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METHODS OF TREATING ANDROGEN RECEPTOR-INDEPENDENT PROSTATE CANCER

Abstract

The present invention relates to methods and compositions for the treatment of BAF-related disorders such as cancer.

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Background/Summary

BACKGROUND

[0001] Disorders can be affected by the BAF complex. BRD9 is a component of the BAF complex. The present invention relates to useful methods and compositions for the treatment of BAF-related disorders, such as cancer.

SUMMARY OF THE INVENTION

[0002] Bromodomain-containing protein 9 (BRD9) is a protein encoded by the BRD9 gene on chromosome 5. BRD9 is a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is present in several SWI/SNF ATPase chromatin remodeling complexes and is upregulated in multiple cancer cell lines. Accordingly, agents that reduce the levels and/or activity of BRD9 may provide new methods for the treatment of disease and disorders, such as cancer and infection. The inventors have found that depleting BRD9 in several varying prostate cancer cell lines has a positive effect in decreasing tumor growth volume while maintaining tolerability. Thus, agents that degrade BRD9 (e.g., compounds) are useful in the treatment of disorders (e.g., cancers or infections) related to BAF and/or BRD9

[0003] Without wishing to be bound by theory, it is believed that depleting or inhibiting BRD9 results in the treatment of androgen receptor-independent prostate cancers.

[0004] In an aspect, the present disclosure features a method of treating androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0005] In an aspect, the present disclosure features a method of slowing progression of androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0006] In an aspect, the present disclosure features a method of reducing recurrence of androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0007] In an aspect, the present disclosure features a method of decreasing the rate of metastatic tumor seeding of androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0008] In an aspect, the present disclosure features a method of decreasing metastatic tumor nodule formation of androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0009] In an aspect, the present disclosure features a method of decreasing the spread of metastatic

tumor nodule formation of androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0010] In an aspect, the present disclosure features a method of decreasing metastatic colonization of androgen receptor-independent prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0011] In some embodiments, the androgen receptor-independent prostate cancer has failed to respond a previous treatment with an anti-cancer therapy.

[0012] In an aspect, the present disclosure features a method of treating prostate cancer that has failed to respond to a previous treatment with an anti-cancer therapy in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof. In some embodiments, the prostate cancer is neuroendocrine prostate cancer.

[0013] In an aspect, the present disclosure features a method of treating neuroendocrine prostate cancer in a subject in need thereof, the method including the step of administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments, the neuroendocrine prostate cancer is androgen receptor-independent. In some embodiments, the neuroendocrine prostate cancer has failed to respond to a previous treatment with an anti-cancer therapy.

[0015] In some embodiments, the compound is 3-(6-(7-((1-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl) piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxoisoindolin-2-yl) piperidine-2,6-dione. having the structure:

##STR00001##

or a pharmaceutically acceptable salt thereof.

[0016] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20-120 mg/kg (e.g., 20-60 mg/kg, 20-40 mg/kg, 40-80 mg/kg, 40-60 mg/kg, 60-80 mg/kg, or 80-120 mg/kg).

[0017] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20 mg/kg. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 40 mg/kg. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 50 mg/kg. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 60 mg/kg. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 80 mg/kg. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 120 mg/kg.

[0018] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered to the subject at least once per week (e.g., once per week).

[0019] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered to the subject at least twice per week (e.g., twice per week).

[0020] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered to the subject at least once

per week.
[0021] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered to the subject at least twice per week.
[0022] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20 mg/kg once per week. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20 mg/kg twice per week.
[0023] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 40 mg/kg once per week. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 40 mg/kg twice per week.
[0024] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 50 mg/kg once per week. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 50 mg/kg twice per week.
[0025] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 60 mg/kg once per week. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 60 mg/kg twice per week.
[0026] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 80 mg/kg once per week. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 80 mg/kg twice per week.
[0027] In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 120 mg/kg once per week. In some embodiments of any of the aspects disclosed herein, the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 120 mg/kg twice per week.
[0028] In some embodiments of any of the aspects disclosed herein, the compound or a pharmaceutically acceptable salt thereof is administered to the subject in a 14-day dosing cycle.
[0029] In some embodiments of any of the aspects disclosed herein, the compound or a pharmaceutically acceptable salt thereof is administered to the subject in a 21-day dosing cycle.
[0030] In some embodiments of any of the aspects disclosed herein, the compound or a pharmaceutically acceptable salt thereof is administered to the subject in a 28-day dosing cycle.
[0031] In some embodiments of any of the aspects disclosed herein, the compound or a pharmaceutically acceptable salt thereof, is administered to the subject intravenously.
[0032] In some embodiments of any of the aspects disclosed herein, the compound or a pharmaceutically acceptable salt thereof, is administered to the subject subcutaneously.
[0033] In some embodiments of any of the aspects disclosed herein, the compound or a pharmaceutically acceptable salt thereof, is administered to the subject intramuscularly.
[0034] In some embodiments, the compound is 3-((4-(4-(1-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-3,3-difluoropiperidin-4-yl) piperazin-1-yl)-3-fluorophenyl)amino) piperidine-2,6-dione having the structure:
##STR00002##

or a pharmaceutically acceptable salt thereof.
[0035] In some embodiments, the prostate cancer is castration-resistant prostate cancer (CRPC). In some embodiments, the prostate cancer is small cell prostate cancer.
[0036] In some embodiments, the effective amount is an amount sufficient to reduce the level of neuroendocrine prostate cancer cells in the subject compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
[0037] In some embodiments, the anti-cancer therapy is active surveillance, surgery, radiation therapy, high-intensity focused ultrasound (HIFU), cryotherapy, hormone therapy, chemotherapy, immunotherapy, vaccine treatment, immune checkpoint inhibitors, targeted therapy drugs, or bone-directed treatment.
[0038] In some embodiments, the anti-cancer therapy is abiraterone acetate, alendronate, apalutamide, bicalutamide, cabazitaxel, carboplatin, cisplatin, darolutamide, degarelix, denosumab, docetaxel, enzalutamide, etoposide, flutamide, goserelin acetate, ibandronate, leuprolide acetate, lynparza, mitoxantrone hydrochloride, nilutamide, olaparib, pamidronate, radium 223 dichloride, relugolix, risedronate, rucaparib camsylate, sipuleucel-T, or zoledronic acid, or combinations thereof. In some embodiments, the anti-cancer therapy is enzalutamide.
[0039] Ins some embodiments, the subject is further administered at least one additional anti-cancer therapy. In some embodiments, the additional anti-cancer therapy is administered prior to the administering of the compound or pharmaceutically acceptable salt thereof. In some embodiments, the additional anti-cancer therapy is administered in addition to the administering of the compound or pharmaceutically acceptable salt thereof. In some embodiments, the additional anti-cancer therapy is administered subsequent to the administering of the compound or pharmaceutically acceptable salt thereof.
[0040] In some embodiments, the subject is further administered a treatment for symptoms of prostate cancer. Nonlimiting examples of symptoms of prostate cancer that may be treated include frequent urination, weak or uninterrupted urine flow or the need to strain to empty the bladder, blood in the urine, a new onset of erectile dysfunction, pain or burning during urination, and discomfort or pain when sitting. In some embodiment, the further treatment is prednisone, methylprednisolone, pembrolizumab, or a combination thereof.
[0041] In some embodiments, the effective amount is an amount sufficient to reduce the level of luminal prostate cancer cell to neuroendocrine prostate cancer cell trans-differentiation measured by lower expression levels of CHGA, SYP, and/or ENO2 compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
[0042] In some embodiments, the effective amount is an amount sufficient to reduce the level of adenocarcinoma to neuroendocrine trans-differentiation measured by lower expression levels of CHGA, SYP, and/or ENO2 compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
[0043] In some embodiments, the effective amount is an amount sufficient to reduce the level of neuroendocrine prostate cancer cells compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
[0044] In some embodiments, the prostate cancer has been determined to have or predicted to have lower expression levels of AR, KLK2, KLK3, CDH1, CYLD, NKX3-1, SLC45A3, TARP, PTEN, SPDEF, TP53, or RB1, or combinations thereof compared to a subject that does not have prostate cancer.
[0045] In some embodiments, the prostate cancer has been determined to have or predicted to have lower expression levels of AR, KLK2, KLK3, CDH1, CYLD, NKX3-1, SLC45A3, TARP, PTEN, SPDEF, TP53, or RB1, or combinations thereof compared to standard levels for prostate cancer.
[0046] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of CHGB, CHGA, SYP, ENO2, PEG10, SNAP25, SRRM4, VGF, VIM, SCGN, PAPPA2, or WNT11, or combinations thereof compared to a subject that does not have

prostate cancer.
[0047] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of CHGB, CHGA, SYP, ENO2, PEG10, SNAP25, SRRM4, VGF, VIM, SCGN, PAPPA2, or WNT11, or combinations thereof compared to standard levels for prostate cancer.
[0048] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of ASCL1, EZH2, DLX5, DLX6, SOX2, NKX2-2, HES6, SOX9, KDM3A, FOXA2, AURKA, MYCN, MYC, AKT, POU3F2/BRN2, NANOG, ONECUT2, or NKX2-1, or combinations thereof compared to a subject that does not have prostate cancer.
[0049] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of ASCL1, EZH2, DLX5, DLX6, SOX2, NKX2-2, HES6, SOX9, KDM3A, FOXA2, AURKA, MYCN, MYC, AKT, POU3F2/BRN2, NANOG, ONECUT2, or NKX2-1, or combinations thereof compared to standard levels for prostate cancer.
[0050] In some embodiments, wherein the prostate cancer has been determined to have or predicted to have lower expression levels of RE1 silencing transcription factor (REST).
[0051] In some embodiments, the prostate cancer has been determined to have or predicted to have expression of AR and KLK3 (PSA).
[0052] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of CHGA and SYP.
[0053] In some embodiments, the prostate cancer has been determined to have or predicted to have expression of AR, KLK3 (PSA), CHGA and SYP.
[0054] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of AR and KLK3 (PSA).
[0055] In some embodiments, the prostate cancer has been determined to have or predicted to have expression of CHGA and SYP.
[0056] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of AR, KLK3 (PSA), CHGA and SYP.
[0057] In some embodiments, the prostate cancer has been determined or predicted to have a high level of TMPRSS2-ERG fusions.
[0058] In some embodiments, the prostate cancer is metastatic.
[0059] In some embodiments, expression of BRD9, GLTSCR1, CXXC5 or TET2 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
[0060] In some embodiments, expression of BRD9 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
[0061] In some embodiments, expression of GLTSCR1 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
[0062] In some embodiments, expression of TET2, CXXC5, H3K27ac, ID1, PFN2, or ID3 in the subject is increased in the prostate cancer determined to or predicted to be resistant to enzalutamide compared to a prostate cancer that responds to treatment with enzalutamide.
[0063] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of PTEN.
[0064] In some embodiments, the prostate cancer has been determined or predicted to be ERG positive.
[0065] In some embodiments, the subject is further administered an inhibitor or degrader of ERG. In some embodiments, the ERG inhibitor or degrader is ERGi-USU (1-[2-Thiazolylazo]-2-naphthol).
[0066] In some embodiments, the subject is further administered a degrader of AR. In some embodiments, the AR degrader is bavdegalutamide (ARV-110), ARV-766, or AR-V7.
[0067] In some embodiments, wherein the subject is further administered an inhibitor of the JAK-STAT pathway. In some embodiments, the JAK-STAT inhibitor is AG490, AZD1480, AZD4205,

baricitinib, dasatinib, fedratinib, filgotinib, itacitnib, lestaurtinib, momelotinib, pacritinib, peficitinib, ruxolitinib, siltuximab, tofacitinib, upadacitinib, or WP1066.

[0068] In some embodiments, the subject is further administered an inhibitor of the MAPK pathway. In some embodiments, the MAPK pathway inhibitor is a Farnesyltransferase inhibitor (FTI), Sorafenib, Vemurafenib, PLX8394, Dabrafenib, Ulixertinib, Simvastatin, Alisertib, or Teriflunomide.

[0069] In some embodiments, the subject is further administered an inhibitor of the PI3K-AKT-mTOR pathway. In some embodiments, the PIK3-AKT-mTOR inhibitor is everolimus, alpelisib, idelalisib or copanlisib.

[0070] In some embodiments, the subject has a PSA level of 4 ng/ml or more prior to the administering of the compound or a pharmaceutically acceptable salt thereof.

Chemical Terms

[0071] The terminology employed herein is for the purpose of describing particular embodiments and is not intended to be limiting.

[0072] For any of the following chemical definitions, a number following an atomic symbol indicates that total number of atoms of that element that are present in a particular chemical moiety. As will be understood, other atoms, such as H atoms, or substituent groups, as described herein, may be present, as necessary, to satisfy the valences of the atoms. For example, an unsubstituted C.sub.2 alkyl group has the formula —CH.sub.2CH.sub.3. When used with the groups defined herein, a reference to the number of carbon atoms includes the divalent carbon in acetal and ketal groups but does not include the carbonyl carbon in acyl, ester, carbonate, or carbamate groups. A reference to the number of oxygen, nitrogen, or sulfur atoms in a heteroaryl group only includes those atoms that form a part of a heterocyclic ring.

[0073] The term “acyl,” as used herein, represents a H or an alkyl group that is attached to a parent molecular group through a carbonyl group, as defined herein, and is exemplified by formyl (i.e., a carboxaldehyde group), acetyl, trifluoroacetyl, propionyl, and butanoyl. Exemplary unsubstituted acyl groups include from 1 to 6, from 1 to 11, or from 1 to 21 carbons.

[0074] The term “alkyl,” as used herein, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of 1 to 20 carbon atoms (e.g., 1 to 16 carbon atoms, 1 to 10 carbon atoms, 1 to 6 carbon atoms, or 1 to 3 carbon atoms).

[0075] An alkylene is a divalent alkyl group. The term “alkenyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon double bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6 carbon atoms, or 2 carbon atoms).

[0076] The term “alkynyl,” as used herein, alone or in combination with other groups, refers to a straight chain or branched hydrocarbon residue having a carbon-carbon triple bond and having 2 to 20 carbon atoms (e.g., 2 to 16 carbon atoms, 2 to 10 carbon atoms, 2 to 6 carbon atoms, or 2 carbon atoms).

[0077] The term “amino,” as used herein, represents —N(R.sup.N1).sub.2, wherein each R.sup.N1 is, independently, H, OH, NO.sub.2, N(R.sup.N2).sub.2, SO.sub.2OR.sup.N2, SO.sub.2R.sup.N2, SOR.sup.N2, an N-protecting group, alkyl, alkoxy, aryl, arylalkyl, cycloalkyl, acyl (e.g., acetyl, trifluoroacetyl, or others described herein), wherein each of these recited R.sup.N1 groups can be optionally substituted; or two R.sup.N1 combine to form an alkylene or heteroalkylene, and wherein each R.sup.N2 is, independently, H, alkyl, or aryl. The amino groups of the invention can be an unsubstituted amino (i.e., —NH.sub.2) or a substituted amino (i.e., —N(R.sup.N1).sub.2).

[0078] The term “aryl,” as used herein, refers to an aromatic mono- or polycarbocyclic radical of 6 to 12 carbon atoms having at least one aromatic ring. Examples of such groups include, but are not limited to, phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, 1,2-dihydronaphthyl, indanyl, and 1H-indenyl.

[0079] The term “arylalkyl,” as used herein, represents an alkyl group substituted with an aryl

group. Exemplary unsubstituted arylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C.sub.1-C.sub.6 alkyl C.sub.6-C.sub.10 aryl, C.sub.1-C.sub.10 alkyl C.sub.6-C.sub.10 aryl, or C.sub.1-C.sub.20 alkyl C.sub.6-C.sub.10 aryl), such as, benzyl and phenethyl. In some embodiments, the alkyl and the aryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

[0080] The term "azido," as used herein, represents a —N.sub.3 group.

[0081] The term "bridged polycycloalkyl," as used herein, refers to a bridged polycyclic group of 5 to 20 carbons, containing from 1 to 3 bridges.

[0082] The term "cyano," as used herein, represents a —CN group.

[0083] The term "carbocyclyl," as used herein, refers to a non-aromatic C.sub.3-C.sub.12 monocyclic, bicyclic, or tricyclic structure in which the rings are formed by carbon atoms. Carbocyclyl structures include cycloalkyl groups and unsaturated carbocyclyl radicals.

[0084] The term "cycloalkyl," as used herein, refers to a saturated, non-aromatic, and monovalent mono- or polycarbocyclic radical of 3 to 10, preferably 3 to 6 carbon atoms. This term is further exemplified by radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, and adamantyl.

[0085] The term "halo," as used herein, means a fluorine (fluoro), chlorine (chloro), bromine (bromo), or iodine (iodo) radical.

[0086] The term "heteroalkyl," as used herein, refers to an alkyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkyl groups. Examples of heteroalkyl groups are an "alkoxy" which, as used herein, refers alkyl-O— (e.g., methoxy and ethoxy). A heteroalkylene is a divalent heteroalkyl group. The term "heteroalkenyl," as used herein, refers to an alkenyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkenyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkenyl groups. Examples of heteroalkenyl groups are an "alkenoxy" which, as used herein, refers alkenyl-O—. A heteroalkenylene is a divalent heteroalkenyl group. The term "heteroalkynyl," as used herein, refers to an alkynyl group, as defined herein, in which one or more of the constituent carbon atoms have been replaced by nitrogen, oxygen, or sulfur. In some embodiments, the heteroalkynyl group can be further substituted with 1, 2, 3, or 4 substituent groups as described herein for alkynyl groups. Examples of heteroalkynyl groups are an "alkynoxy" which, as used herein, refers alkynyl-O—. A heteroalkynylene is a divalent heteroalkynyl group.

[0087] The term "heteroaryl," as used herein, refers to a mono- or polycyclic radical of 5 to 12 atoms having at least one aromatic ring and containing 1, 2, or 3 ring atoms selected from nitrogen, oxygen, and sulfur, with the remaining ring atoms being carbon. One or two ring carbon atoms of the heteroaryl group may be replaced with a carbonyl group. Examples of heteroaryl groups are pyridyl, pyrazoyl, benzooxazolyl, benzoimidazolyl, benzothiazolyl, imidazolyl, oxaxolyl, and thiazolyl.

[0088] The term "heteroarylalkyl," as used herein, represents an alkyl group substituted with a heteroaryl group. Exemplary unsubstituted heteroarylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C.sub.1-C.sub.6 alkyl C.sub.2-C.sub.9 heteroaryl, C.sub.1-C.sub.10 alkyl C.sub.2-C.sub.9 heteroaryl, or C.sub.1-C.sub.20 alkyl C.sub.2-C.sub.9 heteroaryl). In some embodiments, the alkyl and the heteroaryl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.

