid receptors, unbound AR is mainly located in the cytoplasm and associated with a complex of heat shock proteins (HSPs) through interactions with the ligand-binding domain. Upon agonist binding, AR goes through a series of conformational changes: the heat shock proteins dissociate from AR, and the transformed AR undergoes dimerization, phosphorylation, and translocation to the nucleus, which is mediated by the nuclear localization signal. Translocated receptor then binds to the androgen response element (ARE), which is characterized by the six-nucleotide half-site consensus sequence 5′-TGTTCT-3′ spaced by three random nucleotides and is located in the promoter or enhancer region of AR gene targets. Recruitment of other transcription co-regulators (including co-activators and co-repressors) and transcriptional machinery further

ensures the transactivation of AR-regulated gene expression. All of these processes are initiated by the ligand-induced conformational changes in the ligand-binding domain.

[0024] AR signaling is crucial for the development and maintenance of male reproductive organs including the prostate gland, as genetic males harboring loss of function AR mutations and mice engineered with AR defects do not develop prostates or prostate cancer. This dependence of prostate cells on AR signaling continues even upon neoplastic transformation. Androgen depletion (such as using GnRH agonists) continues to be the mainstay of prostate cancer treatment. However androgen depletion is usually effective for a limited duration and prostate cancer evolves to regain the ability to grow despite low levels of circulating androgens. Castration resistant prostate cancer (CRPC) is a lethal phenotype and almost all of patients will die from prostate cancer . Interestingly, while a small minority of CRPC does bypass the requirement for AR signaling, the vast majority of CRPC, though frequently termed "androgen independent prostate cancer" or "hormone refractory prostate cancer," retains its lineage dependence on AR signaling.

[0025] Prostate cancer is the second most common cause of cancer death in men in the US, and approximately one in every six American men will be diagnosed with the disease during his lifetime. Treatment aimed at eradicating the tumor is unsuccessful in 30% of men, who develop recurrent disease that is usually manifest first as a rise in plasma prostate-specific antigen (PSA) followed by spread to distant sites. Given that prostate cancer cells depend on androgen receptor (AR) for their proliferation and survival, these men are treated with agents that block production of testosterone (e.g. GnRH agonists), alone or in combination with anti-androgens (e.g. bicalutamide), which antagonize the effect of any residual testosterone on AR. The approach is effective as evidenced by a drop in PSA and regression of visible tumor (if present) in some patients; however, this is followed by regrowth as a castration resistant prostate cancer (CRPC) to which most patients eventually succumb. Recent studies on the molecular basis of CRPC have demonstrated that CRPC continues to depend on AR signaling and that a key mechanism of acquired resistance is an elevated level of AR protein (*Nat. Med, 2004, 10, 33-39*). AR targeting agents with activity in castration sensitive and castration resistant resistant prostate cancer have great promise in treating this lethal disease.

[0026] The course of prostate cancer from diagnosis to death is best categorized as a series of clinical states based on the extent of disease, hormonal status, and absence or presence

of detectable metastases: localized disease, rising levels of prostate-specific antigen (PSA) after radiation therapy or surgery with no detectable metastases, and clinical metastases in the non-castrate or castrate state. Although surgery, radiation, or a combination of both can be curative for patients with localized disease, a significant proportion of these patients have recurrent disease as evidenced by a rising level of PSA, which can lead to the development of metastases, especially in the high risk group – a transition to the lethal phenotype of the disease.

[0027] Androgen depletion is the standard treatment with a generally predictable outcome: decline in PSA, a period of stability in which the tumor does not proliferate, followed by rising PSA and regrowth as castration-resistant disease. Molecular profiling studies of castration-resistance prostate cancers commonly show increased androgen receptor (AR) expression, which can occur through AR gene amplification or other mechanisms.

[0028] Anti-androgens are useful for the treatment of prostate cancer during its early stages. However, prostate cancer often advances to a 'hormone-refractory' state in which the disease progresses in the presence of continued androgen ablation or anti-androgen therapy. Instances of antiandrogen withdrawal syndrome have also been reported after prolonged treatment with anti-androgens. Antiandrogen withdrawal syndrome is commonly observed clinically and is defined in terms of the tumor regression or symptomatic relief observed upon cessation of antiandrogen therapy. AR mutations that result in receptor promiscuity and the ability of these anti-androgens to exhibit agonist activity might at least partially account for this phenomenon. For example, hydroxyflutamide and bicalutamide act as AR agonists in T877A and W741L/W741C AR mutants, respectively.

[0029] In the setting of prostate cancer cells that were rendered castration resistant via overexpression of AR, it has been demonstrated that certain anti-androgen compounds, such as bicalutamide, have a mixed antagonist/agonist profile (Science, 2009 May 8;324(5928): 787-90). This agonist activity helps to explain a clinical observation, called the anti-androgen withdrawal syndrome, whereby about 30% of men who progress on AR antagonists experience a decrease in serum PSA when therapy is discontinued (*J Clin Oncol, 1993. **11**(8): p. 1566-72*).

Prostate Cancer Stages

[0030] In the early stages of prostate cancer, the cancer is localized to the prostate. In these early stages, treatment typically involes either surgical removal of the prostate or radiation therapy to the prostate or observation only with no active intervention therapy in some

patients. In the early stages where the prostate cancer is localized and requires intervention, surgery or radiation therapy are curative by eradicating the cancerous cells. About 30% of the time these procedures fail, and the prostate cancer continues to progress, as typically evidenced by a rising PSA level. Men whose prostate cancer has progressed following these early treatment strategies are said to have advanced or recurrent prostate cancer.

[0031] Because prostate cancer cells depend on the androgen receptor (AR) for their proliferation and survival, men with advanced prostate cancer are treated with agents that block the production of testosterone (eg, GnRH agonists), alone or in combination with anti-androgens (eg, bicalutamide), which antagonize the effect of any residual testosterone on AR. These treatments reduce serum testosterone to castrate levels, which generally slows disease progression for a period of time. The approach is effective as evidenced by a drop in PSA and the regression of visible tumors in some patients. Eventually, however, this is followed by regrowth referred to as castration-resistant prostate cancer (CRPC), to which most patients eventually succumb.

[0032] Castration-resistant prostate cancer (CRPC) is categorized as non-metastatic or metastatic, depending on whether or not the prostate cancer has metastasized to other parts of the body.

[0033] In some embodiments, prior to treatment with a second-generation anti-androgen men with non-metastatic CRPC are characterized as having the following:

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, with high risk for development of metastases.
2. Castration-resistant prostate cancer demonstrated during continuous androgen deprivation therapy (ADT)/post orchiectomy. For example defined as 3 consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with the last PSA > 2 ng/mL.
3. Maintain castrate levels of testosterone (< 50 ng/dL [1.72 nmol/L]) within 4 weeks of randomization and throughout the study.
4. Absence of distant metastasis by bone scan, CT or MRI scans.

Anti-Androgens

[0034] As used herein, the term "anti-androgen" refers to a group of hormone receptor antagonist compounds that are capable of preventing or inhibiting the biologic effects of androgens on normally responsive tissues in the body. In some embodiments, an anti-androgen is a small molecule. In some embodiments, an anti-androgen is an AR antagonist. In some embodiments, an anti-androgen is an AR full antagonist. In some embodiments, an anti-androgen is a first-generation anti-androgen. In some embodiments, an anti-androgen is a second-generation anti-androgen.

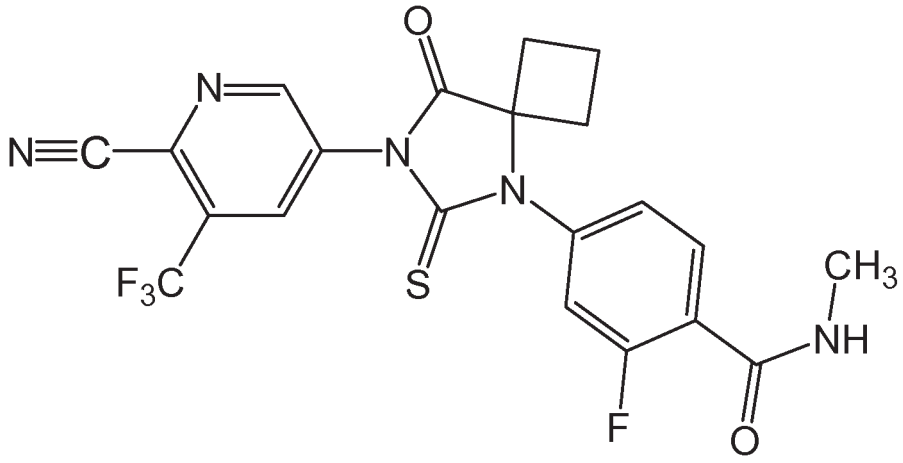
[0035] As used herein, the term "AR antagonist" or "AR inhibitor" are used interchangeably herein and refer to an agent that inhibits or reduces at least one activity of an AR polypeptide. Exemplary AR activities include, but are not limited to, co-activator binding, DNA binding, ligand binding, or nuclear translocation.