[0089] The term "heterocyclyl," as used herein, refers a mono- or polycyclic radical having 3 to 12 atoms having at least one ring containing 1, 2, 3, or 4 ring atoms selected from N, O or S, wherein no ring is aromatic. Examples of heterocyclyl groups include, but are not limited to, morpholinyl, thiomorpholinyl, furyl, piperazinyl, piperidinyl, pyranyl, pyrrolidinyl, tetrahydropyranyl,

tetrahydrofuranyl, and 1,3-dioxanyl.
[0090] The term “heterocyclylalkyl,” as used herein, represents an alkyl group substituted with a heterocyclyl group. Exemplary unsubstituted heterocyclylalkyl groups are from 7 to 30 carbons (e.g., from 7 to 16 or from 7 to 20 carbons, such as C.sub.1-C.sub.6 alkyl C.sub.2-C.sub.9 heterocyclyl, C.sub.1-C.sub.10 alkyl C.sub.2-C.sub.9 heterocyclyl, or C.sub.1-C.sub.20 alkyl C.sub.2-C.sub.9 heterocyclyl). In some embodiments, the alkyl and the heterocyclyl each can be further substituted with 1, 2, 3, or 4 substituent groups as defined herein for the respective groups.
[0091] The term “hydroxyalkyl,” as used herein, represents alkyl group substituted with an —OH group.
[0092] The term “hydroxyl,” as used herein, represents an —OH group.
[0093] The term “N-protecting group,” as used herein, represents those groups intended to protect an amino group against undesirable reactions during synthetic procedures. Commonly used N-protecting groups are disclosed in Greene, “Protective Groups in Organic Synthesis,” 3rd Edition (John Wiley & Sons, New York, 1999). N-protecting groups include, but are not limited to, acyl, aryloyl, or carbamyl groups such as formyl, acetyl, propionyl, pivaloyl, t-butylacetyl, 2-chloroacetyl, 2-bromoacetyl, trifluoroacetyl, trichloroacetyl, phthalyl, o-nitrophenoxyacetyl, α-chlorobutyryl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, and chiral auxiliaries such as protected or unprotected D, L, or D, L-amino acids such as alanine, leucine, and phenylalanine; sulfonyl-containing groups such as benzenesulfonyl, and p-toluenesulfonyl; carbamate forming groups such as benzyloxycarbonyl, p-chlorobenzyloxycarbonyl, p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, p-bromobenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-20 dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, 1-(p-biphenylyl)-1-methylethoxycarbonyl, α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl, benzhydryloxy carbonyl, t-butyloxycarbonyl, diisopropylmethoxycarbonyl, isopropyloxycarbonyl, ethoxycarbonyl, methoxycarbonyl, allyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, phenoxycarbonyl, 4-nitrophenoxy carbonyl, fluorenyl-9-methoxycarbonyl, cyclopentyloxycarbonyl, adamantyloxycarbonyl, cyclohexyloxycarbonyl, and phenylthiocarbonyl, arylalkyl groups such as benzyl, triphenylmethyl, and benzyloxymethyl, and silyl groups, such as trimethylsilyl. Preferred N-protecting groups are alloc, formyl, acetyl, benzoyl, pivaloyl, t-butylacetyl, alanyl, phenylsulfonyl, benzyl, t-butyloxycarbonyl (Boc), and benzyloxycarbonyl (Cbz).
[0094] The term “nitro,” as used herein, represents an —NO.sub.2 group.
[0095] The term “thiol,” as used herein, represents an —SH group.
[0096] The alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, carbocyclyl (e.g., cycloalkyl), aryl, heteroaryl, and heterocyclyl groups may be substituted or unsubstituted. When substituted, there will generally be 1 to 4 substituents present, unless otherwise specified. Substituents include, for example: alkyl (e.g., unsubstituted and substituted, where the substituents include any group described herein, e.g., aryl, halo, hydroxy), aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halo (e.g., fluoro), hydroxyl, heteroalkyl (e.g., substituted and unsubstituted methoxy, ethoxy, or thioalkoxy), heteroaryl, heterocyclyl, amino (e.g., NH.sub.2 or mono- or dialkyl amino), azido, cyano, nitro, or thiol. Another exemplary substituent is oxo. For example, a carbonyl group is a carbon (e.g., alkyl carbon, alkenyl carbon, alkynyl carbon, heteroalkyl carbon, heteroalkenyl carbon, heteroalkynyl carbon, carbocyclyl carbon, etc.) substituted with oxo. Alternatively, sulfur may be substituted with one or two oxo groups (e.g., —SO— or —SO.sub.2— within a substituted heteroalkyl, heteroalkenyl, heteroalkynyl, or heterocyclyl group). Aryl, carbocyclyl (e.g., cycloalkyl), heteroaryl, and heterocyclyl groups may also be substituted with alkyl (unsubstituted and substituted such as arylalkyl (e.g., substituted and unsubstituted benzyl)). In some embodiments, alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, and heteroalkynyl are optionally substituted

with 1, 2, 3, 4, or 5 substituents independently selected from the group consisting of aryl (e.g., substituted and unsubstituted phenyl), carbocyclyl (e.g., substituted and unsubstituted cycloalkyl), halo (e.g., fluoro), hydroxyl, heteroaryl, heterocyclyl, amino (e.g., NH.sub.2 or mono- or dialkyl amino), azido, cyano, nitro, thiol, and oxo. In some embodiments, the substituents are themselves unsubstituted.

[0097] Compounds of the invention can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbents or eluant). That is, certain of the disclosed compounds may exist in various stereoisomeric forms. Stereoisomers are compounds that differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. “Enantiomer” means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms and represent the configuration of substituents around one or more chiral carbon atoms. Enantiomers of a compound can be prepared, for example, by separating an enantiomer from a racemate using one or more well-known techniques and methods, such as, for example, chiral chromatography and separation methods based thereon. The appropriate technique and/or method for separating an enantiomer of a compound described herein from a racemic mixture can be readily determined by those of skill in the art. “Racemate” or “racemic mixture” means a compound containing two enantiomers, wherein such mixtures exhibit no optical activity; i.e., they do not rotate the plane of polarized light. “Geometric isomer” means isomers that differ in the orientation of substituent atoms in relationship to a carbon-carbon double bond, to a cycloalkyl ring, or to a bridged bicyclic system. Atoms (other than H) on each side of a carbon-carbon double bond may be in an E (substituents are on opposite sides of the carbon-carbon double bond) or Z (substituents are oriented on the same side) configuration. “R,” “S,” “S*,” “R*,” “E,” “Z,” “cis,” and “trans,” indicate configurations relative to the core molecule. Certain of the disclosed compounds may exist in atropisomeric forms. Atropisomers are stereoisomers resulting from hindered rotation about single bonds where the steric strain barrier to rotation is high enough to allow for the isolation of the conformers. The compounds of the invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods. When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight optically pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by weight pure. Percent optical purity is the ratio of the weight of the enantiomer or over the weight of the enantiomer plus the weight of its optical isomer. Diastereomeric purity by weight is the ratio of the weight of one diastereomer or over the weight of all the diastereomers. When the stereochemistry

of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. When a single diastereomer is named or depicted by structure, the depicted or named diastereomer is at least 60%, 70%, 80%, 90%, 99%, or 99.9% by mole fraction pure. Percent purity by mole fraction is the ratio of the moles of the enantiomer or over the moles of the enantiomer plus the moles of its optical isomer. Similarly, percent purity by moles fraction is the ratio of the moles of the diastereomer or over the moles of the diastereomer plus the moles of its isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry, and the compound has at least one chiral center, it is to be understood that the name or structure encompasses either enantiomer of the compound free from the corresponding optical isomer, a racemic mixture of the compound, or mixtures enriched in one enantiomer relative to its corresponding optical isomer. When a disclosed compound is named or depicted by structure without indicating the stereochemistry and has two or more chiral centers, it is to be understood that the name or structure encompasses a diastereomer free of other diastereomers, a number of diastereomers free from other diastereomeric pairs, mixtures of diastereomers, mixtures of diastereomeric pairs, mixtures of diastereomers in which one diastereomer is enriched relative to the other diastereomer(s), or mixtures of diastereomers in which one or more diastereomer is enriched relative to the other diastereomers. The invention embraces all of these forms.

[0098] Compounds of the present disclosure also include all of the isotopes of the atoms occurring in the intermediate or final compounds. “Isotopes” refers to atoms having the same atomic number but different mass numbers resulting from a different number of neutrons in the nuclei. For example, isotopes of hydrogen include tritium and deuterium.

[0099] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. Exemplary isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as .sup.2H, .sup.3H, .sup.11C, .sup.13C, .sup.14C, .sup.13N, .sup.15N, .sup.15O, .sup.17O, .sup.18O, .sup.32P, .sup.33P, .sup.35S, .sup.18F, .sup.36Cl, .sup.123I and .sup.125I. Isotopically-labeled compounds (e.g., those labeled with 3H and .sup.14C) can be useful in compound or substrate tissue distribution assays. Tritiated (i.e., .sup.3H) and carbon-14 (i.e., .sup.14C) isotopes can be useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., .sup.2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). In some embodiments, one or more hydrogen atoms are replaced by .sup.2H or .sup.3H, or one or more carbon atoms are replaced by .sup.13C- or .sup.14C-enriched carbon. Positron emitting isotopes such as .sup.15O, .sup.13N, .sup.11C, and .sup.18F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Preparations of isotopically labelled compounds are known to those of skill in the art. For example, isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed for compounds of the present invention described herein, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present disclosure; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

Definitions

[0100] In this application, unless otherwise clear from context, (i) the term “a” may be understood to mean “at least one”; (ii) the term “or” may be understood to mean “and/or”; and (iii) the terms “including” and “including” may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps.

[0101] As used herein, the terms “about” and “approximately” refer to a value that is within 10% above or below the value being described. For example, the term “about 5 nM” indicates a range of from 4.5 to 5.5 nM.

[0102] As used herein, the term “administration” refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) may be by any appropriate route. For example, in some embodiments, administration may be bronchial (including by bronchial instillation), buccal, enteral, interdermal, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intratumoral, intravenous, intraventricular, mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (including by intratracheal instillation), transdermal, vaginal, and vitreal.

[0103] As used herein, the term “BAF complex” refers to the BRG1- or HRBM-associated factors complex in a human cell.

[0104] As used herein, a “combination therapy” or “administered in combination” means that two (or more) different agents or treatments are administered to a subject as part of a defined treatment regimen for a particular disease or condition. The treatment regimen defines the doses and periodicity of administration of each agent such that the effects of the separate agents on the subject overlap. In some embodiments, the delivery of the two or more agents is simultaneous or concurrent and the agents may be co-formulated. In some embodiments, the two or more agents are not co-formulated and are administered in a sequential manner as part of a prescribed regimen. In some embodiments, administration of two or more agents or treatments in combination is such that the reduction in a symptom, or other parameter related to the disorder is greater than what would be observed with one agent or treatment delivered alone or in the absence of the other. The effect of the two treatments can be partially additive, wholly additive, or greater than additive (e.g., synergistic). Sequential or substantially simultaneous administration of each therapeutic agent can be achieved by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination may be administered by intravenous injection while a second therapeutic agent of the combination may be administered orally.

[0105] As used herein, the term “BRD9” refers to bromodomain-containing protein 9, a component of the BAF (BRG1- or BRM-associated factors) complex, a SWI/SNF ATPase chromatin remodeling complex, and belongs to family IV of the bromodomain-containing proteins. BRD9 is encoded by the BRD9 gene, the nucleic acid sequence of which is set forth in SEQ ID NO: 1. The term “BRD9” also refers to natural variants of the wild-type BRD9 protein, such as proteins having at least 85% identity (e.g., 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.9% identity, or more) to the amino acid sequence of wild-type BRD9, which is set forth in SEQ ID NO: 2.

[0106] As used herein, the term “BRD9-related disorder” refers to a disorder that is caused or affected by the level and/or activity of BRD9.

[0107] As used herein, the term “cancer” refers to a condition caused by the proliferation of malignant neoplastic cells, such as tumors, neoplasms, carcinomas, sarcomas, leukemias, and lymphomas.

[0108] As used herein, the term “degrader” refers to a small molecule compound including a degradation moiety, wherein the compound interacts with a protein (e.g., BRD9) in a way which

results in degradation of the protein, e.g., binding of the compound results in at least 5% reduction of the level of the protein, e.g., in a cell or subject.
[0109] As used herein, the term “degradation moiety” refers to a moiety whose binding results in degradation of a protein, e.g., BRD9. In one example, the moiety binds to a protease or a ubiquitin ligase that metabolizes the protein, e.g., BRD9.
[0110] By “determining the level of a protein” is meant the detection of a protein, or an mRNA encoding the protein, by methods known in the art either directly or indirectly. “Directly determining” means performing a process (e.g., performing an assay or test on a sample or “analyzing a sample” as that term is defined herein) to obtain the physical entity or value. “Indirectly determining” refers to receiving the physical entity or value from another party or source (e.g., a third-party laboratory that directly acquired the physical entity or value). Methods to measure protein level generally include, but are not limited to, western blotting, immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immunoprecipitation, immunofluorescence, surface plasmon resonance, chemiluminescence, fluorescent polarization, phosphorescence, immunohistochemical analysis, matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry, liquid chromatography (LC)-mass spectrometry, microcytometry, microscopy, fluorescence activated cell sorting (FACS), and flow cytometry, as well as assays based on a property of a protein including, but not limited to, enzymatic activity or interaction with other protein partners. Methods to measure mRNA levels are known in the art.
[0111] By “modulating the activity of a BAF complex,” is meant altering the level of an activity related to a BAF complex (e.g., GBAF), or a related downstream effect. The activity level of a BAF complex may be measured using any method known in the art, e.g., the methods described in Kadoch et al, Cell 153:71-85 (2013), the methods of which are herein incorporated by reference.
[0112] By “reducing the activity of BRD9,” is meant decreasing the level of an activity related to an BRD9, or a related downstream effect. A non-limiting example of inhibition of an activity of BRD9 is decreasing the level of a BAF complex (e.g., GBAF) in a cell. The activity level of BRD9 may be measured using any method known in the art. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 inhibitor. In some embodiments, an agent which reduces the activity of BRD9 is a small molecule BRD9 degrader.
[0113] By “reducing the level of BRD9,” is meant decreasing the level of BRD9 in a cell or subject. The level of BRD9 may be measured using any method known in the art.
[0114] By “level” is meant a level of a protein, or mRNA encoding the protein, as compared to a reference. The reference can be any useful reference, as defined herein. By a “decreased level” or an “increased level” of a protein is meant a decrease or increase in protein level, as compared to a reference (e.g., a decrease or an increase by about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 100%, about 150%, about 200%, about 300%, about 400%, about 500%, or more; a decrease or an increase of more than about 10%, about 15%, about 20%, about 50%, about 75%, about 100%, or about 200%, as compared to a reference; a decrease or an increase by less than about 0.01-fold, about 0.02-fold, about 0.1-fold, about 0.3-fold, about 0.5-fold, about 0.8-fold, or less; or an increase by more than about 1.2-fold, about 1.4-fold, about 1.5-fold, about 1.8-fold, about 2.0-fold, about 3.0-fold, about 3.5-fold, about 4.5-fold, about 5.0-fold, about 10-fold, about 15-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, about 1000-fold, or more). A level of a protein may be expressed in mass/vol (e.g., g/dL, mg/mL, μg/mL, ng/ml) or percentage relative to total protein or mRNA in a sample.
[0115] As used herein, the term “inhibitor” refers to any agent which reduces the level and/or activity of a protein (e.g., BRD9). Non-limiting examples of inhibitors include small molecule inhibitors, degraders, antibodies, enzymes, or polynucleotides (e.g., siRNA).
[0116] As used herein, the terms “effective amount,” “therapeutically effective amount,” and “a

"sufficient amount" of an agent that reduces the level and/or activity of BRD9 (e.g., in a cell or a subject) described herein refer to a quantity sufficient to, when administered to the subject, including a human, effect beneficial or desired results, including clinical results, and, as such, an "effective amount" or synonym thereto depends on the context in which it is being applied. For example, in the context of treating cancer, it is an amount of the agent that reduces the level and/or activity of BRD9 sufficient to achieve a treatment response as compared to the response obtained without administration of the agent that reduces the level and/or activity of BRD9. The amount of a given agent that reduces the level and/or activity of BRD9 described herein that will correspond to such an amount will vary depending upon various factors, such as the given agent, the pharmaceutical formulation, the route of administration, the type of disease or disorder, the identity of the subject (e.g., age, sex, and/or weight) or host being treated, and the like, but can nevertheless be routinely determined by one of skill in the art. Also, as used herein, a "therapeutically effective amount" of an agent that reduces the level and/or activity of BRD9 of the present disclosure is an amount which results in a beneficial or desired result in a subject as compared to a control. As defined herein, a therapeutically effective amount of an agent that reduces the level and/or activity of BRD9 of the present disclosure may be readily determined by one of ordinary skill by routine methods known in the art. Dosage regimen may be adjusted to provide the optimum therapeutic response.

[0117] The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); or in any other pharmaceutically acceptable formulation.

[0118] A "pharmaceutically acceptable excipient," as used herein, refers any ingredient other than the compounds described herein (for example, a vehicle capable of suspending or dissolving the active compound) and having the properties of being substantially nontoxic and non-inflammatory in a subject. Excipients may include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0119] As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of any of the compounds described herein. For example, pharmaceutically acceptable salts of any of the compounds described herein include those that are within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, pharmaceutically acceptable salts are described in: Berge et al., J. Pharmaceutical Sciences 66:1-19, 1977 and in Pharmaceutical Salts: Properties, Selection, and Use, (Eds. P. H. Stahl and C. G. Wermuth), Wiley-VCH, 2008. The salts can be prepared in situ during the final

isolation and purification of the compounds described herein or separately by reacting a free base group with a suitable organic acid.

[0120] The compounds described herein may have ionizable groups so as to be capable of preparation as pharmaceutically acceptable salts. These salts may be acid addition salts involving inorganic or organic acids or the salts may, in the case of acidic forms of the compounds described herein, be prepared from inorganic or organic bases. Frequently, the compounds are prepared or used as pharmaceutically acceptable salts prepared as addition products of pharmaceutically acceptable acids or bases. Suitable pharmaceutically acceptable acids and bases and methods for preparation of the appropriate salts are well-known in the art. Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Representative acid addition salts include acetate, adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptonate, glycerophosphate, hemisulfate, heptonate, hexanoate, hydrobromide, hydrochloride, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, toluenesulfonate, undecanoate, and valerate salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, and magnesium, as well as nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, and ethylamine.

[0121] By a “reference” is meant any useful reference used to compare protein, mRNA, DNA, or gene expression levels. The reference can be any sample, standard, standard curve, or level that is used for comparison purposes. The reference can be a normal reference sample or a reference standard or level. A “reference sample” can be, for example, a control, e.g., a predetermined negative control value such as a “normal control” or a prior sample taken from the same subject; a sample from a normal healthy subject, such as a normal cell or normal tissue; a sample (e.g., a cell or tissue) from a subject not having a disease; a sample from a subject that is diagnosed with a disease, but not yet treated with a compound described herein; a sample from a subject that has been treated by a compound described herein; or a sample of a purified protein (e.g., any described herein) at a known normal concentration. By “reference standard or level” is meant a value or number derived from a reference sample. A “normal control value” is a pre-determined value indicative of non-disease state, e.g., a value expected in a healthy control subject. Typically, a normal control value is expressed as a range (“between X and Y”), a high threshold (“no higher than X”), or a low threshold (“no lower than X”). A subject having a measured value within the normal control value for a particular biomarker is typically referred to as “within normal limits” for that biomarker. A normal reference standard or level can be a value or number derived from a normal subject not having a disease or disorder (e.g., cancer); a subject that has been treated with a compound described herein. In preferred embodiments, the reference sample, standard, or level is matched to the sample subject sample by at least one of the following criteria: age, weight, sex, disease stage, and overall health. A standard curve of levels of a purified protein, e.g., any described herein, within the normal reference range can also be used as a reference.

[0122] As used herein, the term “subject” refers to any organism to which a composition in accordance with the invention may be administered, e.g., for experimental, diagnostic, prophylactic, and/or therapeutic purposes. Typical subjects include any animal (e.g., mammals such as mice, rats, rabbits, non-human primates, and humans). A subject may seek or be in need of treatment, require treatment, be receiving treatment, be receiving treatment in the future, or be a human or animal who is under care by a trained professional for a particular disease or condition.

[0123] As used herein, the terms “treat,” “treated,” or “treating” mean both therapeutic treatment

and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the subject; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment.

[0124] As used herein, the term “undetectable” refers to a measurement and/or observation that is not able to be obtained either due to insufficient presence of the substance in question or complete lack thereof. Instrumentation limitations can contribute to an undetectable measurement.

[0125] As used herein, the terms “variant” and “derivative” are used interchangeably and refer to naturally-occurring, synthetic, and semi-synthetic analogues of a compound, peptide, protein, or other substance described herein. A variant or derivative of a compound, peptide, protein, or other substance described herein may retain or improve upon the biological activity of the original material.

[0126] As used herein, the term “adenocarcinoma” refers to a form of cancer that originates in glandular cells.

[0127] As used herein, the term “trans-differentiation” refers to the conversion of one a cell type into a second cell type without passing through an intermediate pluripotent state.

[0128] As used herein, the term “luminal prostate cancer” refers to prostate cancer that arises in luminal cells.

[0129] As used herein, the term “neuroendocrine prostate cancer” refers to a subtype of prostate cancer that exists in neuroendocrine cells located in the prostate cancer.

[0130] As used herein, the term “metastatic tumor seeding” refers to a process by which cancerous cells are spread throughout the body and cause the formation of tumors at locations in the body other than the first location in the body where the cancer cells appeared.

[0131] As used herein, the term “metastatic tumor nodule formation” refers to the formation of a tumor nodule at a secondary cancer site.

[0132] As used herein, the term “metastatic colonization” refers to the process by which cancer cells spread throughout the body from a primary cancer site to one or more secondary cancer sites.

[0133] The details of one or more embodiments of the invention are set forth in the description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

[0134] FIG. **1**A is a graph illustrating inhibition of tumor growth in mice engrafted with LNCaP prostate xenograft tumors and treated with Compound 1, enzalutamide and the combination of both compounds.

[0135] FIG. **1**B is a graph showing the bodyweight change of the animals over the course of the study.