[0036] As used herein, a "full antagonist" refers to an antagonist which, at an effective concentration, essentially completely inhibits an activity of an AR polypeptide. As used herein, a "partial antagonist" refers an antagonist that is capable of partially inhibiting an activity of an AR polypeptide, but that, even at a highest concentration is not a full antagonist. By 'essentially completely' is meant at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98% at least about 99%, or greater inhibition of the activity of an AR polypeptide.

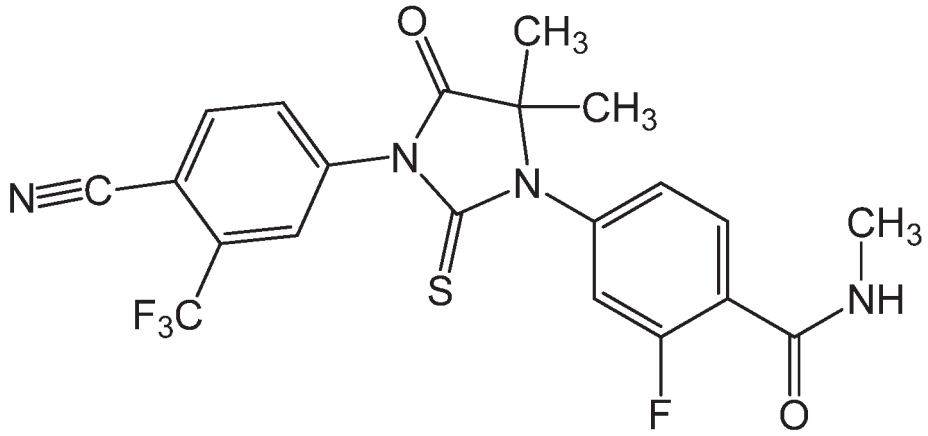
[0037] As used herein, the term "first-generation anti-androgen" refers to an agent that exhibits antagonist activity of a wild-type AR polypeptide. However, first-generation anti-androgens differ from second-generation anti-androgens in that first-generation anti-androgens can potentially act as agonists in castration resistant prostate cancers (CRPC). Exemplary first-generation anti-androgens include, but are not limited to, flutamide, nilutamide and bicalutamide.

[0038] As used herein, the term "second-generation anti-androgen" refers to an agent that exhibits full antagonist activity of a wild-type AR polypeptide. Second-generation anti-androgens differ from first-generation anti-androgens in that second-generation anti-androgens act as full antagonists in cells expressing elevated levels of AR, such as for example, in castration resistant prostate cancers (CRPC). Exemplary second-generation anti-androgens include 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (also known as ARN-509; CAS No. 956104-40-8); 4-(3-(4-

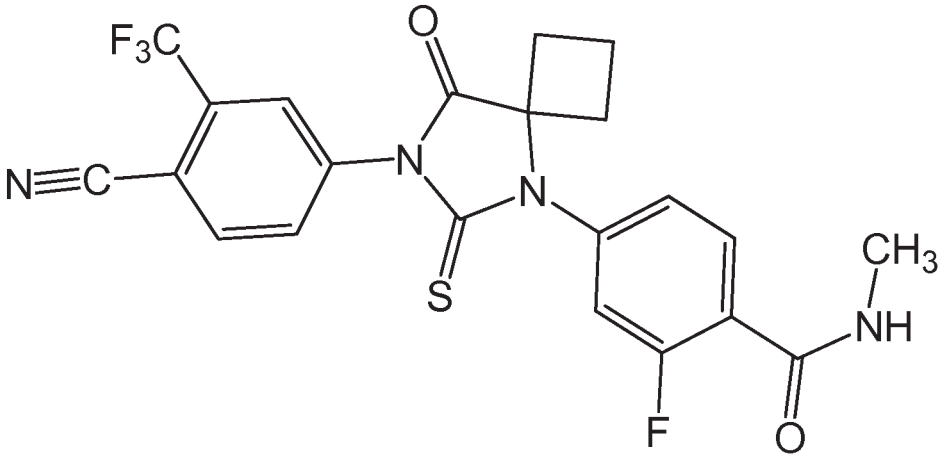
cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide (also known as MDV3100 or enzalutamide; CAS No: 915087-33-1) and 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (RD162; CAS No. 915087-27-3). In some embodiments, a second-generation anti-androgen binds to an AR polypeptide at or near the ligand binding site of the AR polypeptide.



4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (ARN-509)



4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide (enzalutamide)



4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (RD162).

[0039] In some embodiments, an anti-androgen contemplated in the methods described herein inhibits AR nuclear translocation, DNA binding to androgen response elements, and coactivator recruitment. In some embodiments, an anti-androgen contemplated in the methods described herein exhibits no agonist activity in AR-overexpressing prostate cancer cells.

4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide

[0040] 4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is a second-generation anti-androgen that binds directly to the ligand-binding domain of AR, impairing nuclear translocation, AR binding to DNA and AR target gene modulation, thereby inhibiting tumor growth and promoting apoptosis. 4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide binds AR with greater affinity than bicalutamide, and induces partial or complete tumor regression in non-castrate hormone-sensitive and bicalutamide-resistant human prostate cancer xenograft models (Clegg *et al.* Cancer Res March 15, 2012 72; 1494). 4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-

thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide lacks the partial agonist activity seen with bicalutamide in the context of AR overexpression.

[0041] Disclosed herein is the use of 4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide in the treatment of non-metastatic castration-resistant prostate cancer in a male human.

[0042] Also described herein, is the use of a second-generation anti-androgen in the treatment of non-metastatic castration-resistant prostate cancer in a male human.

[0043] In a Phase II clinical trial of male humans with non-metastatic castration-resistant prostate cancer, oral administration of 240mg of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide on a continuous daily dosing schedule resulted in a ≥50% decline in PSA from baseline at week 12 (i.e. about 3 months) in a portion of the patients. At 3 months, a PSA50 (i.e. ≥50% decline in PSA from baseline) and a PSA90 (i.e. ≥90% decline in PSA from baseline) were observed in 91% and 38% of the males that were orally administered 240mg of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide on a continuous daily dosing schedule, respectively. At 6 months, a PSA50 and a PSA90 were observed in 91% and 55% of the males that were orally administered 240mg of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide on a continuous daily dosing schedule, respectively.

Certain Terminology

[0044] Throughout this specification, words are to be afforded their normal meaning, as would be understood by those skilled in the relevant art. However, so as to avoid misunderstanding, the meanings of certain terms will be specifically defined or clarified.

[0045] The term "cancer" as used herein refers to an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread).

[0046] The term "prostate cancer" as used herein refers to histologically or cytologically confirmed adenocarcinoma of the prostate.

[0047] The term "NM-CRPC" as used herein refers to non-metastatic castration-resistant prostate cancer. In some embodiments, NM-CRPC is assessed with bone scan and computed tomography (CT) or magnetic resonance imaging (MRI) scans.

[0048] The term "high risk NM-CRPC" as used herein refers to probability of a man with NM-CRPC developing metastases. In some embodiments, high risk for development of metastases is defined as prostate specific antigen doubling time (PSADT) ≤ 20 months, ≤ 19 months, ≤ 18 months, ≤ 17 months, ≤ 16 months, ≤ 15 months, ≤ 14 months, ≤ 13 months, ≤ 12 months, or ≤ 11 months, ≤ 10 months, ≤ 9 months, ≤ 8 months, ≤ 7 months, ≤ 6 months, ≤ 5 months, ≤ 4 months, ≤ 3 months, ≤ 2 months, or ≤ 1 month. In some embodiments, high risk for development of metastases is defined as prostate specific antigen doubling time (PSADT) ≤ 10 months.

[0049] The terms "co-administration" or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0050] The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an anti-androgen being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an effective amount of an anti-androgen is the amount of the anti-androgen that after administration for 3 months to a male human with non-metastatic castration-resistant prostate cancer provides a PSA50 or PSA90 or demonstrates a robust (such as ≥ 90%) AR blockade (e.g. by FDHT-PET). In some embodiments, an effective amount of an anti-androgen is the amount of the anti-androgen that after administration for 6 months to a male human with non-metastatic castration-resistant prostate cancer provides a PSA50 or PSA90. In some embodiments, the anti-androgen is administered on a continuous daily dosing schedule. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

[0051] The term "FDHT-PET" refers to 18F-16β-fluoro-5α-dihydrotestosterone Positron Emission Tomography and is a technique that uses a tracer based on dihydrotestosterone, and allows for a visual assessment of ligand binding to the androgen

receptor in a patient. It may be used to evaluate pharmacodynamics of an androgen receptor directed therapy

[0052] The term "continuous daily dosing schedule" refers to the administration of an anti-androgen daily without any drug holidays. In some embodiments, a continuous daily dosing schedule comprises administration of an anti-androgen everyday at roughly the same time each day.