[0136] FIG. **2**A is a graph illustrating inhibition of tumor growth in mice engrafted with VCaP prostate xenograft tumors and treated with Compound 1, enzalutamide and the combination of both compounds.

[0137] FIG. **2**B is a graph showing bodyweight change of the animals over the course of the study.
[0138] FIG. **3**A is a graph illustrating inhibition of tumor growth in mice engrafted with PC3 prostate xenograft tumors and treated with Compound 1.
[0139] FIG. **3**B is a graph showing bodyweight change of the animals over the course of the study.
[0140] FIG. **4**A is a graph illustrating inhibition of tumor growth in mice engrafted with NCI-H660 prostate xenograft tumors and treated with Compound 1.
[0141] FIG. **4**B is a graph showing bodyweight change of the animals over the course of the study.
[0142] FIG. **5**A is a graph illustrating inhibition of tumor growth in mice engrafted with C.sub.42B prostate xenograft tumors and treated with Compound 1 or enzalutamide.
[0143] FIG. **5**B is a graph showing bodyweight change of the animals over the course of the study.
[0144] FIG. **6**A is a graph illustrating inhibition of tumor growth in mice engrafted with 22Rv1 prostate xenograft tumors and treated with Compound 1, enzalutamide and the combination of both compounds.
[0145] FIG. **6**B is a graph showing bodyweight change of the animals over the course of the study.
[0146] FIG. **7**A is a graph illustrating inhibition of tumor growth in mice engrafted with DU145 prostate xenograft tumors and treated with Compound 1.
[0147] FIG. **7**B is a graph showing bodyweight change of the animals over the course of the study.
[0148] FIG. **8** is a graph showing plasma concentration over time for Compound 1 in the DU145 PK/PD study.
[0149] FIG. **9** is a graph illustrating a positive correlation between plasma PK and tumor PD for the DU145 PK/PD study.
[0150] FIG. **10**A is a graph illustrating inhibition of tumor growth in mice engrafted with VCaP prostate xenograft tumors and treated with Compound 1, enzalutamide and the combination of both compounds.
[0151] FIG. **10**B is a graph showing bodyweight change of the animals over the course of the study.

DETAILED DESCRIPTION

[0152] The progression of prostate cancer typically depends on activity of the androgen receptor, a transcription factor that effectuates changes in gene expression upon binding to androgenic hormones such as testosterone and dihydroxytestosterone. Accordingly, existing treatments for prostate cancer include androgen starvation, e.g., reduction in androgen levels caused by surgical or chemical castration, or the administration of androgen receptor signaling inhibitors. However, subtypes of prostate cancer such as castration-resistant prostate cancer (CRPC) can grow and spread even with very low levels of androgen, and resistance typically develops to androgen receptor signaling inhibitors. The present inventors have discovered that forms of prostate cancer that grow and spread independently of the androgen receptor may be treated with compounds that reduce the level and/or activity of bromodomain containing protein 9 (BRD9). Accordingly, the present invention features methods of treating androgen receptor-independent prostate cancer with compounds that reduce the level and/or activity of BRD9.

BRD9 Inhibitors

[0153] Compounds that reduce the level of an activity related to BRD9, or a related downstream effect, or reduce the level of BRD9 in a cell or subject, may be used in accordance with the methods of the invention. BRD9 inhibitors are disclosed in US20220098190, US20220048906, US20210230190, US 20210009568, US20190247509, US20180044335, WO 2020051235, WO 2020160192, WO 2020160193, WO 2020160198, WO 2021055295, and WO 2021178920, the BRD9 inhibitors of which are incorporated by reference into the present application. In some embodiments of the method of the invention, the BRD9 inhibitors are BRD9 degraders.
[0154] In a preferred embodiment of the methods of the present invention, the BRD9 inhibitor has the structure of Compound 1, or a pharmaceutically acceptable salt thereof.
##STR00003##

[0155] Methods for synthesizing compound 1 are disclosed in US 2021-0230190 A1, the synthetic methods of which are incorporated by reference into the present application.
[0156] The BRD9 inhibitor may be, e.g., a compound of Formula I:
##STR00004## [0157] where
[0158] R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; [0159] Z.sup.1 is CR.sup.2 or N; [0160] R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;
##STR00005##
is
##STR00006## [0161] X.sup.1 is a bond, O, NR.sup.3a,
##STR00007## or CR.sup.4aR.sup.5a; [0162] X.sup.2 is O, NR.sup.3b,
##STR00008## or CR.sup.4bR.sup.5b; [0163] X.sup.3 is O, NR.sup.3c,
##STR00009## or CR.sup.4cR.sup.5c; [0164] X.sup.4 is a bond, O, NR.sup.3d,
##STR00010## or CR.sup.4dR.sup.5d; [0165] X.sup.5 is O or NR.sup.3e and X.sup.6 is CR.sup.4fR.sup.5f, or X.sup.5 is CR.sup.4eR.sup.5e and X.sup.6 is O or NR.sup.3f; [0166] X.sup.7 is O, NR.sup.3g, or CR.sup.4gR.sup.5g; [0167] X.sup.8 is O, NR.sup.3h, or CR.sup.4hR.sup.5h; [0168] each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; [0169] each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; [0170] each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; [0171] each of R.sup.3e, R.sup.3f, R.sup.3g, and R.sup.3h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-

C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; [0172] each of R.sup.4e, R.sup.4f, R.sup.4g, and R.sup.4h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3e and R.sup.4f or R.sup.4e and R.sup.3f, together with the atoms to which each is attached, combine to form optionally substituted heterocyclycl; [0173] each of R.sup.5e, R.sup.5f, R.sup.5g, and R.sup.5h is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and [0174] G is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

[0175] In some embodiments,

##STR00011##

is

##STR00012##

In some embodiments,

##STR00013##

is

##STR00014##

In some embodiments,

##STR00015##

is

##STR00016##

or

##STR00017##

In some embodiments,

##STR00018##

is

##STR00019##

[0176] The BRD9 inhibitor may be, e.g., a compound of Formula I:

##STR00020## [0177] where [0178] R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; [0179] Z.sup.1 is CR.sup.2 or N; [0180] R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;

##STR00021##

is

##STR00022## [0181] X.sup.1 is a bond, O, NR.sup.3a, or CR.sup.4aR.sup.5a; [0182] X.sup.2 is O, NR.sup.3b, or CR.sup.4bR.sup.5b; [0183] X.sup.3 is O, NR.sup.3c, or CR.sup.4cR.sup.5c; [0184] X.sup.4 is a bond, O, NR.sup.3d, or CR.sup.4dR.sup.5d; [0185] each of R.sup.3a, R.sup.3b, R.sup.3c, and R.sup.3d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, optionally substituted sulfonamide, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; [0186] each of R.sup.4a, R.sup.4b, R.sup.4c, and R.sup.4d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, optionally substituted C.sub.1-C.sub.6 acyl, thiol, optionally substituted sulfone, or optionally substituted amino, or R.sup.3a and R.sup.4b, R.sup.4a and R.sup.3b, R.sup.4b and R.sup.4a, R.sup.3b and R.sup.4c, R.sup.4b and R.sup.4c, R.sup.3c and R.sup.4b, R.sup.3c and R.sup.4d, R.sup.4c and R.sup.4d, and/or R.sup.3d and R.sup.4c, together with the atoms to which each is attached, combine to form optionally substituted C.sub.2-C.sub.9 heterocyclyl; [0187] each of R.sup.5a, R.sup.5b, R.sup.5c, and R.sup.5d is, independently, H, halogen, hydroxyl, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.2-C.sub.9 heteroaryl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.2-C.sub.6 heteroalkenyl, hydroxyl, thiol, or optionally substituted amino; and G is optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heteroaryl, or C.sub.2-C.sub.9 heterocyclyl, or a pharmaceutically acceptable salt thereof.

[0188] The BRD9 inhibitor may be, e.g., a compound of Formula II:

##STR00023## [0189] where [0190] R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; [0191] Z.sup.1 is CR.sup.2 or N; [0192] R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl;

##STR00024##

is

##STR00025## [0193] X.sup.1 is CR.sup.X1 or N; [0194] X.sup.2 is O or S; [0195] R.sup.X1 is H or optionally substituted C.sub.1-C.sub.6 alkyl; [0196] R.sup.3 is H, cyano, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, optionally substituted C.sub.3-C.sub.10 heterocyclyl, or optionally substituted C.sub.2-C.sub.9 heteroaryl; and [0197] G is optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl, or a pharmaceutically

acceptable salt thereof.
[0198] The BRD9 inhibitor may be, e.g., a compound of Formula III:

A-L-B Formula III, [0199] where [0200] A is a BRD9 binding moiety; [0201] B is a degradation moiety; and [0202] L has the structure of Formula II:

A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1—(F.sup.3).sub.o2-(E.sup.2).sub.p-A.sup.2, Formula IIIA [0203] where [0204] A.sup.1 is a bond between the linker and A; [0205] A.sup.2 is a bond between B and the linker; [0206] each of m, n, o1, o2, and p is, independently, 0 or 1; [0207] each of E.sup.1 and E.sup.2 is, independently, O, S, NR.sup.N, optionally substituted C.sub.1-10 alkylene, optionally substituted C.sub.2-10 alkenylene, optionally substituted C.sub.2-10 alkynylene, optionally substituted C.sub.2-C.sub.10 polyethylene glycol, or optionally substituted C.sub.1-10 heteroalkylene; [0208] E.sup.3 is optionally substituted C.sub.1-C.sub.6 alkylene, optionally substituted C.sub.1-C.sub.6 heteroalkylene, O, S, or NR.sup.N; [0209] each R.sup.N is, independently, H, optionally substituted C.sub.1-4 alkyl, optionally substituted C.sub.2-4 alkenyl, optionally substituted C.sub.2-4 alkynyl, optionally substituted C.sub.2-6 heterocyclyl, optionally substituted C.sub.6-12 aryl, or optionally substituted C.sub.1-7 heteroalkyl; [0210] C.sub.3 is carbonyl, thiocarbonyl, sulphonyl, or phosphoryl; and [0211] each of F.sup.1, F.sup.2, and F.sup.3 is, independently, optionally substituted C.sub.3-C.sub.10 carbocyclylene, optionally substituted C.sub.2-10 heterocyclylene, optionally substituted C.sub.6-C.sub.10 arylene, or optionally substituted C.sub.2-C.sub.9 heteroarylene, [0212] or a pharmaceutically acceptable salt thereof.
[0213] In some embodiments, the linker has the structure of Formula IIA-a:

A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sup.m-(E.sup.2).sub.p-A.sup.2. Formula IIA-a
[0214] In some embodiments, the linker has the structure of Formula IIA-b:

A.sup.1-(E.sup.1)-(F.sup.1)-(E.sup.2).sub.p-A.sup.2. Formula IIA-b
[0215] In some embodiments, the linker has the structure of Formula IIA-c:

A.sup.1-(E.sup.1)-(F.sup.1)-A.sup.2. Formula IIA-c
[0216] In some embodiments, the linker has the structure of Formula IIA-d:

A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m—(F.sup.2).sub.o1-A.sup.2. Formula IIA-d
[0217] In some embodiments, the linker has the structure of Formula IIA-e:

A.sup.1-(E.sup.1)-(F.sup.1)-(E.sup.3).sub.n-(F.sup.2).sub.o1-(E.sup.2).sub.p-A.sup.2. Formula IIA-e
[0218] In some embodiments, the linker has the structure of Formula IIA-f:

A.sup.1-(E.sup.1)-(F.sup.1)—(C.sup.3).sub.m-(E.sup.3).sub.n-(F.sup.2).sub.o1-(E.sup.2).sub.p-A.sup.2. Formula IIA-f
[0219] In some embodiments, the linker has the structure of Formula IIA-g:

A.sup.1-(E.sup.1)-(F.sup.1)-(E.sup.3).sub.n-(F.sup.2).sub.o1-A, Formula IIA-g
[0220] The BRD9 inhibitor may be, e.g., a compound of Formula IV:
##STR00026## [0221] where [0222] R.sup.1 is H, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.2-C.sub.6 alkenyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, or optionally substituted C.sub.3-C.sub.10 carbocyclyl; [0223] Z.sup.1 is CR.sup.2 or N; [0224] R.sup.2 is H, halogen, optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-

C.sub.6 heteroalkyl, optionally substituted C.sub.3-C.sub.10 carbocyclyl, optionally substituted C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl; [0225] X.sup.1 is N or CH, and X.sup.2 is C—R.sup.7; or X.sup.1 is C—R.sup.7, and X.sup.2 is N or CH; [0226] R.sup.7 is optionally substituted C.sub.1-C.sub.6 alkyl, optionally substituted C.sub.1-C.sub.6 heteroalkyl, optionally substituted C.sub.1-C.sub.6 alkoxy, optionally substituted amino, optionally substituted sulfone, optionally substituted sulfonamide, optionally substituted carbocyclyl having 3 to 6 atoms, or optionally substituted heterocyclyl having 3 to 6 atoms; [0227] X.sup.3 is N or CH; [0228] X.sup.4 is N or CH; [0229] G is optionally substituted C.sub.3-C.sub.10 carbocyclyl, C.sub.2-C.sub.9 heterocyclyl, optionally substituted C.sub.6-C.sub.10 aryl, or optionally substituted C.sub.2-C.sub.9 heteroaryl, or a pharmaceutically acceptable salt thereof.

[0230] The BRD9 inhibitor may be, e.g., a compound of Formula V:

##STR00027## [0231] wherein, [0232] R.sup.1 is —C.sub.1-3alkyl or -cyclopropyl; [0233] R.sup.2 is selected from halogen, —C.sub.1-3alkyl, —C.sub.1-3haloalkyl, —NH.sub.2, —NHC.sub.1-3alkyl and —OH, [0234] X.sub.1 is N or CR.sup.3 [0235] X.sup.2 is N or CR.sup.4 [0236] wherein X.sub.1 and X.sub.2 cannot be both N in the same molecule [0237] R.sup.3 is H or —C.sub.1-3alkyl; [0238] R.sup.4 is H or —C.sub.1-3alkyl; [0239] wherein R.sup.3 and R.sup.4 cannot be both —C.sub.1-3alkyl in the same molecule; [0240] alternatively, R.sup.2 and R.sup.3 taken together form a benzene ring or a 5-6 membered heteroarene ring, each of which rings can be optionally and independently substituted with one or more groups selected from halogen, —OH, —NH.sub.2, —NH—C.sub.1-3alkyl and —C.sub.1-3alkyl, wherein the —C.sub.1-3alkyl group can be optionally substituted with 5-6 membered heteroaryl or phenyl, [0241] R.sup.5 and R.sup.9 can be the same or different and are independently selected from —H, —O—C.sub.1-3alkyl and —C.sub.1-3alkyl; [0242] R.sup.6 and R.sup.8 can be the same or different and are independently selected from —H, —OH, halogen, —NH.sub.2, —C.sub.1-3alkyl, —O—C.sub.1-3alkyl, —O—C.sub.1-3haloalkyl, —C.sub.1-3alkyl-O—C.sub.1-3alkyl, 4-7 membered heterocycloalkyl, —C.sub.1-3alkyl-SO.sub.2—C.sub.1-3alkyl, —C.sub.1-3alkyl-NH.sub.2, —C.sub.1-3alkyl-N(—C.sub.1-3alky).sub.2, —N(C.sub.1-3alkyl).sub.2, —NH—R.sup.13; [0243] R.sup.13 is selected from —SO.sub.2—C.sub.1-3alkyl and —C.sub.1-3alkyl, wherein the —C.sub.1-3alkyl groups can be optionally substituted with 5 to 6 membered heteroaryl; [0244] alternatively, R.sup.5 and R.sup.6 taken together form a benzene ring; [0245] alternatively, R.sup.7 and R.sup.6 or R.sup.7 and R.sup.8 taken together form a 5-7 membered heterocycloalkyl optionally substituted with —C.sub.1-3alkyl; [0246] R.sup.7 is selected from —H, —NH.sub.2, —Y—R.sup.12, —C.sub.1-3alkyl and 4-7 membered heterocycloalkyl; [0247] Y is selected from —CR.sup.10R.sup.11—, —SO.sub.2— and —CO—; [0248] R.sup.10 and R.sup.11 can be the same or different and are independently selected from —H or —C.sub.1-3alkyl; or R.sup.10 and R.sup.11 taken together form a —C.sub.3-4cycloalkyl, [0249] R.sup.12 is selected from —NH.sub.2, —OH, —C.sub.1-3alkyl, —N(R.sup.15, R.sup.16), —O—R.sup.17, aryl, 5-6 membered heteroaryl, wherein the aryl or heteroaryl is optionally and independently substituted with one or more halogen, 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally and independently substituted with one or more groups selected from halogen, —OH, —NH.sub.2, —C.sub.1-3alkyl, —NHC.sub.1-3alkyl, —N(C.sub.1-3alkyl).sub.2, —O—C.sub.1-3alkyl and —CH.sub.2—R.sup.14; [0250] R.sup.14 is selected from 5-10 membered mono- or bicyclic aryl or heteroaryl, which is optionally substituted with —NH.sub.2, —OH, halogen, —CN, —C.sub.1-3alkyl, —O—C.sub.1-3alkyl; [0251] R.sup.15 is —H or —C.sub.1-3alkyl; [0252] R.sup.16 is selected from —C.sub.1-3alkyl, —C.sub.2-3alkyl-N(C.sub.1-3alkyl).sub.2, —C.sub.1-3alkyl-NHC.sub.1-3alkyl and 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally substituted with —C.sub.1-3alkyl; [0253] R.sup.17 is C.sub.1-3alkyl or 4-7 membered heterocycloalkyl, which heterocycloalkyl is optionally substituted with C.sub.1-3alkyl; [0254] wherein when R.sup.7 is Y—R.sup.12, R.sup.6 and R.sup.8 can be the same or different and are independently selected from —H, —OH, halogen, —NH.sub.2, —CN, —

C.sub.1-3alkyl, —C.sub.1-3haloalkyl, —O—C.sub.1-3alkyl, —O—C.sub.1-3haloalkyl and —C.sub.1-3alkyl-O—C.sub.1-3alkyl; [0255] wherein at least one of the substituents R.sup.5 to R.sup.9 is not hydrogen; [0256] or a pharmaceutically acceptable salt thereof.

[0257] The BRD9 inhibitor may be, e.g., a compound of Formula VI, VII, or VIII:

##STR00028## [0258] or a pharmaceutically acceptable salt thereof, [0259] wherein [0260] Degron is selected from the group consisting of:

##STR00029## [0261] TL1 is a moiety that binds to BRD9 selected from the group consisting of:

##STR00030## [0262] TL2 is a moiety that binds to BRD9 selected from the group consisting of:

##STR00031## [0263] L.sup.1 is selected from the group consisting of:

##STR00032## ##STR00033## [0264] X.sup.1, X.sup.2, X.sup.3, and X.sup.4 are independently selected from CR.sup.4 and N, wherein no more than two of X.sup.1, X.sup.2, X.sup.3, and X.sup.4 may be selected to be N; [0265] X.sup.5 and X.sup.6 are independently selected from CR.sup.4 and N; [0266] Z.sup.2 and Z.sup.3 are selected from —CH.sub.2— and —C(O)— wherein at least one of Z.sup.2 and Z.sup.3 is —C(O)—; [0267] n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; [0268] is 1, 2, 3, or 4; [0269] each Q is independently 0, S, or NR.sup.5; [0270] R.sup.1 is hydrogen or C.sub.1-C.sub.6 alkyl; [0271] R.sup.2, R.sup.3, and R.sup.5 are independently selected from hydrogen and C.sub.1-C.sub.6alkyl; [0272] each R.sup.4 is independently selected from hydrogen, halogen, hydroxyl, C.sub.1-C.sub.6alkyl, C.sub.1-C.sub.6alkoxy, and C.sub.1-C.sub.6haloalkyl; [0273] each R.sup.5 is independently hydrogen, C.sub.1-C.sub.6alkyl, or —C(O)alkyl; [0274] R.sup.7 is selected from halogen, hydrogen, C.sub.1-C.sub.6alkyl, C.sub.1-C.sub.6alkoxy, and C.sub.1-C.sub.6haloalkyl; and [0275] each R.sup.6 is independently selected from hydrogen, C.sub.1-C.sub.6alkyl, and C.sub.1-C.sub.6haloalkyl; or two R.sup.8 groups together with the carbon to which they are attached form a cyclopropyl group.