[0053] The terms "treat," "treating" or "treatment," as used herein, include alleviating, abating or ameliorating at least one symptom of a disease disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, delaying progression of condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically. In some embodiments, in the context of administering an anti-androgen to a male human with NM-CRPC, treating comprises any one, or a combination, of the following: providing a PSA50 or PSA90 in men with NM-CRPC as compared to placebo at 3 months; providing a PSA50 or PSA90 in men with NM-CRPC as compared to placebo at 6 months; demonstrating superiority in the metastasis-free survivial (MFS) of men with NM-CRPC as compared to placebo (i.e. not administering a second-generation anti-androgen); increasing the overall survisial (OS) of men with NM-CRPC as compared to placebo; increasing the time to metastasis (TTM) in men with NM-CRPC as compared to placebo; increasing the progression-free survival (PFS) in men with NM-CRPC as compared to placebo; increasing the time to PSA progression (TTPP) in men with NM-CRPC as compared to placebo; increasing the health-related quality of life and prostate cancer-specific symptoms in men with NM-CRPC as compared to placebo. In some embodiments, the NM-CRPC is high-risk NM-CRPC.

[0054] The term "metastasis-free survival" or "MFS" refers to the the percentage of subjects in a study who have survived without cancer spread for a defined period of time or death. MFS is usually reported as time from the beginning of treatment in the study. MFS is reported for an individual or a study population. In the context of treatment of NM-CRPC with an anti-androgen, an increase in the metastasis-free survival is the additional time that is observed without cancer having spread or death, whichever occurs first, as compared to treatment with placebo. In some embodiments, the increase in the metastasis-free survival is

about 1 month, about 2 months, about 2 months, about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 10 months, about 11 months, about 12 months, about 13 months, about 14 months, about 15 months, about 16 months, about 17 months, about 18 months, about 19 months, about 20 months, or greater than 20 months.

[0055] The term "placebo" as used herein means administration of a pharmaceutical composition that does not include a second-generation anti-androgen. In the context of treatment of NM-CRPC, men that are administered an anti-androgen or placebo will need to continue to maintain castrated levels of testosterone by either coadministration of a GnRH agonist/antagonist or orchiectomy.

Routes of Administration

[0056] Suitable routes of administration of the anti-androgen include, but are not limited to, oral or parenteral (e.g., intravenous, subcutaneous, intramuscular). The anti-androgen is administered in the form of a dispersion, solution, suspension, tablet, capsule, or pill. All formulations for oral administration are in dosages suitable for such administration. A summary of pharmaceutical compositions can be found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

A therapeutically effective amount of an anti-androgen can vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the anti-androgen used and other factors.

[0057] The term "acceptable" with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the male human being treated.

Methods of Dosing and Treatment Regimens

[0058] In one aspect, a second-generation anti-androgen is administered daily to men with NM-CRPC. In some embodiments, the second-generation anti-androgen is orally administered to men with NM-CRPC. In some embodiments, the second-generation anti-

androgen is administered once-a-day to men with NM-CRPC. In some embodiments, the second-generation anti-androgen is administered twice-a-day to men with NM-CRPC. In some embodiments, the second-generation anti-androgen is administered three times-a-day to men with NM-CRPC.

[0059] In general, doses of a second-generation anti-androgen employed for treatment of NM-CRPC in adult male humans are typically in the range of 10 mg-1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day. In some embodiments, the second-generation anti-androgen is conveniently presented in divided doses that are administered simultaneously (or over a short period of time) once a day. In some embodiments, the second-generation anti-androgen is conveniently presented in divided doses that are administered in equal portions twice-a-day.

[0060] In some embodiments, the second-generation anti-androgen is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered daily to the male human. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30mg per day to about 960mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30mg per day to about 480mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 180mg per day to about 480mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30mg per day, about 60mg per day, about 90mg per day, about 120mg per day, about 180mg per day, about 240mg per day, about 300mg per day, about

390mg per day, about 480mg per day, about 600mg per day, about 780mg per day, or about 960mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 240mg per day. In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human on a continuous daily dosing schedule.

[0061] In some embodiments, 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human with NM-CRPC at a dose of about 240mg per day. In some embodiments, greater than 240mg per day of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered to the male human with NM-CRPC. In some embodiments, the amount of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered once-a-day. In some other embodiments, the amount of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered twice-a-day.

[0062] In some embodiments, 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide is administered orally to the male human with NM-CRPC at a dose of about 160mg per day. In some embodiments, greater than 160mg per day of 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide is administered orally to the male human with NM-CRPC.

[0063] In certain embodiments wherein improvement in the status of the NM-CRPC in the male is not observed, the daily dose of the second-generation anti-androgen is increased. In some embodiments, a once-a-day dosing schedule is changed to a twice-a-day dosing schedule. In some embodiments, a three times a day dosing schedule is employed to increase the amount of second-generation anti-androgen that is administered.

[0064] In some embodiments, the amount of the second-generation anti-androgen that is given to the men with NM-CRPC varies depending upon factors such as, but not limited to,

the particular second-generation anti-androgen, condition and severity of the NM-CRPC, and the identity (*e.g.*, weight) of the man.

[0065] The following listing of Embodiments in intended to complement, rather than displace or supersede, the previous descriptions.

[0066] Embodiment 1. A method of treating non-metastatic castration-resistant prostate cancer in a male human comprising administering a therapeutically effective amount of an anti-androgen to a male human with a non-metastatic castration-resistant prostate cancer

[0067] Embodiment 2. The method of Embodiment 1, wherein the non-metastatic castration-resistant prostate cancer is a high risk non-metastatic castration-resistant prostate cancer.

[0068] Embodiment 3. The method of Embodiment 2, wherein the male human with the high risk non-metastatic castration-resistant prostate cancer has a prostate-specific antigen doubling time (PSADT) that is less than or equal to 10 months.

[0069] Embodiment 4. The method of any one of Embodiments 1 to 3, wherein administration of the anti-androgen provides an increase in the metastasis-free survival of the male human.

[0070] Embodiment 5. A method of providing an increase in the metastasis-free survival of a male human with prostate cancer comprising administering administering a therapeutically effective amount of an anti-androgen to the male human with prostate cancer.

[0071] Embodiment 6. The method of Embodiment 5, wherein the prostate cancer is non-metastatic castration-resistant prostate cancer.

[0072] Embodiment 7. The method of Embodiment 5, wherein the prostate cancer is high risk non-metastatic castration-resistant prostate cancer.

[0073] Embodiment 8. The method of Embodiment 7, wherein the male human with high risk non-metastatic castration-resistant prostate cancer has a prostate-specific antigen doubling time (PSADT) that is less than or equal to 10 months.

[0074] Embodiment 9. The method of any one of Embodiments 1 to 8, wherein the anti-androgen is a non-steroidal anti-androgen.

[0075] Embodiment 10. The method of any one of Embodiments 1 to 9, wherein the anti-androgen binds directly to the ligand-binding domain of the androgen receptor.

[0076] Embodiment 11. The method of any one of Embodiments 1 to 10, wherein the anti-androgen is a second-generation anti-androgen.

[0077] Embodiment 12. The method of any one of Embodiments 1 to 11, wherein the anti-androgen is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide; 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide (enzalutamide); or 4-[7-(4-cyano-3-trifluoromethylphenyl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (RD162).

[0078] Embodiment 13. The method of any one of Embodiments 1 to 12, wherein the anti-androgen is 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide.

[0079] Embodiment 14. The method of Embodiment 13, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered daily to the male human.

[0080] Embodiment 15. The method of Embodiment 13 or 14, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human.

[0081] Embodiment 16. The method of any one of Embodiments 13 to 15, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30 mg per day to about 480 mg per day.

[0082] Embodiment 17. The method of any one of Embodiments 13 to 15, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 180 mg per day to about 480 mg per day.

[0083] Embodiment 18. The method of any one of Embodiments 13 to 15, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 30 mg per day, about 60 mg per day, about 90 mg per day, about 120 mg per day, about 180 mg per day, about 240 mg per day, about 300 mg per day, about 390 mg per day, or about 480 mg per day.

[0084] Embodiment 19. The method of any one of Embodiments 13 to 15, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human at a dose of about 240 mg per day.

[0085] Embodiment 20. The method of any one of Embodiments 13 to 19, wherein 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide is administered orally to the male human on a continuous daily dosing schedule.

EXAMPLES

[0086] These examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

Example 1: Phase III Clinical Trial of 4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide in Men with Non-Metastatic Castration-Resistant Prostate Cancer (NM-CRPC)

[0087] This is a randomized, multicenter, double-blind, Phase III clinical trial evaluating the efficacy and safety of 4-[7-(6-cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide (treatment arm A) versus placebo (treatment arm B) in men with high risk NM-CRPC, defined as PSA Doubling Time (PSADT) $\leq$ 10 months. All men participating in the clinical trial should maintain castrated levels of testosterone (< 50 ng/dL [1.72 nmol/L]) by continuous administration of a GnRH agonist or antagonist, or by orchiectomy.

[0088] 4-[7-(6-Cyano-5-trifluoromethylpyridin-3-yl)-8-oxo-6-thioxo-5,7-diazaspiro[3.4]oct-5-yl]-2-fluoro-N-methylbenzamide will be administered orally on a continuous daily dosing schedule, at a starting dose of 240 mg per day in treatment arm A. Matched placebo will be administered orally on a continuous daily dosing schedule, at a starting dose of 240 mg per day in treatment arm B.

[0089] Patients will be followed for safety and efficacy as per the schedule of assessments and will remain on study treatment until documented progression (development of metastases as assessed by blinded independent central review) or unacceptable toxicity.