[0276] The BRD9 inhibitor may be, e.g., a compound of Formula IX:

##STR00034## [0277] where [0278] the Targeting Ligand is a group that is capable of binding to a bromodomain-containing protein, e.g., BRD9; [0279] the Linker is a group that covalently links the Targeting Ligand to the Targeting Ligase Binder; [0280] the Targeting Ligase Binder is a group that is capable of binding to a ligase (e.g., Cereblon E3 Ubiquitin ligase).

[0281] The Targeting Ligand may be, e.g., a group Formula TL-I or TL-II:

##STR00035## [0282] where [0283] n is 0, 1, or 2; [0284] R1 and R2 are independently selected from the group consisting of hydrogen and C1-6 alkyl; or R1 and R2 together with the atoms to which they are attached form an aryl or heteroaryl; [0285] each R3 may be independently selected from the group consisting of C1-6 alkyl, C1-6 alkoxy, and halogen; and [0286] R5 is selected from the group consisting of hydrogen and C1-6 alkyl.

[0287] The Linker may be, e.g., a group of Formula L-I:

-L1-X1-L2-X2-L3-, Formula L-1 [0288] where [0289] L1 is selected from the group consisting of a bond, O, NR′, C(O), C1-6 alkylene, [0290] C1-6 heteroalkylene, *C(O)—C1-6 alkylene, C(O)—C1-6 alkenylene*, C1-6 alkenylene, and *C(O)—C1-6 heteroalkylene, where * denotes the point of attachment of L1 to the Targeting Ligand; [0291] X1 and X2 are each independently selected from the group consisting of a bond, carbocyclyl, and heterocyclyl, where the carbocyclyl and heterocyclyl are substituted with 0-4 occurrences of Ra, where each Ra is independently selected from the group consisting of C1-6 alkyl, C1-6 alkoxyl, and halogen; [0292] L2 is selected from the group consisting of a bond, O, NR′, C1-6 alkylene, and C1-6 heteroalkylene; or X1-L2-X2 form a spiroheterocyclyl; and [0293] L3 is selected from the group consisting of a bond, O, C(O), C1-6 alkylene, C1-6 heteroalkylene, *C(O)—C1-6 alkylene, *C(O)—C1-6 heteroalkylene, and *C(O)—C1-6 alkylene-O, where * denotes the point of attachment of L3 to X2; where no more than 2 of L1, X1, X2, L2, and L3 can simultaneously be a bond.

[0294] The Targeting Ligase Binder may be, e.g., a compound of Formula TLB-I:

##STR00036## [0295] where [0296] R4 is selected from the group consisting of C1-6 alkyl, C1-6

alkoxyl, and halogen; and m is 0, 1.
[0297] The Targeting Ligase Binder may be, e.g., a compound of Formula TLB-1:
##STR00037## [0298] where [0299] Rd1 and Rd2 are each independently selected from the group consisting of H, C1-6 alkyl, C1-6 alkoxyl, C1-6 haloalkyl, and C1-6 heteroalkyl; [0300] Rd3 is H; Rd4 is selected from the group consisting of H, C1-6 alkyl, halo, C1-6 haloalkyl, and C1-6 heteroalkyl; and [0301] Rd5 is selected from the group consisting of H, C1-6 alkyl, halo, C1-6 haloalkyl, and C1-6 heteroalkyl.
[0302] The BRD9 inhibitor may be, e.g., a compound of Formula IXa:
##STR00038## [0303] or a pharmaceutically acceptable salt thereof, [0304] where [0305] L1 is selected from the group consisting of a bond, O, NR′, C(O), C1-6 alkylene, C1-6 heteroalkylene, *C(O)—C1-6 alkylene, C(O)—C1-6 alkenylene*, C1-6 alkenylene, and *C(O)—C1-6 heteroalkylene, where * denotes the point of attachment of L1 to the Targeting Ligand; [0306] X1 and X2 are each independently selected from the group consisting of a bond, carbocyclyl, and heterocyclyl, where the carbocyclyl and heterocyclyl are substituted with 0-4 occurrences of Ra, where each Ra is independently selected from the group consisting of C1-6 alkyl, C1-6 alkoxyl, and halogen; [0307] L.sup.2 is selected from the group consisting of a bond, O, NR′, C1-6 alkylene, and C1-6 heteroalkylene; or X1-L2-X2 form a spiroheterocyclyl; and [0308] L3 is selected from the group consisting of a bond, O, C(O), C1-6 alkylene, C1-6 heteroalkylene, *C(O)—C1-6 alkylene, *C(O)—C1-6 heteroalkylene, and *C(O)—C1-6 alkylene-O, where * denotes the point of attachment of L3 to X2.
[0309] In some embodiments, no more than 2 of L1, X1, X2, L2, and L3 can simultaneously be a bond.
[0310] The BRD9 inhibitor may be, e.g., a compound of Formula X, XI, XII, XIII, XIV, or XV:
##STR00039## [0311] or a pharmaceutically acceptable salt thereof, [0312] each a is independently 0, 1, or 2; [0313] each y is independently 0, 1, or 2; [0314] X3, X4, X5, and X6, are selected from the group consisting of N, CH and CR3, wherein no more than 3 of X3, X4, X5, and X6 are N; [0315] X7 is N or CH; [0316] X8 and X9 are each independently at each occurrence selected from the group consisting of N and CH; wherein at least one of X8 or X9 is CH; [0317] X12 is a 5-membered heteroaryl group with 1, 2, or 3 atoms independently selected from N, O, and S, wherein X12 is optionally substituted with 1, 2, or 3 groups independently selected from R3; [0318] X17 is aryl, heteroaryl, bicycle, or cycloalkyl, each of which is optionally substituted with 1, 2, 3, or 4 substituents independently selected from R3; [0319] Q1 is independently at each occurrence selected from the group consisting of NH, N(alkyl), N(haloalkyl), CH.sub.2, O, and S; [0320] wherein if X7 is N, then Q1 is CH2; R is independently at each occurrence selected from the group consisting of hydrogen, C1-C4haloalkyl, C1-C4alkyl, fluorine, chlorine, bromine, iodine, CH2F, CHF2, CF3, CH2Cl, CHCl2, CCl3, CH2Br, CHBr2, and CBr3; [0321] R1 is hydrogen, C1-4 alkyl, C1-4 haloalkyl, or cycloalkyl; [0322] R3 is independently at each occurrence selected from the group consisting of hydrogen, hydroxyl, alkoxy, C1-4 alkyl, C1-4 haloalkyl, cycloalkyl, fluorine, chlorine, bromine, and iodine; [0323] B is selected from B1 and B2; [0324] B1 is selected from the group consisting of:
##STR00040## [0325] B2 is selected from the group consisting of:
##STR00041## [0326] X10 is C(R7).sub.2, C(O), or O; X11 is heterocycle, heteroaryl, aryl, cycloalkyl, or a bicycle, each of which X11 groups is optionally substituted with 1, 2, 3, or 4 groups independently selected from R3; or X10 and X11 are taken together to form
##STR00042## [0327] X13, X14, X15, and X16, are independently selected from the group consisting of N, CH and CR4, wherein no more than 3 of X13, X14, X15, and X16 are N; [0328] each R4 is independently selected from hydrogen, aryl, heteroaryl, C1-4 alkoxy, C1-4 haloalkyl, C1-4 haloalkoxy, C1-4 alkyl, fluorine, chlorine, bromine, and iodine; wherein two R4 groups on adjacent carbon atoms may optionally combine to form a fused cycle, wherein the fused cycle is optionally substituted with 1, 2, or 3 R substituents, thus, non-limiting examples of

##STR00043##
include
##STR00044##
wherein two R4 groups combined to form a pyrrole; [0329] R5 is hydrogen, C1-C4alkyl, allyl, crotyl, alkenyl, alkynyl, haloalkyl, or cycloalkyl; [0330] each R6 is independently selected from hydrogen, C1-4 alkoxy, C1-4 alkyl, C1-4 haloalkyl, fluorine, chlorine, bromine, and iodine; [0331] each R7 is independently hydrogen or C1-4 alkyl; [0332] R8 is hydrogen, C1-C4alkyl, allyl, crotyl, alkenyl, alkynyl, haloalkyl, or cycloalkyl; and [0333] L is a bivalent linking group.
[0334] The BRD9 inhibitor may be, e.g., a compound selected from the group consisting of:
TABLE-US-00001 Compound No. Structure F1 [00045]embedded image F2 [00046]
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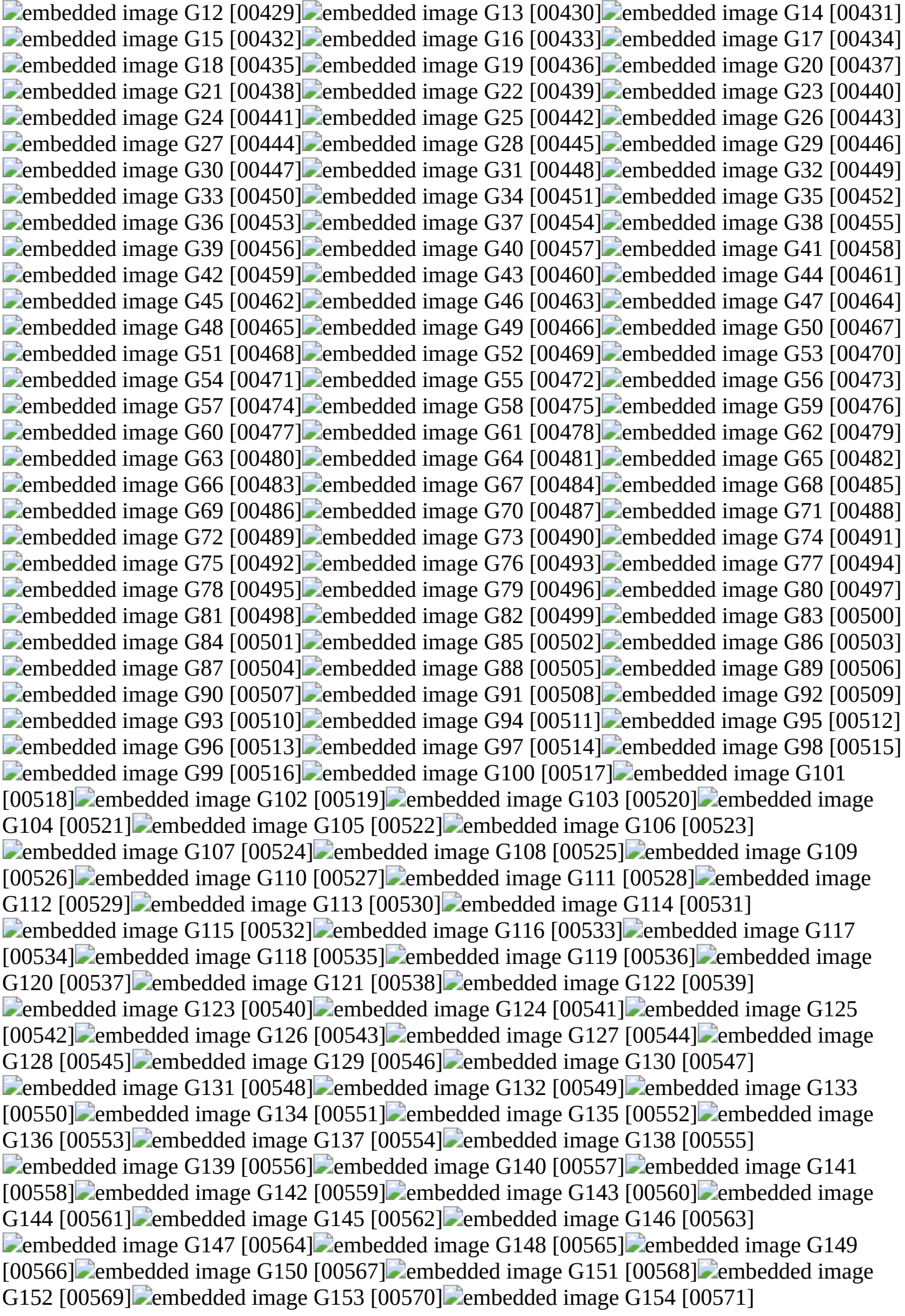
[00411]embedded image F368 [00412]embedded image F369 [00413]embedded image F370
[00414]embedded image F371 [00415]embedded image F372 [00416]embedded image
F373 [00417]embedded image [0335] or a pharmaceutically acceptable salt thereof.

[0336] The BRD9 inhibitor may be, e.g., a compound selected from the group consisting of:

TABLE-US-00002 Compound No. Structure G1 [00418]embedded image G2 [00419]
embedded image G3 [00420]embedded image G4 [00421]embedded image G5 [00422]
embedded image G6 [00423]embedded image G7 [00424]embedded image G8 [00425]
embedded image G9 [00426]embedded image G10 [00427]embedded image G11 [00428]



embedded image G155 [00572]
embedded image G156 [00573]
embedded image G157 [00574]
embedded image G158 [00575]
embedded image G159 [00576]
embedded image G160 [00577]
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embedded image G162 [00579]

embedded image G163 [00580]
embedded image G164 [00581]
embedded image G165 [00582]
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embedded image G171 [00588]
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embedded image G179 [00596]
embedded image G180 [00597]
embedded image G181 [00598]
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embedded image G183 [00600]
embedded image G184 [00601]
embedded image G185 [00602]
embedded image G186 [00603]

embedded image G187 [00604]
embedded image G188 [00605]
embedded image G189 [00606]
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embedded image G191 [00608]
embedded image G192 [00609]
embedded image G193 [00610]
embedded image G194 [00611]

embedded image G195 [00612]
embedded image G196 [00613]
embedded image G197 [00614]
embedded image G198 [00615]
embedded image G199 [00616]
embedded image G200 [00617]
embedded image G201 [00618]
embedded image G202 [00619]

embedded image G203 [00620]
embedded image G204 [00621]
embedded image G205 [00622]
embedded image G206 [00623]
embedded image G207 [00624]
embedded image G208 [00625]
embedded image G209 [00626]
embedded image G210 [00627]

embedded image G211 [00628]
embedded image G212 [00629]
embedded image G213 [00630]
embedded image G214 [00631]
embedded image G215 [00632]
embedded image G216 [00633]
embedded image G217 [00634]
embedded image G218 [00635]

embedded image G219 [00636]
embedded image G220 [00637]
embedded image G221 [00638]
embedded image G222 [00639]
embedded image [0337] or a pharmaceutically acceptable salt thereof.

[0338] The BRD9 inhibitor may be, e.g., a compound selected from the group consisting of:

TABLE-US-00003 Compound No. Structure H1 [00640]
embedded image H2 [00641]

embedded image H3 [00642]
embedded image H4 [00643]
embedded image H5 [00644]

embedded image H6 [00645]
embedded image H7 [00646]
embedded image H8 [00647]

embedded image H9 [00648]
embedded image H10 [00649]
embedded image H11 [00650]

embedded image H12 [00651]
embedded image H13 [00652]
embedded image H14 [00653]

embedded image H15 [00654]
embedded image H16 [00655]
embedded image H17 [00656]

embedded image H18 [00657]
embedded image H19 [00658]
embedded image H20 [00659]

embedded image H21 [00660]
embedded image H22 [00661]
embedded image H23 [00662]

embedded image H24 [00663]
embedded image H25 [00664]
embedded image H26 [00665]

embedded image H27 [00666]
embedded image H28 [00667]
embedded image H29 [00668]

embedded image H30 [00669]
embedded image H31 [00670]
embedded image H32 [00671]

embedded image H33 [00672]
embedded image H34 [00673]
embedded image H35 [00674]

embedded image H36 [00675]
embedded image H37 [00676]
embedded image H38 [00677]

embedded image H39 [00678]
embedded image H40 [00679]
embedded image H41 [00680]

embedded image H42 [00681]
embedded image H43 [00682]
embedded image H44 [00683]

embedded image H45 [00684]
embedded image H46 [00685]
embedded image H47 [00686]

embedded image H48 [00687]
embedded image H49 [00688]
embedded image H50 [00689]

embedded image H51 [00690]
embedded image H52 [00691]
embedded image H53 [00692]

embedded image H54 [00693]
embedded image H55 [00694]
embedded image H56 [00695]

embedded image H57 [00696]
embedded image H58 [00697]
embedded image H59 [00698]

embedded image H60 [00699]
embedded image H61 [00700]
embedded image H62 [00701]

embedded image H63 [00702]
embedded image H64 [00703]
embedded image H65 [00704]

embedded image H203 [00842]embedded image H204 [00843]embedded image H205 [00844]embedded image H206 [00845]embedded image H207 [00846]embedded image H208 [00847]embedded image H209 [00848]embedded image H210 [00849]embedded image H211 [00850]embedded image H212 [00851]embedded image H213 [00852]embedded image H214 [00853]embedded image H215 [00854]embedded image H216 [00855]embedded image H217 [00856]embedded image H218 [00857]embedded image H219 [00858]embedded image H220 [00859]embedded image H221 [00860]embedded image H222 [00861]embedded image H223 [00862]embedded image H224 [00863]embedded image H225 [00864]embedded image H226 [00865]embedded image H227 [00866]embedded image H228 [00867]embedded image H229 [00868]embedded image H230 [00869]embedded image H231 [00870]embedded image H232 [00871]embedded image H233 [00872]embedded image H234 [00873]embedded image H235 [00874]embedded image H236 [00875]embedded image H237 [00876]embedded image H238 [00877]embedded image H239 [00878]embedded image H240 [00879]embedded image H241 [00880]embedded image H242 [00881]embedded image H243 [00882]embedded image H244 [00883]embedded image H245 [00884]embedded image H246 [00885]embedded image H247 [00886]embedded image H248 [00887]embedded image H249 [00888]embedded image H250 [00889]embedded image H251 [00890]embedded image H252 [00891]embedded image H253 [00892]embedded image H254 [00893]embedded image H255 [00894]embedded image H256 [00895]embedded image H257 [00896]embedded image H258 [00897]embedded image H259 [00898]embedded image H260 [00899]embedded image H261 [00900]embedded image H262 [00901]embedded image H263 [00902]embedded image H264 [00903]embedded image H265 [00904]embedded image H266 [00905]embedded image H267 [00906]embedded image H268 [00907]embedded image H269 [00908]embedded image H270 [00909]embedded image H271 [00910]embedded image H272 [00911]embedded image H273 [00912]embedded image H274 [00913]embedded image H275 [00914]embedded image H276 [00915]embedded image H277 [00916]embedded image H278 [00917]embedded image H279 [00918]embedded image H280 [00919]embedded image H281 [00920]embedded image H282 [00921]embedded image H283 [00922]embedded image H284 [00923]embedded image H285 [00924]embedded image H286 [00925]embedded image H287 [00926]embedded image H288 [00927]embedded image H289 [00928]embedded image H290 [00929]embedded image H291 [00930]embedded image H292 [00931]embedded image H293 [00932]embedded image H294 [00933]embedded image H295 [00934]embedded image H296 [00935]embedded image H297 [00936]embedded image H298 [00937]embedded image H299 [00938]embedded image H300 [00939]embedded image H301 [00940]embedded image H302 [00941]embedded image H303 [00942]embedded image H304 [00943]embedded image H305 [00944]embedded image H306 [00945]embedded image H307 [00946]embedded image H308 [00947]embedded image H309 [00948]embedded image H310 [00949]embedded image H311 [00950]embedded image H312 [00951]embedded image H313 [00952]embedded image H314 [00953]embedded image H315 [00954]embedded image H316 [00955]embedded image [0339] or a pharmaceutically acceptable salt thereof.

[0340] The BRD9 inhibitor may be, e.g., a compound selected from the group consisting of: TABLE-US-00004 Cmpd # Structure & Name 200 [00956]embedded image 2-((4-(1,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)-2,6- dimethoxybenzyl)(methyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)octyl)acetamide 201 [00957]embedded image 2-((2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)benzyl)(methyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-

yl)amino)octyl)acetamide 202 [00958]embedded image 2-((2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin- 4-yl)benzyl)amino)-N-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-5- yl)nonyl)acetamide 203 [00959]embedded image 2-((2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin- 4-yl)benzyl)amino)-N-(8-(4-(4-((2,6-dioxopiperidin-3- yl)amino)phenyl)piperazin-1-yl)octyl)acetamide 204 [00960]embedded image 2-((2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin- 4-yl)benzyl)amino)-N-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)nonyl)acetamide 206 [00961]
embedded image 2-((4-(1,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)-2,6-dimethoxybenzyl)amino)-N-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-5-yl)nonyl)acetamide 207 [00962]embedded image N-(5-(2-((2,6-dimethoxy-4-(6-methyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4- c]pyridin-4-yl)benzyl)amino)acetamido)pentyl)-3-(2-(2,6-dioxopiperidin-3-yl)- 1,3-dioxoisoindolin-5-yl)propanamide 208 [00963]embedded image 2-((4-(1,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrazolo[3,4-c]pyridin-4-yl)-2,6- dimethoxybenzyl)amino)-N-(9-(2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)nonyl)acetamide 209 [00964]
embedded image 2-((4-(1,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-2,6-dimethoxybenzyl)(methyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)octyl)acetamide 218 [00965]embedded image N-(8-(2-((4-(1,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)- 2,6-dimethoxybenzyl)(methyl)amino)acetamido)octyl)-1-(2,6-dioxopiperidin-3- yl)-6-oxo-1,6-dihydropyridine-3-carboxamide 220 [00966]
embedded image 2-((4-(1,6-dimethyl-7-oxo-6,7-dihydro-1H-pyrrolo[2,3-c]pyridin-4-yl)-2,6-dimethoxybenzyl)(methyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1- oxoisoindolin-4-yl)amino)octyl)acetamide 221 [00967]embedded image 2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4- yl)benzyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)octyl)acetamide 222 [00968]embedded image N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)-2-((2- fluoro-6-methoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4- yl)benzyl)(methyl)amino)acetamide 223 [00969]
embedded image 2-((2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)benzyl)oxy)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)octyl)acetamide 224 [00970]embedded image 2-((1-(2,6-dimethoxy-4-(2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4- yl)phenyl)ethyl)(methyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)octyl)acetamide 225 [00971]embedded image 2-((4-(4,6-dimethyl-5-oxo-4,5-dihydropyrazin-2-yl)-2,6- dimethoxybenzyl)(methyl)amino)-N-(8-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)octyl)acetamide 300 [00972]
embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)butyl)carbamoyl)phenyl)-4-(phenylamino)quinoline-3- carboxamide 301 [00973]embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)butyl)carbamoyl)phenyl)-4- (phenylamino)quinoline-3-carboxamide 302 [00974]embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)butyl)carbamoyl)phenyl)-4- (phenylamino)quinoline-3-carboxamide 303 [00975]embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)acetamido)butyl)carbamoyl)phenyl)-4- (phenylamino)quinoline-3-carboxamide 306 [00976]embedded image 6-(4-((3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)propyl)carbamoyl)phenyl)-4-(phenylamino)quinoline- 3-carboxamide 307 [00977]embedded image 6-(4-((3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)propyl)carbamoyl)phenyl)-4- (phenylamino)quinoline-3-carboxamide 308 [00978]embedded image 6-(4-(((1s,4s)-4-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin- 4-yl)oxy)acetamido)acetamido)cyclohexyl)carbamoyl)phenyl)-4-(phenylamino)quinoline-3-carboxamide 309 [00979]embedded image 4-((4′-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)butyl)carbamoyl)-[1,1′-biphenyl]-4-yl)amino)quinoline-3-carboxamide 310 [00980]embedded image 6-(4-(6-(2-((2-(2,6-

dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)hexanoyl)piperazin-1-yl)-4-(phenylamino)quinoline-3- carboxamide 311 [00981]  embedded image 6-(4-((2-(2-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)ethoxy)ethyl)carbamoyl)phenyl)-4- (phenylamino)quinoline-3-carboxamide 312 [00982]  embedded image 6-(1-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)hexanoyl)piperidin-4-yl)-4-(phenylamino)quinoline-3-carboxamide 340 [00983]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)butyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 341 [00984]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 343 [00985]  embedded image 6-(4-((4-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)piperazin-1-yl)-4-oxobutyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 344 [00986]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)butyl)carbamoyl)phenyl)-7-methoxy-N-methyl-4- (phenylamino)quinoline-3-carboxamide 345 [00987]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)butyl)carbamoyl)phenyl)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 346 [00988]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)butyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 347 [00989]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)butyl)carbamoyl)piperidin-1-yl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 348 [00990]  embedded image N6-(2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)glycyl)piperazin-1-yl)-2-oxoethyl)-N3-methyl-4- (phenylamino)quinoline-3,6-dicarboxamide 350 [00991]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)-3-fluorophenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 351 [00992]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)butyl)carbamoyl)-3-fluorophenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 353 [00993]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)-3-methylphenyl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 354 [00994]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)butyl)carbamoyl)-3-methylphenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 356 [00995]  embedded image 6-(4-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)methyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)phenyl)-N- methyl-4-(phenylamino)quinoline-3-carboxamide 357 [00996]  embedded image 6-(6-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)butyl)carbamoyl)pyridin-3-yl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 358 [00997]  embedded image 6-(6-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)pyridin-3-yl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 359 [00998]  embedded image 6-(4-((4-(4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)piperazin-1-yl)butyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 360 [00999]  embedded image 6-(1-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)hexyl)-1H-pyrazol-4-yl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 361 [01000]  embedded image 6-(1-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)hexyl)-1H-pyrazol-3-yl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 363 [01001]embedded image 6-(4-((3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)propyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 365 [01002]  embedded image 6-(6-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)amino)pyridin-3-yl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 366 [01003]embedded image 6-(4-((3-(4-((2-

(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)piperidin-1-yl)propyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 367 [01004]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)butyl)carbamoyl)-3-fluorophenyl)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 369 [01005]  embedded image 6-(6-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butoxy)pyridin-3-yl)-N-methy-4-(phenylamino)quinoline-3-carboxamide 370 [01006] embedded image 6-((1-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butanoyl)piperidin-4-yl)methoxy)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 371 [01007]  embedded image 6-((1-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)butyl)piperidin-4-yl)methoxy)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 372 [01008]  embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)butyl)carbamoyl)-3-fluorophenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 373 [01009] embedded image N-(tert-butyl)-6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamooyl)pyridin-3-yl)-7-methoxy-4-(phenylamino)quinoline- 3-carboxamide 374 [01010] embedded image 6-(4-((4-(3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4- yl)propanamido)butyl)carbamoyl)phenyl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 375 [01011] embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)-3-fluorophenyl)-N-methyl-4- (phenylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 376 [01012] embedded image 6-(4-((2-(4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)piperidin-1-yl)ethyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 378 [01013] embedded image 6-(4-((8-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4- yl)octyl)carbamoyl)phenyl)-N-methyl-4-(phenylamino)quinoline-3- carboxamide 379 [01014] embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)butyl)carbamoyl)-3-fluorophenyl)-N-methyl-4- (phenylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 380 [01015] embedded image 6-(5-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)methyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)pyrazin-2-yl)- 7-methoxy-N-methyl-4-(phenylamino)quinoline-3-carboxamide 381 [01016] embedded image 6-(6-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)propanamido)butyl)carbamoyl)pyridin-3-yl)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 382 [01017] embedded image 6-(6-((4-((2R)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)butyl)carbamoyl)pyridin-3-yl)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 384 [01018] embedded image 6-(6-((4-((2R)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propanamido)butyl)carbamoyl)pyridin-3-yl)-7-methoxy-N- methyl-4-(phenylamino)quinoline-3-carboxamide 385 [01019] embedded image 6-(6-(5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)pentyl)pyridin-3-yl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 386 [01020] embedded image 6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)methyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)pyridin-3-yl)- N-methyl-4-(phenylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 387 [01021] embedded image N-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)-2-(3-(methylcarbamoyl)-4- (phenylamino)quinolin-6-yl)thiazole-4-carboxamide 388 [01022] embedded image 6-(6-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)pyridin-3-yl)-N-methyl-4-(phenylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 389 [01023] embedded image 6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)methyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)pyridin-3-yl)-7- fluoro-N-methyl-4-(phenylamino)quinoline-3-carboxamide 395 [01024] embedded image N-cyclopropyl-6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-

dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)pyridin-3-yl)-7-methoxy-4-((4- methoxybenzyl)amino)quinoline-3-carboxamide 396 [01025]  embedded image N-cyclopropyl-6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)pyridin-3-yl)-7-methoxy-4-(phenylamino)quinoline- 3-carboxamide 397 [01026]  embedded image N-cyclopropyl-6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)pyridin-3-yl)-7-methoxy-4-(methylamino)quinoline- 3-carboxamide 398 [01027]  embedded image 4-amino-N-cyclopropyl-6-(6-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)pyridin-3-yl)-7-methoxyquinoline-3-carboxamide 401 [01028]  embedded image N-cyclopropyl-6-(4-((7-(6-(2,6-dioxopiperidin-3-yl)-7-oxo-6,7-dihydro- 5H-pyrrolo[3,4-b]pyridin-3-yl)heptyl)carbamoyl)-3-fluorophenyl)-7- fluoro-4-(methylamino)quinoline-3-carboxamide 404 [01029]  embedded image N-cyclopropyl-6-(4-((7-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-5,7-dihydro- 5H-pyrrolo[3,4-b]pyridin-2-yl)heptyl)carbamoyl)-3-fluorophenyl)-4- (methylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 405 [01030]  embedded image N-cyclopropyl-6-(4-((8-(6-(2,6-dioxopiperidin-3-yl)-7-oxo-6,7-dihydro- 5H-pyrrolo[3,4-b]pyridin-3-yl)octyl)carbamoyl)-3-fluorophenyl)-7- fluoro-4-(methylamino)quinoline-3-carboxamide 408 [01031]  embedded image N-cyclopropyl-6-(4-((8-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-5,7-dihydro- 5H-pyrrolo[3,4-b]pyridin-2-yl)octyl)carbamoyl)-3-fluorophenyl)-7- fluoro-4-(methylamino)quinoline-3-carboxamide 409 [01032]  embedded image N-cyclopropyl-6-(4-((8-(6-(2,6-dioxopiperidin-3-yl)-5-oxo-6,7-dihydro- 5H-pyrrolo[3,4-b]pyridin-2-yl)octyl)carbamoyl)-3-fluorophenyl)-4- (methylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 411 [01033]  embedded image N-cyclopropyl-6-(4-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)methyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)-3-fluorophenyl)-7-fluoro-4- (methylamino)quinoline-3-carboxamide 412 [01034]  embedded image N-cyclopropyl-6-(4-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-7-fluoro-4- (methylamino)quinoline-3-carboxamide 413 [01035]  embedded image N-cyclopropyl-6-(4-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)oxy)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-7-fluoro-4- (phenylamino)quinoline-3-carboxamide 414 [01036]  embedded image N-cyclopropyl-6-(4-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-7-methoxy-4- (phenylamino)quinoline-3-carboxamide 415 [01037]  embedded image N-cyclopropyl-6-(4-((4-(4-(((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)oxy)methyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-4-(phenylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 416 [01038]embedded image N-cyclopropyl-6-(4-((4-(3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin- 4-yl)propanamido)butyl)carbamoyl)-3-fluorophenyl)-7-fluoro-4- (methylamino)quinoline-3-carboxamide 421 [01039]embedded image N-cyclopropyl-6-(4-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)cyclopropyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-4-(methlylamino)-7- (trifluoromethyl)quinoline-3-carboxamide 424 [01040]embedded image 4-(bicyclo[1.1.1]pentan-1-ylamino)-N-cyclopropyl-6-(4-((4-(2-((2-(2,6- dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)butyl)carbamoyl)-3-fluorophenyl)-7- fluoroquinoline-3-carboxamide 429 [01041]embedded image N-cyclopropyl-6-(4-(1-(5-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)acetamido)pentanamido)ethyl)-3- fluorophenyl)-7-fluoro-4-(phenylamino)quinoline-3-carboxamide 430 [01042]embedded image N-cyclopropyl-6-(4-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)-3-fluorophenyl)-4-(methylamino)-7- (trifluoromethyl)quinoline-3-carboxamide 431 [01043]embedded image N-cyclopropyl-6-(6-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)pyridin-3-yl)-4-(methylamino)-7- (trifluoromethyl)quinoline-3-carboxamide 432 [01044]embedded image

N-cyclopropyl-6-(4-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-7-methoxy-4-(phenylamino)quinoline-3-carboxamide 433 [01045]embedded image N-cyclopropyl-6-(4-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-1-yl)butyl)carbamoyl)-3-fluorophenyl)-7-fluoro-4- (phenylamino)quinoline-3-carboxamide 434 [01046]embedded image N-cyclopropyl-6-(4-((4-(4-(1-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)ethyl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-4-(phenylamino)-7- (trifluoromethyl)quinoline-3-carboxamide 435 [01047]embedded image N-cyclopropyl-6-(4-((4-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)propan-2-yl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-4-(methylamino)-7-(trifluoromethyl)quinoline-3-carboxamide 436 [01048]embedded image N-cyclopropyl-6-(4-((4-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)propan-2-yl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)-3-fluorophenyl)-7-fluoro-4- (methylamino)quinoline-3-carboxamide 437 [01049]embedded image N-cyclopropyl-6-(6-((4-(4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)propan-2-yl)-1H-1,2,3-triazol-1- yl)butyl)carbamoyl)pyridin-3-yl)-4-(methylamino)-7- (trifluoromethyl)quinoline-3-carboxamide 439 [01050]embedded image N-cyclopropyl-6-(4-((2-(5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin- 4-yl)-2-hydroxypentanamido)ethyl)carbamoyl)-3-fluorophenyl)-7-fluoro- 4-(phenylamino)quinoline-3-carboxamide 440 [01051]embedded image N-cyclopropyl-6-(4-((3-(3-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)amino)-2-hydroxypropanamido)propyl)carbamoyl)- 3-fluorophenyl)-7-fluoro-4-(phenylamino)quinoline-3-carboxamide 441 [01052]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4- yl)amino)acetamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline- 3-carboxamide 442 [01053]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)propanamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline- 3-carboxamide 443 [01054]embedded image 6-((10-((2R)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 444 [01055]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 445 [01056]embedded image 6-((10-((2S)-2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)propanamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 446 [01057]embedded image N6-(9-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)nonyl)-N3-methyl-4-(phenylamino)quinoline-3,6- dicarboxamide 447 [01058]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)decyl)amino)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 448 [01059]embedded image 4-(benzylamino)-6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)oxy)acetamido)decyl)amino)-N-methylquinoline-3- carboxamide 449 [01060]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline-3- carboxamide 450 [01061]embedded image N6-(10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)decyl)-N3-methyl-4-(phenylamino)quinoline-3,6-dicarboxamide 451 [01062]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)decyl)amino)-N-methyl-4-(phenylamino)quinoline- 3-carboxamide 452 [01063]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)decyl)amino)-N-ethyl-4-(phenylamino)quinoline-3-carboxamide 453 [01064]embedded image N6-(8-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)octyl)-N3-methyl-4-(phenylamino)quinoline-3,6-dicarboxamide 454 [01065]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)decyl)amino)-7-methoxy-N-methyl-4-(phenylamino)quinoline-3-carboxamide 455 [01066]embedded image N6-(12-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)dodecyl)-N3-methyl-4-

(phenylamino)quinoline-3,6- dicarboxamide 456 [01067]embedded image 6-((9-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)nonanamido)methyl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 457 [01068]embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)decyl)amino)-N-isopropyl-4-(phenylamino)quinoline- 3-carboxamide 458 [01069]embedded image N6-(6-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)hexyl)-N3-methyl-4-(phenylamino)quinoline-3,6- dicarboxamide 459 [01070]embedded image 6-(2-((8-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)octyl)amino)-2-oxoethyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 460 [01071]embedded image 4-(cyclopropylamino)-6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3- dioxoisoindolin-4-yl)oxy)acetamido)decyl)amino)-N-methylquinoline-3- carboxamide 464 [01072]
embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)amino)acetamido)decyl)amino)-4-(phenylamino)quinoline-3- carboxamide 465 [01073]
embedded image 6-((10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)decyl)amino)-4-(phenylamino)quinoline-3- carboxamide 466 [01074]
embedded image 6-((8-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)octyl)amino)-4-(phenylamino)quinoline-3- carboxamide 467 [01075]
embedded image 6-(10-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)oxy)acetamido)decanamido)-4-(phenylamino)quinoline-3- carboxamide 471 [01076]
embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)butyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 472 [01077]embedded image 6-(4-((3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)amino)acetamido)propyl)carbamoyl)phenyl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 473 [01078]embedded image 6-(4-((3-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)propyl)carbamoyl)phenyl)-N-methyl-4- (phenylamino)quinoline-3-carboxamide 474 [01079]embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)(methyl)amino)acetamido)butyl)carbamoyl)phenyl)-N-methyl-4-(phenylamino)quinoline-3-carboxamide 475 [01080]embedded image 6-(4-((4-(2-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4- yl)oxy)acetamido)butyl)carbamoyl)phenyl)-7-methoxy-N-methyl-4- (phenylamino)quinoline-3-carboxamide [0341] or a pharmaceutically acceptable salt thereof.

[0342] The BRD9 inhibitor may be, e.g., a compound selected from the group consisting of:

TABLE-US-00005 Compound Number Compound Structure A1 [01081]embedded image A2 [01082]embedded image A3 [01083]embedded image A4 [01084]embedded image A5 [01085]embedded image A6 [01086]embedded image A7 [01087]embedded image A8 [01088]embedded image A9 [01089]embedded image A10 [01090]embedded image A11 [01091]embedded image A12 [01092]embedded image A13 [01093]embedded image A14 [01094]embedded image A15 [01095]embedded image A16 [01096]embedded image A17 [01097]embedded image A18 [01098]embedded image A19 [01099]embedded image A20 [01100]embedded image A21 [01101]embedded image A22 [01102]embedded image A23 [01103]embedded image A24 [01104]embedded image A25 [01105]embedded image A26 [01106]embedded image A27 [01107]embedded image A28 [01108]embedded image A29 [01109]embedded image A30 [01110]embedded image A31 [01111]embedded image A32 [01112]embedded image A33 [01113]embedded image A34 [01114]embedded image A35 [01115]embedded image A36 [01116]embedded image A37 [01117]embedded image A38 [01118]embedded image A39 [01119]embedded image A40 [01120]embedded image A41 [01121]embedded image A42 [01122]embedded image B1 [01123]embedded image B2 [01124]embedded image B3 [01125]embedded image B4 [01126]embedded image B5 [01127]embedded image B6 [01128]embedded image B7 [01129]embedded image B8

[01130]embedded image B9 [01131]embedded image B10 [01132]embedded image B11
[01133]embedded image B12 [01134]embedded image B13 [01135]embedded image B14
[01136]embedded image B15 [01137]embedded image B16 [01138]embedded image B17
[01139]embedded image B18 [01140]embedded image B19 [01141]embedded image B20
[01142]embedded image B22 [01143]embedded image B23 [01144]embedded image B24
[01145]embedded image B25 [01146]embedded image B26 [01147]embedded image B27
[01148]embedded image B28 [01149]embedded image B29 [01150]embedded image B30
[01151]embedded image B31 [01152]embedded image B32 [01153]embedded image B40
[01154]embedded image B41 [01155]embedded image B42 [01156]embedded image B43
[01157]embedded image B44 [01158]embedded image B45 [01159]embedded image B46
[01160]embedded image B47 [01161]embedded image B48 [01162]embedded image B49
[01163]embedded image B50 [01164]embedded image C1 [01165]embedded image C2
[01166]embedded image C3 [01167]embedded image C4 [01168]embedded image D1
[01169]embedded image D2 [01170]embedded image D3 [01171]embedded image D4
[01172]embedded image E1 [01173]embedded image E2 [01174]embedded image E7
[01175]embedded image E17 [01176]embedded image E18 [01177]embedded image E23
[01178]embedded image E24 [01179]embedded image E27 [01180]embedded image E28
[01181]embedded image E30 [01182]embedded image E35 [01183]embedded image E37
[01184]embedded image and E39 [01185]embedded image
WO2021178920 Compounds
##STR01186## ##STR01187## ##STR01188## ##STR01189## ##STR01190## ##STR01191##
##STR01192## ##STR01193##
##STR01194## ##STR01195## ##STR01196## ##STR01197## ##STR01198## ##STR01199##
##STR01200## ##STR01201##
##STR01202## ##STR01203## ##STR01204## ##STR01205## ##STR01206## ##STR01207##
##STR01208##
##STR01209## ##STR01210## ##STR01211## ##STR01212##
##STR01213## ##STR01214## ##STR01215## ##STR01216## ##STR01217## ##STR01218##
##STR01219## ##STR01220## ##STR01221## ##STR01222## ##STR01223## ##STR01224##
##STR01225## ##STR01226## ##STR01227## ##STR01228## ##STR01229## ##STR01230##
##STR01231## ##STR01232## ##STR01233## ##STR01234## ##STR01235## ##STR01236##
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##STR01397## ##STR01398## ##STR01399## ##STR01400## ##STR01401## ##STR01402##
##STR01403## ##STR01404## ##STR01405## [0343] or a pharmaceutically acceptable salt thereof.