[0090] Patients discontinuing treatment due to disease progression will be followed for survival and subsequent anticancer therapies every 4 months until death, loss of follow-up, or withdrawal of consent, whichever comes first.

[0091] Patients discontinuing treatment prior to disease progression will continue to have scheduled disease assessments until progression, initiation of a subsequent anticancer therapy in the absence of documented disease progression, withdrawal of consent, loss of follow-up, or until death, whichever comes first.

ENDPOINTS

[0092] The primary endpoint is metastasis-free survival (MFS).

[0093] The secondary endpoints include overall survival (OS); time to metastasis (TTM); progression-free survival (PFS); health-related quality of life and prostate cancer-specific symptoms; type, incidence, severity, timing, seriousness, and relatedness of adverse events and laboratory abnormalities; pharmacokinetics parameters.

TARGET POPULATION

[0094] Inclusion Criteria

1. Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features, with high risk for development of metastases, defined as PSADT $\leq$ 10 months
2. Castration-resistant prostate cancer demonstrated during continuous androgen deprivation therapy (ADT)/post orchiectomy, defined as 3 consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with the last PSA > 2 ng/mL
3. Maintain castrate levels of testosterone (< 50 ng/dL [1.72 nmol/L]) within 4 weeks of randomization and throughout the study
4. Patients currently receiving bone loss prevention treatment with bone-sparing agents (e.g., bisphosphonates, denosumab [Prolia®]) must be on stable doses for at least 4 weeks prior to randomization
5. Patients who received a first generation anti-androgen (e.g., bicalutamide, flutamide, nilutamide) as part of an initial combined androgen blockade therapy or as second-line

hormonal therapy must show continuing disease (PSA) progression off the anti-androgen for at least 4 weeks prior to randomization

6. At least 4 weeks must have elapsed from the use of 5-α reductase inhibitors (e.g., dutasteride, finasteride, aminoglutethamide), estrogens, and any other anti-cancer therapy prior to randomization, including chemotherapy given in the adjuvant/neoadjuvant setting (e.g., clinical trial)
7. At least 4 weeks must have elapsed from major surgery or radiation therapy prior to randomization
8. Age ≥ 18 years
9. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 or 1
10. Resolution of all acute toxic effects of prior therapy or surgical procedure to Grade ≤ 1 or baseline prior to randomization
11. Adequate organ function as defined by the following criteria:
    - Serum aspartate transaminase (AST; serum glutamic oxaloacetic transaminase [SGOT]) and serum alanine transaminase (ALT; serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 x upper limit of normal (ULN)
    - Total serum bilirubin ≤ 1.5 x ULN
    - Serum creatinine ≤ 2 x ULN
    - Absolute neutrophil count (ANC) ≥ 1500/μL
    - Platelets ≥ 100,000/μL
    - Hemoglobin ≥ 9.0 g/dL
    - Administration of growth factors or blood transfusions will not be allowed within 4 weeks of the hematology labs required to confirm eligibility
12. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to randomization
13. Willingness and ability to comply with scheduled visits, treatment plans, laboratory and radiographic assessments, and other study procedures, including ability to swallow large capsules, the completion of patient reported outcomes questionnaires and long-term survival follow-up visits

[0095] Exclusion Criteria

1. Presence of distant metastases, including CNS and vertebral or meningeal involvement. **Exception:** pelvic lymph nodes < 2 cm in short axis (N1) located below the iliac bifurcation are allowed
2. Symptomatic loco-regional disease requiring medical intervention, such as moderate or severe urinary obstruction or hydronephrosis due to primary tumor (e.g., tumor obstruction of bladder trigone)
3. Prior treatment with second-generation antiandrogens (e.g., enzalutamide)
4. Prior treatment with CYP17 inhibitors (e.g., abiraterone acetate, orteronel, galeterone, ketoconazole)
5. Prior treatment with radiopharmaceutical agents (e.g., Strontium-89), immunotherapy (e.g., sipuleucel-T) or any other investigational agent for NM-CRPC
6. Prior chemotherapy, except if administered in the adjuvant/neoadjuvant setting
7. History of seizure or condition that may pre-dispose to seizure (e.g., prior stroke within 1 year prior to randomization, brain arteriovenous malformation, Schwannoma, meningioma, or other benign CNS or meningeal disease which may require treatment with surgery or radiation therapy)
8. Concurrent therapy with any of the following (all must have been discontinued or substituted for at least 4 weeks prior to randomization):
   - Medications known to lower the seizure threshold
   - Herbal and non-herbal products that may decrease PSA levels (i.e., saw palmetto, pomegranate juice)
   - Systemic (oral/IV/IM) corticosteroids. Short term use (≤ 4 weeks) of corticosteroids during the study is allowed if clinically indicated, but it should be tapered off as soon as possible
   - Any other experimental treatment on another clinical trial
9. History or evidence of any of the following conditions:
   - Any prior malignancy (other than adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) within 5 years prior to randomization