[0344] Any suitable BRD9 inhibitor, e.g., a BRD9 inhibitor with an ionizable functional group, may be administered as a pharmaceutically acceptable salt, e.g., a salt of an acid selected from the group consisting of formic acid, acetic acid, propionic acid, lactic acid, butyric acid, isobutyric acid, trifluoroacetic acid, malic acid, maleic acid, malonic acid, fumaric acid, succinic acid, succinic acid monoamide, glutamic acid, tartaric acid, oxalic acid, ciitric acid, glycolic acid, glucuronic acid, ascorbic acid, benzoic acid, phthalic acid, salicylic acid, anthranilic acid, benzensulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, dichloroacetic acid, aminooxy acetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, carbonic acid, and boric acid.

Androgen Receptor-Independent Prostate Cancer

[0345] The androgen receptor is a transcription factor that effectuates changes in DNA expression upon binding to androgenic ligands such as testosterone and dihydroxytestosterone. Subtypes of prostate cancer may grow and spread independently of gene expression mediated by the androgen receptor. Androgen-independent prostate cancer is prostate cancer that grows and spreads in the absence of a functional androgen receptor. Androgen receptor-independent prostate cancer cannot be successfully treated with androgen starvation therapy or with androgen receptor signaling inhibitors (ARSi).

Castrate-Resistant Prostate Cancer

[0346] Castrate-resistant prostate cancer is a form of prostate cancer that continues to grow even when the amount of testosterone in a subject is reduced to a very low level, e.g., even after surgical or medical castration. The estimated mean survival of a subject diagnosed with castrate-resistant prostate cancer is approximately 9 to 36 months, and the quality of life for subjects diagnosed with castrate-resistant prostate cancer and receiving the standard of care is poor.

Small Cell Prostate Cancer

[0347] Small cell prostate cancer is an aggressive subtype of prostate cancer that is characterized by cancer cells that are smaller in size than other forms of prostate cancer, e.g., cells that are smaller than 4 lymphocytes in diameter. Small cell prostate cancer cells possess unique and strict morphological features, scant cytoplasm, ill-defined borders, finely granular “salt and pepper” chromatic, absent or inconspicuous nucleoli, frequent nuclear molding, and a high mitotic count.

Neuroendocrine Prostate Cancer and Adenocarcinoma

[0348] Neuroendocrine prostate cancer is a subtype of prostate cancer that develops in the neuroendocrine cells of the prostate. Neuroendocrine prostate cancer rarely arises de novo and often develops from the trans-differentiation of adenocarcinomas. Neuroendocrine prostate cancers are typically not responsive to treatments that target androgen receptor signaling.

[0349] Treatment of an adenocarcinoma with a compound that reduces the level and/or activity of

BRD9, or a pharmaceutically acceptable salt thereof, may reduce the level of adenocarcinoma to neuroendocrine trans-differentiation. The decrease in the level of adenocarcinoma to neuroendocrine trans-differentiation may be measured by any reproducible means of measurement. For example, after treatment, the decrease in the level of adenocarcinoma to neuroendocrine trans-differentiation may be measured by lower expression levels of CHGA, SYP, and/or ENO2 compared to a subject that is not administered the compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof. The expression levels of CHGA, SYP, and/or ENO2 may be reduced by greater than 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) after treatment relative to expression levels in a subject that has not received treatment.

[0350] In some embodiments, the prostate cancer has been determined to have or predicted to have lower expression levels of AR, KLK2, KLK3, CDH1, CYLD, NKX3-1, SLC45A3, TARP, PTEN, SPDEF, TP53, or RB1, or combinations thereof compared to a subject that does not have prostate cancer.

[0351] In some embodiments, the prostate cancer has been determined to have or predicted to have lower expression levels of AR, KLK2, KLK3, CDH1, CYLD, NKX3-1, SLC45A3, TARP, PTEN, SPDEF, TP53, or RB1, or combinations thereof compared to standard levels for prostate cancer.

[0352] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of CHGB, CHGA, SYP, ENO2, PEG10, SNAP25, SRRM4, VGF, VIM, SCGN, PAPPA2, or WNT11, or combinations thereof compared to a subject that does not have prostate cancer.

[0353] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of CHGB, CHGA, SYP, ENO2, PEG10, SNAP25, SRRM4, VGF, VIM, SCGN, PAPPA2, or WNT11, or combinations thereof compared to standard levels for prostate cancer.

[0354] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of ASCL1, EZH2, DLX5, DLX6, SOX2, SOX11, NKX2-2, HES6, SOX9, KDM3A, FOXA2, AURKA, MYCN, MYC, AKT, POU3F2/BRN2, NANOG, ONECUT2, or NKX2-1, or combinations thereof compared to a subject that does not have prostate cancer.

[0355] In some embodiments, the prostate cancer has been determined to have or predicted to have higher expression levels of ASCL1, EZH2, DLX5, DLX6, SOX2, SOX11, NKX2-2, HES6, SOX9, KDM3A, FOXA2, AURKA, MYCN, MYC, AKT, POU3F2/BRN2, NANOG, ONECUT2, or NKX2-1, or combinations thereof compared to standard levels for prostate cancer.

[0356] In some embodiments, the prostate cancer has been determined to have or predicted to have lower expression levels of RE1 silencing transcription factor (REST).

[0357] In some embodiments, the prostate cancer has been determined to have or predicted to have expression of AR and KLK3 (PSA).

[0358] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of CHGA and SYP.

[0359] In some embodiments, the prostate cancer has been determined to have or predicted to have expression of AR, KLK3 (PSA), CHGA and SYP.

[0360] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of AR and KLK3 (PSA).

[0361] In some embodiments, the prostate cancer has been determined to have or predicted to have expression of CHGA and SYP.

[0362] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of AR, KLK3 (PSA), CHGA and SYP.

[0363] In some embodiments, the prostate cancer has been determined or predicted to have a high level of TMPRSS2-ERG fusions.

[0364] In some embodiments, expression of BRD9, GLTSCR1, CXXC5 or TET2 is increased in

the prostate cancer compared to a subject that does not have prostate cancer.
[0365] In some embodiments, expression of BRD9 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
[0366] In some embodiments, expression of GLTSCR1 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
[0367] In some embodiments, expression of TET2, CXXC5, H3K27ac, ID1, PFN2, or ID3 in the subject is increased in the prostate cancer determined to or predicted to be resistant to enzalutamide compared to a prostate cancer that responds to treatment with enzalutamide.
[0368] In some embodiments, the prostate cancer has been determined to have or predicted to have undetectable expression of PTEN.

ERG Inhibitors

[0369] The ETS-related gene (ERG) encodes a transcription factor with oncogenic properties that plays a role in the development of prostate cancer. In prostate cancers, the ETS gene commonly fuses with the promoter region of the TMPRRSS2 gene, which leads to overexpression of the ETS transcription factor. In some embodiments, the present invention provides methods for treating androgen receptor-independent prostate cancer that include further administering an inhibitor or degrader of ERG to a subject with androgen receptor-independent prostate cancer. A nonlimiting example of an ERG inhibitor that may be administered to a subject in accordance with the methods of the present disclosure is ERGi-USU (1-[2-Thiazolylazo]-2-naphthol).

Androgen Receptor (AR) Degraders

[0370] In some embodiments, the present invention provides methods for treating androgen receptor-independent prostate cancer that include further administering a degrader of the androgen receptor to the subject. Nonlimiting examples of AR degraders that may be administered to a subject in accordance with the methods of the present disclosure include bavdegalutamide (ARV-110), ARV-766, and AR-V7.

JAK-STAT Pathway Inhibitors

[0371] Aberrant activation of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway is related to tumor growth and disease progression in prostate cancer. Accordingly, in some embodiments, the methods of the present invention include further administering to the subject an inhibitor of the JAK-STAT pathway. Nonlimiting examples of JAK-STAT pathway inhibitors that may be administered to a subject in accordance with the methods of the present invention include AG490, AZD1480, AZD4205, baricitinib, dasatinib, fedratinib, filgotinib, itacitnib, lestaurtinib, momelotinib, pacritinib, peficitinib, ruxolitinib, siltuximab, tofacitinib, upadacitinib, or WP1066.

MAPK Pathway Inhibitors

[0372] The mitogen activated protein kinase (MAPK) pathway includes the proteins p38, JNK, and ERK, and is implicated in the progression of prostate cancer. Accordingly, in some embodiments, the methods of the present invention include further administering to the subject an inhibitor of the MAPK pathway. Nonlimiting examples of MAPK pathway inhibitors that may be administered to a subject in accordance with the methods of the present invention include a Farnesyltransferase inhibitor (FTI), Sorafenib, Vemurafenib, PLX8394, Dabrafenib, Ulixertinib, Simvastatin, Alisertib, or Teriflunomide.

Methods of Treatment

[0373] The present disclosure features methods of treating disorders related to BRD9 such as cancer, e.g., androgen receptor-independent prostate cancer and/or neuroendocrine prostate cancer, in a subject in need thereof.
[0374] Cancer is a group of diseases characterized by the harmful, abnormal, uncontrolled, and undesirable growth of cells. In some embodiments, the uncontrolled growth is due to cells that divide and proliferate in the absence of signals (e.g., growth factors) instructing them to do so. In some embodiments, the uncontrolled growth is due to cells which fail to respond to signals

instructing them to stop growing and/or engage in programmed cell death (i.e., apoptosis). In some embodiments, cancer cells may spread throughout the body (i.e., metastasize). In some embodiments, cancer cells may form tumors. In some embodiments, cancer cells may form solid tumors.

[0375] In some embodiments, the compound is administered in an amount and for a time effective to result in one of (or more, e.g., two or more, three or more, four or more of: (a) reduced tumor size, (b) reduced rate of tumor growth, (c) increased tumor cell death (d) reduced tumor progression, (e) reduced number of metastases, (f) reduced rate of metastasis, (g) decreased tumor recurrence (h) increased survival of subject, (i) increased progression free survival of a subject, (j) slowed progression of cancer, (k) reduced recurrence of cancer, (l) decreased rate of metastatic tumor seeding, (m) decreased metastatic tumor nodule formation, (n) decreased spread of metastatic tumor nodule formation, and (o) decreased metastatic colonization.

[0376] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, can result in a reduction in size or volume of a tumor. For example, after treatment, tumor size is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to its size prior to treatment. Size of a tumor may be measured by any reproducible means of measurement. For example, the size of a tumor may be measured as a diameter of the tumor.

[0377] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, may further result in a decrease in number of tumors. For example, after treatment, tumor number is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or greater) relative to number prior to treatment. Number of tumors may be measured by any reproducible means of measurement, e.g., the number of tumors may be measured by counting tumors visible to the naked eye or at a specified magnification (e.g., 2×, 3×, 4×, 5×, 10×, or 50×).

[0378] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, can result in a decrease in the spread of metastatic nodules, e.g., a decrease in the number of metastatic nodules in other tissues or organs distant from the primary tumor site. For example, after treatment, the number of metastatic nodules is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) relative to number prior to treatment. The number of metastatic nodules may be measured by any reproducible means of measurement. For example, the number of metastatic nodules may be measured by counting metastatic nodules visible to the naked eye or at a specified magnification (e.g., 2×, 10×, or 50×).

[0379] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, can result in a decrease in the level of neuroendocrine prostate cancer cells in the subject. For example, after treatment, the level of neuroendocrine prostate cancer cells in the subject is reduced by 5% or greater (e.g., 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or greater) relative to level prior to treatment. The level of neuroendocrine prostate cancer cells may be measured by any reproducible means of measurement. For example, the level of neuroendocrine prostate cancer cells may be measured by obtaining a sample of prostate tissue from a subject with prostate cancer and conducting cell sorting experiments to determine the proportion of the cells in the sample that are neuroendocrine prostate cancer cells.

[0380] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, can result in the treatment of a cancer that had previously failed to respond to an anti-cancer therapy, e.g., an anti-cancer therapy that did not target BRD9. For example, the methods of the present invention may result in the treatment of a cancer that had previously failed to respond to

active surveillance, surgery, radiation therapy, high-intensity focused ultrasound (HIFU), cryotherapy, hormone therapy, chemotherapy, immunotherapy, vaccine treatment, immune checkpoint inhibitors, targeted therapy drugs, or bone-directed treatment.

[0381] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, can result in an increase in average survival time of a population of subjects treated according to the present invention in comparison to a population of untreated subjects. For example, the average survival time is increased by more than 30 days (more than 60 days, 90 days, or 120 days). An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with the compound described herein. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0382] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, can also result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. For example, the mortality rate is decreased by more than 2% (e.g., more than 5%, 10%, or 25%). A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with a pharmaceutically acceptable salt of a compound described herein. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

[0383] Treating cancer, e.g., treating androgen receptor-independent prostate cancer with a compound that reduces the level and/or activity of BRD9, or a pharmaceutical salt thereof, may result in a reduced recurrence of cancer relative to the recurrence of cancer in a subject that has not been treated with a compound that reduces the level and/or activity of BRD9, or a pharmaceutical salt thereof. A decrease in the recurrence of cancer may be measured, for example, by monitoring the number of incidences of recurrence of cancer over a period of time (e.g., one week, one month, one year, five years) in a population of cancer subjects with cancer treated with a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, and comparing that number of incidences to the number of incidences of recurrence of cancer in a population of subjects with cancer who are not administered a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, over the same period of time.

Combination Therapies

[0384] A method of the invention can be used alone or in combination with an additional therapeutic agent, e.g., other agents that treat cancer or symptoms associated therewith, or in combination with other types of therapies to treat cancer. In combination treatments, the dosages of one or more of the therapeutic compounds may be reduced from standard dosages when administered alone. For example, doses may be determined empirically from drug combinations and permutations or may be deduced by isobolographic analysis (e.g., Black et al., *Neurology* 65: S3-S6 (2005)). In this case, dosages of the compounds when combined should provide a therapeutic effect.

[0385] In some embodiments, the androgen-independent prostate cancer and/or neuroendocrine prostate cancer has failed to respond to a previous treatment. In some embodiments, the previous treatment is a second therapeutic agent. In some embodiments the previous treatment is an anti-

cancer therapy. In some embodiments, a subject is further administered an anti-cancer therapy. In some embodiments, the anti-cancer therapy is administered prior to the administering of a compound of the present disclosure. In some embodiments, the anti-cancer therapy is administered in addition to the administering of a compound of the present disclosure. In some embodiments, the anti-cancer therapy is administered subsequent to the administering of a compound of the present disclosure. In some embodiments, the anti-cancer therapy is active surveillance, surgery, radiation therapy, high-intensity focused ultrasound (HIFU), cryotherapy, hormone therapy, chemotherapy, immunotherapy, vaccine treatment, immune checkpoint inhibitors, targeted therapy drugs, or bone-directed treatment. In some embodiments, an anti-cancer therapy is abiraterone acetate, alendronate, apalutamide, bicalutamide, cabazitaxel, carboplatin, cisplatin, darolutamide, degarelix, denosumab, docetaxel, enzalutamide, etoposide, flutamide, goserelin acetate, ibandronate, leuprolide acetate, lynparza, mitoxantrone hydrochloride, nilutamide, olaparib, pamidronate, radium 223 dichloride, relugolix, risedronate, rucaparib camsylate, sipuleucel-T, or zoledronic acid, or combinations thereof.

[0386] In some embodiments, the second therapeutic agent is a chemotherapeutic agent (e.g., a cytotoxic agent or other chemical compound useful in the treatment of cancer). These include alkylating agents, antimetabolites, folic acid analogs, pyrimidine analogs, purine analogs and related inhibitors, vinca alkaloids, epipodopyyllotoxins, antibiotics, L-Asparaginase, topoisomerase inhibitors, interferons, platinum coordination complexes, anthracenedione substituted urea, methyl hydrazine derivatives, adrenocortical suppressant, adrenocorticosteroides, progestins, estrogens, antiestrogen, androgens, antiandrogen, and gonadotropin-releasing hormone analog. Also included is 5-fluorouracil (5-FU), leucovorin (LV), irenotecan, oxaliplatin, capecitabine, paclitaxel, and doxetaxel. Non-limiting examples of chemotherapeutic agents include alkylating agents such as thiotepa and cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., *Agnew, Chem. Intl. Ed Engl.* 33:183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® (doxorubicin, including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone,

dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2′,2″-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, e.g., TAXOL® (paclitaxel; Bristol-Myers Squibb Oncology, Princeton, NJ), ABRAXANE®, cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, IL), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum coordination complexes such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE® vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (e.g., CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; or zoledronic acid and pharmaceutically acceptable salts, acids or derivatives of any of the above. Two or more chemotherapeutic agents can be used in a cocktail to be administered in combination with the first therapeutic agent described herein. Suitable dosing regimens of combination chemotherapies are known in the art and described in, for example, Saltz et al., *Proc. Am. Soc. Clin. Oncol.* 18: 233a (1999), and Douillard et al., *Lancet* 355 (9209): 1041-1047 (2000).

[0387] In some embodiments, the second therapeutic agent is a therapeutic agent which is a biologic such a cytokine (e.g., interferon or an interleukin (e.g., IL-2)) used in cancer treatment. In some embodiments the biologic is an anti-angiogenic agent, such as an anti-VEGF agent, e.g., bevacizumab (AVASTIN®). In some embodiments the biologic is an immunoglobulin-based biologic, e.g., a monoclonal antibody (e.g., a humanized antibody, a fully human antibody, an Fc fusion protein or a functional fragment thereof) that agonizes a target to stimulate an anti-cancer response, or antagonizes an antigen important for cancer. Such agents include RITUXAN® (rituximab); ZENAPAX® (daclizumab); SIMULECT® (basiliximab); SYNAGIS® (palivizumab); REMICADE® (infliximab); HERCEPTIN® (trastuzumab); MYLOTARG® (gemtuzumab ozogamicin); CAMPATH® (alemtuzumab); ZEVALIN® (ibritumomab tiuxetan); HUMIRA® (adalimumab); XOLAIR® (omalizumab); BEXXAR® (tositumomab-I-131); RAPTIVA® (efalizumab); ERBITUX® (cetuximab); AVASTIN® (bevacizumab); TYSABRI® (natalizumab); ACTEMRA® (tocilizumab); VECTIBIX® (panitumumab); LUCENTIS® (ranibizumab); SOLIRIS® (eculizumab); CIMZIA® (certolizumab pegol); SIMPONI® (golimumab); ILARIS® (canakinumab); STELARA® (ustekinumab); ARZERRA® (ofatumumab); PROLIA® (denosumab); NUMAX® (motavizumab); ABTHRAX® (raxibacumab); BENLYSTA® (belimumab); YERVOY® (ipilimumab); ADCETRIS® (brentuximab vedotin); PERJETA® (pertuzumab); KADCYLA® (ado-trastuzumab emtansine); and GAZYVA® (obinutuzumab). Also included are antibody-drug conjugates.

[0388] The second agent may be a therapeutic agent which is a non-drug treatment. For example, the second therapeutic agent is radiation therapy, cryotherapy, hyperthermia, and/or surgical excision of tumor tissue.

[0389] The second agent may be a checkpoint inhibitor. In one embodiment, the inhibitor of checkpoint is an inhibitory antibody (e.g., a monospecific antibody such as a monoclonal antibody). The antibody may be, e.g., humanized or fully human. In some embodiments, the

inhibitor of checkpoint is a fusion protein, e.g., an Fc-receptor fusion protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an agent, such as an antibody, that interacts with the ligand of a checkpoint protein. In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of CTLA-4 (e.g., an anti-CTLA4 antibody or fusion a protein such as ipilimumab/YERVOY® or tremelimumab). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PD-1 (e.g., nivolumab/OPDIVO®; pembrolizumab/KEYTRUDA®; pidilizumab/CT-011). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of PDL1 (e.g., MPDL3280A/RG7446; MEDI4736; MSB0010718C; BMS 936559). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or Fc fusion or small molecule inhibitor) of PDL2 (e.g., a PDL2/Ig fusion protein such as AMP 224). In some embodiments, the inhibitor of checkpoint is an inhibitor (e.g., an inhibitory antibody or small molecule inhibitor) of B7-H3 (e.g., MGA271), B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands, or a combination thereof.