- Severe/unstable angina, myocardial infarction, symptomatic congestive heart failure, arterial or venous thromboembolic events (e.g., pulmonary embolism, cerebrovascular accident including transient ischemic attacks), or clinically significant ventricular arrhythmias within 6 months prior to randomization
- Uncontrolled hypertension (≥ 160 mmHg systolic blood pressure and/or diastolic blood pressure ≥ 100 mmHg)
- Gastrointestinal disorder affecting absorption
- Active infection, such as human immunodeficiency virus (HIV)
- Any other condition that, in the opinion of the Investigator, would impair the patient's ability to comply with study procedures

ASSESSMENT SCHEDULE

Safety Assessment Plan

[0096] Patients will be assessed for adverse events at each monthly clinic visit while on the study. Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Adverse events will be assessed by the investigator as related or not related to study drug. Dose interruptions and/or reductions to the next lower dose level will be permitted as needed, provided that study discontinuation criteria have not been met (e.g., documented disease progression or unacceptable toxicity, such as seizure).

[0097] An independent third-party Data Monitoring Committee (DMC) will monitor the safety of the patients, with meetings at least twice per year to determine overall safety and benefit:risk assessment. Periodic quarterly adverse event data review will also be performed by designated members of the sponsor's primary study team and will be blinded to treatment assignment with adverse event from both treatment groups combined. Any safety issues of concern identified by the primary study team will be promptly reported to the DMC, as per the DMC charter.

[0098] As those skilled in the art will appreciate, numerous modifications and variations of the present invention are possible in light of these teachings, and all such are contemplated hereby. For example, in addition to the embodiments described herein, the present invention contemplates and claims those inventions resulting from the combination of

features of the invention cited herein and those of the cited prior art references which complement the features of the present invention. Similarly, it will be appreciated that any described material, feature, or article may be used in combination with any other material, feature, or article, and such combinations are considered within the scope of this invention.

[0099] The disclosures of each patent, patent application, and publication cited or described in this document are hereby incorporated herein by reference, each in its entirety, for all purposes.

WHAT IS CLAIMED IS:

1. The use of 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide in the manufacture of a medicament for treating non-metastatic castration-resistant prostate cancer in a male human, wherein the medicament is to be used in combination with a gonadotropin-releasing hormone (GnRH) agonist.

2. The use according to claim 1, wherein the non-metastatic castration-resistant prostate cancer is a high risk non-metastatic castration-resistant prostate cancer.

3. The use according to claim 2, wherein the male human with the high risk non-metastatic castration-resistant prostate cancer has a prostate-specific antigen doubling time (PSADT) that is less than or equal to 10 months.

4. The use according to claim 1, wherein administration of the medicament provides an increase in the metastasis-free survival of the male human.

5. The use according to claim 1, wherein the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide is present in the medicament at a dose of about 160 mg.

6. The use according to claim 1, wherein the medicament is for treatment by oral administration of the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide to the male human.

7. The use according to claim 1, wherein the medicament is for treatment by oral administration of the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide on a continuous daily dosing schedule to the male human.

8. The use according to claim 1, wherein the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide is present in the medicament in a unit dosage form, wherein the unit dosage form is in the form of a tablet.

9. The use according to claim 1, wherein the medicament is for administration of the GnRH agonist at a different time as the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide.

10. The use according to claim 1, wherein the medicament is for administration of the GnRH agonist at the same time as the 4-(3-(4-cyano-3-(trifluoromethyl)phenyl)-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl)-2-fluoro-N-methylbenzamide.

11. The use according to claim 1, wherein the male human previously received a first-generation anti-androgen, and wherein the first-generation anti-androgen is bicalutamide, flutamide or nilutamide.

12. The use according to claim 1, wherein the GnRH agonist is leuprolide, buserelin, nafarelin, histrelin, goserelin, or deslorelin.

13. The use according to claim 1, wherein the GnRH agonist is leuprolide.

14. The use according to claim 1, wherein the GnRH agonist is buserelin.

15. The use according to claim 1, wherein the GnRH agonist is nafarelin.

16. The use according to claim 1, wherein the GnRH agonist is histrelin.

17. The use according to claim 1, wherein the GnRH agonist is goserelin.

18. The use according to claim 1, wherein the GnRH agonist is deslorelin.