[0390] In some embodiments, the anti-cancer therapy is a T cell adoptive transfer (ACT) therapy. In some embodiments, the T cell is an activated T cell. The T cell may be modified to express a chimeric antigen receptor (CAR). CAR modified T (CAR-T) cells can be generated by any method known in the art. For example, the CAR-T cells can be generated by introducing a suitable expression vector encoding the CAR to a T cell. Prior to expansion and genetic modification of the T cells, a source of T cells is obtained from a subject. T cells can be obtained from a number of sources, including peripheral blood mononuclear cells, bone marrow, lymph node tissue, cord blood, thymus tissue, tissue from a site of infection, ascites, pleural effusion, spleen tissue, and tumors. In certain embodiments of the present invention, any number of T cell lines available in the art, may be used. In some embodiments, the T cell is an autologous T cell. Whether prior to or after genetic modification of the T cells to express a desirable protein (e.g., a CAR), the T cells can be activated and expanded generally using methods as described, for example, in U.S. Pat. Nos. 6,352,694; 6,534,055; 6,905,680; 6,692,964; 5,858,358; 6,887,466; 6,905,681; 7,144,575; 7,067,318; 7,172,869; 7,232,566; 7,175,843; 5,883,223; 6,905,874; 6,797,514; 6,867,041; and U.S. Patent Application Publication No. 20060121005.

[0391] In any of the combination embodiments described herein, the first and second therapeutic agents are administered simultaneously or sequentially, in either order. The first therapeutic agent may be administered immediately, up to 1 hour, up to 2 hours, up to 3 hours, up to 4 hours, up to 5 hours, up to 6 hours, up to 7 hours, up to, 8 hours, up to 9 hours, up to 10 hours, up to 11 hours, up to 12 hours, up to 13 hours, 14 hours, up to hours 16, up to 17 hours, up 18 hours, up to 19 hours up to 20 hours, up to 21 hours, up to 22 hours, up to 23 hours up to 24 hours or up to 1-7, 1-14, 1-21 or 1-30 days before or after the second therapeutic agent.

Pharmaceutical Compositions

[0392] The pharmaceutical compositions described herein are preferably formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration in vivo.

[0393] The compounds described herein may be used in the form of the free base, in the form of salts, solvates, and as prodrugs. All forms are within the methods described herein. In accordance with the methods of the invention, the described compounds or salts, solvates, or prodrugs thereof may be administered to a subject in a variety of forms depending on the selected route of administration, as will be understood by those skilled in the art. The compounds described herein may be administered, for example, by oral, parenteral, buccal, sublingual, nasal, rectal, patch, pump, intratumoral, or transdermal administration and the pharmaceutical compositions formulated accordingly. Parenteral administration includes intravenous, intraperitoneal, subcutaneous,

intramuscular, transepithelial, nasal, intrapulmonary, intrathecal, rectal, and topical modes of administration. Parenteral administration may be by continuous infusion over a selected period of time.

[0394] A compound described herein may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly with the food of the diet. For oral therapeutic administration, a compound described herein may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, and wafers. A compound described herein may also be administered parenterally. Solutions of a compound described herein can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, DMSO, and mixtures thereof with or without alcohol, and in oils. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms. Conventional procedures and ingredients for the selection and preparation of suitable formulations are described, for example, in Remington's Pharmaceutical Sciences (2012, 22nd ed.) and in The United States Pharmacopeia: The National Formulary (USP 41 NF36), published in 2018. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that may be easily administered via syringe. Compositions for nasal administration may conveniently be formulated as aerosols, drops, gels, and powders. Aerosol formulations typically include a solution or fine suspension of the active substance in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in single or multidose quantities in sterile form in a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal after use. Where the dosage form includes an aerosol dispenser, it will contain a propellant, which can be a compressed gas, such as compressed air or an organic propellant, such as fluorochlorohydrocarbon. The aerosol dosage forms can also take the form of a pump-atomizer. Compositions suitable for buccal or sublingual administration include tablets, lozenges, and pastilles, where the active ingredient is formulated with a carrier, such as sugar, acacia, tragacanth, gelatin, and glycerine. Compositions for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter. A compound described herein may be administered intratumorally, for example, as an intratumoral injection. Intratumoral injection is injection directly into the tumor vasculature and is specifically contemplated for discrete, solid, accessible tumors. Local, regional, or systemic administration also may be appropriate. A compound described herein may advantageously be contacted by administering an injection or multiple injections to the tumor, spaced for example, at approximately, 1 cm intervals. In the case of surgical intervention, the present invention may be used preoperatively, such as to render an inoperable tumor subject to resection. Continuous administration also may be applied where appropriate, for example, by implanting a catheter into a tumor or into tumor vasculature.

[0395] The compounds described herein may be administered to an animal, e.g., a human, alone or in combination with pharmaceutically acceptable carriers, as noted herein, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration, and standard pharmaceutical practice.

Dosages

[0396] The dosage of the compounds described herein, and/or compositions including a compound described herein, can vary depending on many factors, such as the pharmacodynamic properties of the compound; the mode of administration; the age, health, and weight of the recipient; the nature

and extent of the symptoms; the frequency of the treatment, and the type of concurrent treatment, if any; and the clearance rate of the compound in the animal to be treated. One of skill in the art can determine the appropriate dosage based on the above factors. The compounds described herein may be administered initially in a suitable dosage that may be adjusted as required, depending on the clinical response. In general, satisfactory results may be obtained when the compounds described herein are administered to a human at a daily dosage of, for example, between 0.05 mg and 3000 mg (measured as the solid form). Dose ranges include, for example, between 10-1000 mg.

[0397] Alternatively, the dosage amount can be calculated using the body weight of the subject. For example, the dose of a compound, or pharmaceutical composition thereof, administered to a subject may range from 0.1-100 mg/kg.

[0398] In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 20-120 mg/kg (e.g., 20-60 mg/kg, 20-40 mg/kg, 40-80 mg/kg, 40-60 mg/kg, 60-80 mg/kg, or 80-120 mg/kg).

[0399] In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 20 mg/kg. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 40 mg/kg. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 50 mg/kg. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 60 mg/kg. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 80 mg/kg. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 120 mg/kg.

[0400] In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered at least once per week.

[0401] In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered at least twice per week.

[0402] In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 20 mg/kg once per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 40 mg/kg once per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 50 mg/kg once per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 60 mg/kg once per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 80 mg/kg once per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 120 mg/kg once per week.

[0403] In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 20 mg/kg twice per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 40 mg/kg twice per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 50 mg/kg twice per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 60 mg/kg twice per week. In some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 80 mg/kg twice per week. In

some embodiments, the effective amount of a compound of the present disclosure or a pharmaceutically acceptable salt thereof is administered in a dose of 120 mg/kg twice per week.
[0404] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a 14-day dosing cycle.
[0405] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a 2 week dosing cycle.
[0406] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a 21-day dosing cycle.
[0407] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a 3 week dosing cycle.
[0408] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a 28-day dosing cycle.
[0409] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a 4 week dosing cycle.
[0410] In some embodiments, the effective amount of a compound of the present disclosure of a pharmaceutically acceptable salt thereof is administered to the subject in a one month dosing cycle.
[0411] In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 14 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 2 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 21 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 3 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 28 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 4 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 1 ng/ml of compound for at least 1 month after administration.
[0412] In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/ml of compound for at least 14 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/ml of compound for at least 2 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/ml of compound for at least 21 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/ml of compound for at least 3 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/ml of compound for at least 28 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/ml of compound for at least 4 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 2 ng/mL of compound for at least 1 month after administration.
[0413] In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/ml of compound for at least 14 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/ml of compound for at least 2 weeks

after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/ml of compound for at least 21 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/ml of compound for at least 3 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/mL of compound for at least 28 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/ml of compound for at least 4 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 3 ng/ml of compound for at least 1 month after administration.

[0414] In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 14 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 2 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 21 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 3 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 28 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 4 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 5 ng/ml of compound for at least 1 month after administration.

[0415] In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/ml of compound for at least 14 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/ml of compound for at least 2 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/ml of compound for at least 21 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/ml of compound for at least 3 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/ml of compound for at least 28 days after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/ml of compound for at least 4 weeks after administration. In some embodiments, a formulation of the present disclosure is administered in an amount sufficient to maintain a concentration of at least 10 ng/mL of compound for at least 1 month after administration.

[0416] In one aspect, the present disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, wherein the effective amount is an amount sufficient to decrease a BRD9 immunohistochemistry score of the subject. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 14 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 21 days. In some embodiments of any of the aspects disclosed herein, the effective

amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 28 days.

[0417] In one aspect, the present disclosure provides a method of decreasing a BRD9 immunohistochemistry score in a subject, the method comprising administering an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 14 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 21 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 28 days.

[0418] In one aspect, the present disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, wherein the effective amount is an amount sufficient to reduce the level of BRD9 expression in the subject. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 14 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 21 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 28 days.

[0419] In one aspect, the present disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, wherein the effective amount is an amount sufficient to cause a greater than or equal to 10% decrease in tumor size and/or a greater than or equal to 15% decrease in tumor attenuation. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 14 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 21 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 28 days.

[0420] In one aspect, the present disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof, wherein the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/ml of the compound in a subject, over at least 14 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/mL of the compound in a subject, over at least 21 days. In some embodiments of any of the aspects disclosed herein, the effective amount is an amount sufficient to maintain a plasma concentration of 3 ng/mL of the compound in a subject, over at least 28 days. Advantageously, a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) may exhibit prolonged efficacy at BRD9 degradation, thus allowing for intermittent dosing regimens. For example, a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) may be administered to the subject in need thereof twice weekly or less frequently (e.g., twice weekly to once bimonthly, twice weekly

to once monthly, twice weekly to once biweekly, once weekly to once monthly, or once weekly to once biweekly; e.g., once weekly, once biweekly, once every three weeks, or once monthly).

[0421] A BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) may be administered in cycles (e.g., four- to eight-week-long cycles; e.g., four-week-long, six-week-long, or eight-week-long cycles). In some variants, the regimen may include once weekly dosages of an effective amount of a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof). For example, a total of two to three once weekly dosages may be administered per cycle, e.g., an effective amount of a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) is administered on weeks 1 and 2 of the cycle, or an effective amount of a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) is administered on weeks 1, 2, and 3 of the cycle. For example, a once weekly dosing may be implemented as follows: the first dose of an effective amount of a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) may be administered on Day 1 of the cycle, and the second once weekly dose may be administered on Day 8 or 9 (preferably, Day 8) of the cycle. If a third dose is administration, the third dose may be administered on Day 15 or Day 16 (preferably, Day 15) of the cycle. Alternatively, the regimen may include once biweekly, once every three weeks, once monthly, or once bimonthly dosages of an effective amount of a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof). Typically, the first dose of a BRD9 inhibitor (e.g., compound 1 or a pharmaceutically acceptable salt thereof) is administered on week 1 of the cycle.

Kits

[0422] The invention also features kits including (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, and (b) a package insert with instructions to perform any of the methods described herein. In some embodiments, the kit includes (a) a pharmaceutical composition including an agent that reduces the level and/or activity of BRD9 in a cell or subject described herein, (b) an additional therapeutic agent (e.g., an anti-cancer agent), and (c) a package insert with instructions to perform any of the methods described herein.

[0423] The following Examples are illustrative only and not intended to limit the invention in any way.

EXAMPLES

Example 1. BRD9 Degrader Causes Range of Effects Against Prostate Cell Line Xenograft Tumor Models In Vivo

[0424] Procedure: The experimental details of the studies, including tumor model, mouse strain, cell number implanted, vehicle used, days of treatment, treatment details, and average tumor size at start of dosing are outlined in Table 1. All study mice were purchased from Beijing Anikeeper Biotech and Matrigel was utilized as a basement membrane for all xenograft models. All xenografts were engrafted subcutaneously in the right flank region. The vehicles and Compound 1 (3 mg/kg) were administered twice weekly (BIW) intraperitoneally and enzalutamide (30 mg/kg) was administered orally once daily (QD), when applicable. Tumor volumes and body weights were measured over the course of study, and doses were adjusted by body weight to achieve the proper dose in terms of mg/kg. Animals were sacrificed on the final day of treatment as indicated in Table 1.

[0425] Results: Treatment with Compound 1 lead to a range of outcomes across the prostate xenograft models. Treatments in all models were well tolerated based on % body weight change observed (FIGS. **1**B, **2**B, **3**B, **4**B, **5**B, **6**B). Compound 1 treatment did not result in tumor growth inhibition (TGI) in the LNCaP xenograft model, however enzalutamide treatment did lead to tumor growth inhibition in this model. (FIG. **1**A). In the VCaP xenograft model, treatment with Compound 1 lead to tumor growth inhibition that was greater than the inhibition provided by enzalutamide treatment. The combination did not show any additional tumor growth inhibition beyond that of single agent Compound 1. (FIG. **2**A). Similar anti-tumor effect was observed after

treatment of Compound 1 in prostate xenograft models PC3 (FIG. **3**A) and NCI-H660 (FIG. **4**A). In xenograft model C42B, Compound 1 treatment resulted in modest tumor growth inhibition which was less than the TGI provided by enzalutamide treatment. (FIG. **5**A). In the prostate xenograft model 22RV1, Compound 1 treatment resulted in modest tumor growth inhibition which was less than the TGI provided by enzalutamide treatment. The combination did not show any additional tumor growth inhibition beyond that of single agent enzalutamide. (FIG. **6**A).

[0426] The androgen receptor (AR) status and TGI values for Compound 1 treatments across all models can be found Table 2. Anti-androgen therapies, such as enzalutamide, are part of current standard of care (SOC) for androgen-dependent prostate cancers. However, cancers bearing the V7 splice variant of AR have been shown to be resistant to anti-androgen therapies. The anti-tumor effect demonstrated by Compound 1 treatment (see Table 2, TGI), especially in models that are either androgen-independent (AR-) or predicted to be resistant to current SOC anti-androgen therapies (e.g., AR-V7+), demonstrates that BRD9 degradation by Compound 1 can be a successful method by which to treat these tumors.

TABLE-US-00006 TABLE 1 Study details for cell line derived xenograft (CDX) models described in Example 1 Average Cell tumor size at number Days of start of Model Strain (millions) Vehicle treatment Treatments dosing (mm3) LNCaP NOD/SCID 10 20% 39 Compound 1, 114 sulfobutylether- enzalutamide, β-cyclodextrin combination (SBECD) VCaP BALB/c 10 20% (2- 35 Compound 1, 138 nude Hydroxypropyl)- enzalutamide, β-cyclodextrin combination (HPBCD) PC3 BALB/c 5 20% HPBCD 25 Compound 1 130 nude NCI-H660 BALB/c 10 20% HPBCD 25 Compound 1 133 nude C42B NOD/SCID 5 20% HPBCD 25 Compound 1, 123 enzalutamide 22RV1 BALB/c 5 20% SBECD 43 Compound 1, 111 nude enzalutamide, combination

TABLE-US-00007 TABLE 2 AR status and Compound 1-driven TGI values for all CDX models described in Example 1. TGI with TGI with Compound 1 Enzalutamide Cell line AR status 3 mg/kg 30 mg/kg LNCaP AR+ 6.0% 92.1% VCaP AR V7+ 57.8% 46.8% PC3 AR− 61.7% N/A NCI-H660 AR− 56.9% N/A C42B AR+ 28.7% 68.5% 22RV1 AR V7+ 73.2% 40.3%

Example 2. BRD9 Degrader Treatment Results in Tumor Growth Inhibition in an Enzalutamide-Resistant Model of Castration Resistant Prostate Cancer (CRPC)

[0427] The CDX model 22Rv1 has been previously described to express the V7 splice variant of AR and harbor resistance to enzalutamide treatment. Tumors expressing the AR-V7 variant have also been shown to have worse prognosis than those with wild type AR.

[0428] When treated with Compound 1, tumor growth of the CDX model 22Rv1 was inhibited (FIG. **6**A). While enzalutamide was modestly active in this model (40.3% TGI), the anti-tumor effect of Compound 1 was greater (73.2% TGI) and the combination treatment of Compound 1 and enzalutamide was greater still (82.2% TGI) (Table 2).

Example 3. BRD9 Degrader Treatment Results in Tumor Growth Inhibition in a Metastatic, AR-Independent CDX Model of CRPC

[0429] The PC3 model has been previously described as an androgen-independent model of CRPC Metastatic CRPC currently has no approved targeted therapies, with chemotherapy being the optimal treatment for androgen-independent CRPC.

[0430] When treated with Compound 1, tumor growth of the CDX model PC-3 was inhibited (FIG. **3**A, TGI 61.7%).

Example 4. BRD9 Degrader Treatment Results in Tumor Growth Inhibition in a CDX Model of Neuroendocrine Prostate Cancer (NEPC)

[0431] The CDX model NCI-H660 has been previously reported to have a molecular signature identifying it as a model of NEPC. Markers in this model include overexpression of Aurora kinase and N-Myc. Currently, there are no approved targeted therapies for subjects with NEPC.

[0432] When treated with Compound 1, tumor growth of the CDX model NCI-H660 was inhibited (FIG. **4**A, TGI 56.9%).

Example 5. BRD9 Degrader Treatment Results in Tumor Growth Inhibition in Castration Resistant,

AR-Independent CDX Model DU145

[0433] Procedure: The experimental details of the studies, including tumor model, mouse strain, cell number implanted, vehicle used, days of treatment, treatment details, and average tumor size at start of dosing are outlined in Table 3. All study mice were obtained and the studies were conducted at Pharmaron. Each mouse was inoculated subcutaneously on the right flank with the single cell suspension of DU145 human prostate cancer tumor cells (5×10.sup.6) in 0.1 mL with Matrigel (1:1) in MEM with 10% FBS for tumor development.

[0434] Based on tumor volume, mice were randomly assigned to respective groups using a computer-generated randomization procedure. The study groups and the number of animals per group are shown in Table 4A (efficacy study) and Table 4B (PKPD study).

[0435] Treatment for the efficacy cohort was initiated when the mean tumor volume reached 145 mm.sup.3 on Day 7 post tumor cell inoculation. Animals for the efficacy study were randomized into 3 groups: 1) Vehicle Control BIW IP (administered twice per week, intraperitoneally (IP); 2) Compound 1 at 3 mg/kg BIW IP; and 3) Compound 1 at 15 mg/kg BIW IP.

[0436] Treatment for the PKPD cohort was initiated when the mean tumor volume reached 281 mm.sup.3 on Day 14 post tumor cell inoculation. Animals were randomized into 5 groups: 1) Vehicle Control, 3 doses intraperitoneally (IP); 2) Compound 1 at 1 mg/kg, single dose IP; 3) Compound 1 at 15 mg/kg, single dose IP; 4) Compound 1 at 1 mg/kg, 3 doses IP; and 5) Compound 1 at 15 mg/kg, 3 doses IP.

[0437] Animals that were observed to be in a continuing deteriorating condition or had a tumor size exceeding 2000 mm.sup.3 were euthanized prior to death, or before reaching a comatose state. In the case of an animal reaching a tumor size exceeding 2000 mm.sup.3, the entire group was terminated. Plasma and tumor samples were collected at 4 hours and 72 hours post last dose for all groups. For the PKPD Cohort, the tumors were cut into 2 pieces: one for Western Blotting (WB) with BRD9 analysis, and one for RNAseq analysis. For the Efficacy Cohort, the tumors were analyzed for BRD9 levels by Western Blotting (WB).

TABLE-US-00008 TABLE 3 Study details for cell line derived xenograft (CDX) model DU145 Cell Average tumor number Days of size at start of Model Strain (millions) Vehicle treatment Treatments dosing (mm.sup.3) DU145 BALA/c 5 20% (2- 43 Compound 1 145 (Efficacy) nude Hydroxypropyl)- 281 (PKPD) β-cyclodextrin (HPBCD)

TABLE-US-00009 TABLE 4A Groups and Treatment for Efficacy Cohort Animals/ Dose Vol Group # Drug group (mg/kg) (ml/kg) Route Frequency 1 Vehicle 3 — 5 IP BIW control* (43 days) 2 Compound 1 9 3 5 IP BIW (43 days) 3 Compound 1 9 15 5 IP BIW (43 days) *Vehicle Control = (20% HP-β-CD in 5 mM citrate buffer of pH 3), adjusted the final PH to 5 by the addition of 1N NaOH.

TABLE-US-00010 TABLE 4B Groups and Treatment for PKPD Cohort Animals/ Dose Vol Group # Drug group (mg/kg) (ml/kg) Route Frequency 1 Vehicle 3 — 5 IP BIW (3 doses) control* 2 Compound 1 6 1 5 IP Single dose 3 Compound 1 6 15 5 IP Single dose 4 Compound 1 6 1 5 IP BIW (3 doses) 5 Compound 1 6 15 5 IP BIW (3 doses) *Vehicle Control = (20% HP-β-CD in 5 mM citrate buffer of pH 3), adjusted the final PH to 5 by the addition of 1N NaOH.

Results:

[0438] In the efficacy study, mean tumor volume (TV) of the vehicle group reached 1784 mm.sup.3 on Day 49 post tumor cell inoculation. Compound 1 at dose levels of 3 mg/kg and 15 mg/kg BIW showed significant antitumor activity with tumor growth inhibition (TGI) values of 42.2% and 55.3% ($P<0.001$ vs. vehicle control, Table 5, FIG. **7**B), respectively. Regarding safety profile, the animals tolerated Compound 1 well at dose levels of 1 mg/kg, 3 mg/kg and 15 mg/kg during the treatment period. No obvious clinical abnormalities were observed on any of the animals treated. The growth curves of body weight for each study group over the entire course of study period are shown in FIG. **7**A.

[0439] PK results illustrated that there were time and dose dependent exposures of Compound 1 in

plasma. There was no obvious exposure difference between a single dose and three doses for Compound 1 at each dose level. The PK results of the test articles in plasma of different treatment groups are shown in Table 6A (4 hours) and Table 6B (72 hours). No difference in PK between a single dose or three doses of 1 mg/kg Compound 1 was observed (FIG. **8**). Moreover, the 15 mg/kg (single dose) group had better PK exposure than the 15 mg/kg (three doses) group (FIG. **8**).

[0440] Western Blot (WB) results showed that PK/PD cohorts 15 mg/kg (single dose) and 15 mg/kg (three doses) of Compound 1 statistically and significantly degrade BRD9 protein in a DU145 AR negative prostate CDX model at 72 h post last dose ($P<0.05$ vs. vehicle control). Compound 1 plasma PK positively corelates with in vivo BRD9 degradation in DU145 AR-negative prostate CDX model (FIG. **9**).

TABLE-US-00011 TABLE 5 Antitumor Activity of Different Treatment Groups in DU145 Subcutaneous Model Efficacy Study Tumor Size Tumor Group (mm.sup.3) Growth % T/C* TGI P-# Treatment on Day 49 on Day 49 (%) (%) Value 1 Vehicle 1784 ± 25 1,228 ± 49 — — — 2 3 mg/kg of 1029 ± 30 710 ± 19 57.8 42.2 <0.001 Compound 1 3 15 mg/kg of 793 ± 31 549 ± 26 44.7 55.3 <0.001 Compound 1 *T/C = 100*(Vt relative volumes (% tumor growth)/VC relative volumes)

TABLE-US-00012 TABLE 6A Plasma Concentration of Compound 1 in PK/PD Cohort at 4 Hours Mouse Concentration Treatment Identifier of Compound 1 Mean SD CV Group # Treatment (ng/mL) (ng/mL) (ng/mL) (%) 2 11 1 mg/kg of 8.07 11.8 5.4 45.5 Compound 1, single dose 2 29 1 mg/kg of 18.0 Compound 1, single dose 2 30 1 mg/kg of 9.37 Compound 1, single dose 3 5 15 mg/kg of 147 124 28 22.9 Compound 1, single dose 3 9 15 mg/kg of 132 Compound 1, single dose 3 12 15 mg/kg of 92.3 Compound 1, single dose 4 8 1 mg/kg of 10.9 10.8 3.8 35.1 Compound 1, BIW 3 doses 4 20 1 mg/kg of 14.4 Compound 1, BIW 3 doses 4 52 1 mg/kg of 6.89 Compound 1, BIW 3 doses 5 16 15 mg/kg of 82.9 72.5 9.8 13.5 Compound 1, BIW 3 doses 5 37 15 mg/kg of 63.4 Compound 1, BIW 3 doses 5 42 15 mg/kg of 71.3 Compound 1, BIW 3 doses

TABLE-US-00013 TABLE 6B Plasma Concentration of Compound 1 in PK/PD Cohort at 72 Hours Mouse Concentration Treatment Identifier of Compound 1 Mean SD CV Group # Treatment (ng/mL) (ng/mL) (ng/mL) (%) 2 33 1 mg/kg of BLOQ* 1.39 N/A N/A Compound 1, single dose 2 50 1 mg/kg of 1.18 Compound 1, single dose 2 62 1 mg/kg of 1.59 Compound 1, single dose 3 32 15 mg/kg of 15.7 31.5 17.4 55.3 Compound 1, single dose 3 45 15 mg/kg of 50.2 Compound 1, single dose 3 63 15 mg/kg of 28.6 Compound 1, single dose 4 55 1 mg/kg of 2.02 2.21 0.48 21.7 Compound 1, BIW 3 doses 4 59 1 mg/kg of 2.75 Compound 1, BIW 3 doses 4 64 1 mg/kg of 1.85 Compound 1, BIW 3 doses 5 14 15 mg/kg of 6.43 7.9 2.3 28.5 Compound 1, BIW 3 doses 5 39 15 mg/kg of 10.5 Compound 1, BIW 3 doses 5 70 15 mg/kg of 6.77 Compound 1, BIW 3 doses

*BLOQ = Below quantifiable limit of 1.05 ng/mL

Example 6: BRD9 Degrader Treatment Results in Moderate Tumor Growth Inhibition in AR-Positive, CDX Model of CRPC (VCaP Model)

[0441] Procedure: The experimental details of the studies, including tumor model, mouse strain, cell number implanted, vehicle used, days of treatment, treatment details, and average tumor size at start of dosing are outlined in Table 7. All study mice were obtained and the studies were conducted at Pharmaron. Each mouse was inoculated subcutaneously on the right flank with the single cell suspension of VCAP human prostate cancer tumor cells (1×10.sup.7) in 0.1 mL with Matrigel (1:1) in DMEM medium with 10% FBS for tumor development. The mice were castrated by removing the testes via a scrotal approach when the tumor volume reached 270 mm.sup.3. After castration, the tumor volume decreased. Treatment started when the mean tumor volume grew back 265 mm.sup.3. Based on tumor volume, mice were randomly assigned to respective groups using a computer-generated randomization procedure and treated according to the study design in Table 8.

TABLE-US-00014 TABLE 7 Study details for cell line derived xenograft (CDX) model VCaP Average tumor size Cell at start of number Days of dosing Model Strain (millions) Vehicle treatment Treatments (mm3) CRPC NCG 10 20% (2- 25 Compound 1 265 VCaP Hydroxypropyl)-

alone; β-cyclodextrin enzalutamide (HPBCD) alone, and a combination of Compound 1 and enzalutamide

TABLE-US-00015 TABLE 8 Study Groups and Treatments Group Animals/ Dose Vol # Drug group (mg/kg) (ml/kg) Route Frequency Duration 1 Vehicle* 8 — 5 IP BIW 25 days 2 Compound 1 8 10 5 IP BIW 25 days 3 Enzalutamide 8 30 10 PO QD 25 days 4 Compound 1 + 8 10 5 IP BIW 25 days Enzalutamide 30 10 PO QD *Vehicle for Enzalutamide = 5% DMSO/95% (1% CMC/0.1% Tween80, v/v), v/v

[0442] Results: The mean tumor size of vehicle treated mice reached 814 mm.sup.3 on day 57 after tumor inoculation. The treatments were initiated when mean tumor volume reached 265 mm.sup.3 on Day 36 post tumor inoculation. The inhibition rates of tumor growth are summarized in Table 9 and FIG. **10**B. Compound 1 at dose level of 10 mg/kg showed minimal antitumor trend with TGI of 13.8%. Enzalutamide at dose level of 30 mg/kg showed moderate antitumor activity with TGI of 23.3% (P=0.001vs. vehicle group). Compound 1 at dose level of 10 mg/kg plus enzalutamide at dose level of 30 mg/kg showed moderate antitumor activity with TGI of 25.9% (P<0.001vs. vehicle group).

[0443] Regarding the safety profile, treatment was well tolerated, as body weight did not decrease significantly during the course of the study (FIG. **10**A). One animal treated with Compound 1 at 10 mg/kg, and two animals treated with Compound 1 at 10 mg/kg +Enzalutamide at 30 mg/kg were found dead at the late stage of the treatment period. These male mice had been castrated by removing the testes via a scrotal approach when the tumor volume reached 270 mm.sup.3, thus, it is suspected that surgery may have led to these deaths. Additionally, no other clinical abnormalities were observed on all animals treated.

TABLE-US-00016 TABLE 9 Antitumor Activity of Different Treatment Groups in VCAP CRPC Model Tumor Size Tumor Growth (mm3) % T/C TGI on Day 57 on Day 57 (%) (%) P Value G1: Vehicle 814 ± 39 310 ± 10 — — — G2: Compound 1 697 ± 44 267 ± 20 86.2 13.8 0.028 at 10 mg/kg G3: Enzalutamide 626 ± 28 238 ± 9 76.7 23.3 0.001 at 30 mg/kg G4: Compound 1 611 ± 51 230 ± 15 74.1 25.9 <0.001 at 10 mg/kg + Enzalutamide at 30 mg/kg

OTHER EMBODIMENTS

[0444] All publications, patents, and patent applications mentioned in this specification are incorporated herein by reference in their entirety to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. Where a term in the present application is found to be defined differently in a document incorporated herein by reference, the definition provided herein is to serve as the definition for the term.

[0445] While the invention has been described in connection with specific embodiments thereof, it will be understood that invention is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure that come within known or customary practice within the art to which the invention pertains and may be applied to the essential features hereinbefore set forth, and follows in the scope of the claims.

[0446] Other embodiments are in the claims.

Claims

1. A method of treating androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.

2. A method of slowing progression of androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt

thereof.
3. A method of reducing recurrence of androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
4. A method of decreasing the rate of metastatic tumor seeding of androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
5. A method of decreasing metastatic tumor nodule formation of androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
6. A method of decreasing the spread of metastatic tumor nodule formation of androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
7. A method of decreasing metastatic colonization of androgen receptor-independent prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
8. The method of any one of claims 1-7, wherein the androgen receptor-independent prostate cancer has failed to respond a previous treatment with an anti-cancer therapy.
9. A method of treating prostate cancer that has failed to respond to a previous treatment with an anti-cancer therapy in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
10. The method of any one of claims 1-9, wherein the prostate cancer is neuroendocrine prostate cancer.
11. A method of treating neuroendocrine prostate cancer in a subject in need thereof, the method comprising administering to the subject an effective amount of a compound that reduces the level and/or activity of BRD9, or a pharmaceutically acceptable salt thereof.
12. The method of claim 11, wherein the neuroendocrine prostate cancer is androgen receptor-independent.
13. The method of claim 11 or 12, wherein the neuroendocrine prostate cancer has failed to respond to a previous treatment with an anti-cancer therapy.
14. The method of any one of claims 1 to 13, wherein the compound is 3-(6-(7-((1-(4-(6-(azetidin-1-yl)-2-methyl-1-oxo-1,2-dihydro-2,7-naphthyridin-4-yl)-2,6-dimethoxybenzyl) piperidin-4-yl)methyl)-2,7-diazaspiro[3.5]nonan-2-yl)-1-oxoisoindolin-2-yl) piperidine-2,6-dione or a pharmaceutically acceptable salt thereof.
15. The method of any one of claims 1 to 13, wherein the compound is 3-((4-(4-(1-(2,6-dimethoxy-4-(1,4,5-trimethyl-6-oxo-1,6-dihydropyridin-3-yl)benzyl)-3,3-difluoropiperidin-4-yl) piperazin-1-yl)-3-fluorophenyl)amino) piperidine-2,6-dione or a pharmaceutically acceptable salt thereof.
16. The method of any one of claims 1 to 15, wherein the prostate cancer is castration-resistant prostate cancer (CRPC).
17. The method of any one of claims 1 to 16, wherein the prostate cancer is small cell prostate cancer.
18. The method of claim 2, wherein the effective amount is an amount sufficient to reduce the level of neuroendocrine prostate cancer cells in the subject compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.

19. The method of any one of claims 1 to 18, wherein the anti-cancer therapy is active surveillance, surgery, radiation therapy, high-intensity focused ultrasound (HIFU), cryotherapy, hormone therapy, chemotherapy, immunotherapy, vaccine treatment, immune checkpoint inhibitors, targeted therapy drugs, or bone-directed treatment.
20. The method of any one of claims 1 to 19, wherein the anti-cancer therapy is abiraterone acetate, alendronate, apalutamide, bicalutamide, cabazitaxel, carboplatin, cisplatin, darolutamide, degarelix, denosumab, docetaxel, enzalutamide, etoposide, flutamide, goserelin acetate, ibandronate, leuprolide acetate, lynparza, mitoxantrone hydrochloride, nilutamide, olaparib, pamidronate, radium 223 dichloride, relugolix, risedronate, rucaparib camsylate, sipuleucel-T, or zoledronic acid, or combinations thereof.
21. The method of claim 20, wherein the anti-cancer therapy is enzalutamide.
22. The method of any one of claims 1 to 21, wherein the subject is further administered at least one additional anti-cancer therapy.
23. The method of claim 22, wherein the additional anti-cancer therapy is administered prior to the administering of the compound or pharmaceutically acceptable salt thereof.
24. The method of claim 22, wherein the additional anti-cancer therapy is administered in addition to the administering of the compound or pharmaceutically acceptable salt thereof.
25. The method of claim 22, wherein the additional anti-cancer therapy is administered subsequent to the administering of the compound or pharmaceutically acceptable salt thereof.
26. The method of any one of the preceding claims, wherein the subject is further administered a treatment for symptoms of prostate cancer.
27. The method of claim 26, wherein the further treatment is prednisone, methylprednisolone, pembrolizumab, or a combination thereof.
28. The method of any one of the preceding claims, wherein the effective amount is an amount sufficient to reduce the level of luminal prostate cancer cell to neuroendocrine prostate cancer cell trans-differentiation measured by lower expression levels of CHGA, SYP, and/or ENO2 compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
29. The method of any one of the preceding claims, wherein the effective amount is an amount sufficient to reduce the level of adenocarcinoma to neuroendocrine trans-differentiation measured by lower expression levels of CHGA, SYP, and/or ENO2 compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
30. The method of any one of the preceding claims, wherein the effective amount is an amount sufficient to reduce the level of neuroendocrine prostate cancer cells compared to a subject that is not administered the compound or pharmaceutically acceptable salt thereof.
31. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have lower expression levels of AR, KLK2, KLK3, CDH1, CYLD, NKX3-1, SLC45A3, TARP, PTEN, SPDEF, TP53, or RB1, or combinations thereof compared to a subject that does not have prostate cancer.
32. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have lower expression levels of AR, KLK2, KLK3, CDH1, CYLD, NKX3-1, SLC45A3, TARP, PTEN, SPDEF, TP53, or RB1, or combinations thereof compared to standard levels for prostate cancer.
33. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have higher expression levels of CHGB, CHGA, SYP, ENO2, PEG10, SNAP25, SRRM4, VGF, VIM, SCGN, PAPPA2, or WNT11, or combinations thereof compared to a subject that does not have prostate cancer.
34. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have higher expression levels of CHGB, CHGA, SYP, ENO2, PEG10, SNAP25, SRRM4, VGF, VIM, SCGN, PAPPA2, or WNT11, or combinations thereof compared to standard levels for prostate cancer.

35. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have higher expression levels of ASCL1, EZH2, DLX5, DLX6, SOX2, NKX2-2, HES6, SOX9, KDM3A, FOXA2, AURKA, MYCN, MYC, AKT, POU3F2/BRN2, NANOG, ONECUT2, or NKX2-1, or combinations thereof compared to a subject that does not have prostate cancer.
36. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have higher expression levels of ASCL1, EZH2, DLX5, DLX6, SOX2, NKX2-2, HES6, SOX9, KDM3A, FOXA2, AURKA, MYCN, MYC, AKT, POU3F2/BRN2, NANOG, ONECUT2, or NKX2-1, or combinations thereof compared to standard levels for prostate cancer.
37. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have lower expression levels of RE1 silencing transcription factor (REST).
38. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have expression of AR and KLK3 (PSA).
39. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have undetectable expression of CHGA and SYP.
40. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have expression of AR, KLK3 (PSA), CHGA and SYP.
41. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have undetectable expression of AR and KLK3 (PSA).
42. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have expression of CHGA and SYP.
43. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have undetectable expression of AR, KLK3 (PSA), CHGA and SYP.
44. The method of any one of the preceding claims, wherein the prostate cancer has been determined or predicted to have a high level of TMPRSS2-ERG fusions.
45. The method of any one of the preceding claims, wherein the prostate cancer is metastatic.
46. The method of any one of the preceding claims, wherein expression of BRD9, GLTSCR1, CXXC5 or TET2 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
47. The method of claim 46, wherein expression of BRD9 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
48. The method of claim 46, wherein expression of GLTSCR1 is increased in the prostate cancer compared to a subject that does not have prostate cancer.
49. The method of any one of the preceding claims, wherein expression of TET2, CXXC5, H3K27ac, ID1, PFN2, or ID3 in the subject is increased in the prostate cancer determined to or predicted to be resistant to enzalutamide compared to a prostate cancer that responds to treatment with enzalutamide.
50. The method of any one of the preceding claims, wherein the prostate cancer has been determined to have or predicted to have undetectable expression of PTEN.
51. The method of any one of the preceding claims, wherein the prostate cancer has been determined or predicted to be ERG positive.
52. The method of any one of the preceding claims, wherein the subject is further administered an inhibitor or degrader of ERG.
53. The method of claim 52, wherein the ERG inhibitor or degrader is ERGi-USU (1-[2-Thiazolylazo]-2-naphthol).
54. The method of any one of the preceding claims, wherein the subject is further administered a degrader of AR.

55. The method of claim 54, wherein the AR degrader is bavdegalutamide (ARV-110), ARV-766, or AR-V7.
56. The method of any one of the preceding claims, wherein the subject is further administered an inhibitor of the JAK-STAT pathway.
57. The method of claim 56, wherein the JAK-STAT inhibitor is AG490, AZD1480, AZD4205, baricitinib, dasatinib, fedratinib, filgotinib, itacitnib, lestaurtinib, momelotinib, pacritinib, peficitinib, ruxolitinib, siltuximab, tofacitinib, upadacitinib, or WP1066.
58. The method of any one of the preceding claims, wherein the subject is further administered an inhibitor of the MAPK pathway.
59. The method of claim 58, wherein the MAPK pathway inhibitor is a Farnesyltransferase inhibitor (FTI), Sorafenib, Vemurafenib, PLX8394, Dabrafenib, Ulixertinib, Simvastatin, Alisertib, or Teriflunomide.
60. The method of any one of the preceding claims, wherein the subject is further administered an inhibitor of the PI3K-AKT-mTOR pathway.
61. The method of claim 60, wherein the PIK3-AKT-mTOR inhibitor is everolimus, alpelisib, idelalisib or copanlisib.
62. The method of any one of the preceding claims, wherein the subject has a PSA level of 4 ng/ml or more prior to the administering of the compound or a pharmaceutically acceptable salt thereof.
63. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20-80 mg/kg.
64. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20-60 mg/kg.
65. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20-40 mg/kg.
66. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20 mg/kg.
67. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 40 mg/kg.
68. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 50 mg/kg.
69. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 60 mg/kg.
70. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 80 mg/kg.
71. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 120 mg/kg.
72. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered to the subject at least once per week.
73. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered to the subject at least twice per week.
74. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20 mg/kg once per week.
75. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 20 mg/kg twice per week.
76. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 40 mg/kg once per week.
77. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 40 mg/kg twice per week.
78. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 50 mg/kg once per week.

79. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 50 mg/kg twice per week.
80. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 60 mg/kg once per week.
81. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 60 mg/kg twice per week.
82. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 80 mg/kg once per week.
83. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 80 mg/kg twice per week.
84. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 120 mg/kg once per week.
85. The method of any one of claims 1-62, wherein the effective amount of the compound or a pharmaceutically acceptable salt thereof, is administered in a dose of 120 mg/kg twice per week.
86. The method of any one of claims 1-85, wherein the compound or a pharmaceutically acceptable salt thereof is administered to the subject in a 14-day dosing cycle.
87. The method of any one of claims 1-86, wherein the compound or a pharmaceutically acceptable salt thereof is administered to the subject in a 21-day dosing cycle.
88. The method of any one of claims 1-87, wherein the compound or a pharmaceutically acceptable salt thereof is administered to the subject in a 28-day dosing cycle.
89. The method of any one of the preceding claims, wherein the compound or a pharmaceutically acceptable salt thereof, is administered to the subject intravenously.
90. The method of any one of the preceding claims, wherein the compound or a pharmaceutically acceptable salt thereof, is administered to the subject subcutaneously.
91. The method of any one of the preceding claims, wherein the compound or a pharmaceutically acceptable salt thereof, is administered to the subject intramuscularly.