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(54) Titre : METHODES DE TRAITEMENT DES NEOPLASMES MYELOPROLIFERATIFS
(54) Title: METHODS OF TREATING MYELOPROLIFERATIVE NEOPLASMS

(57) Abrégé/Abstract:
Therapeutic methods and pharmaceutical compositions for treating a myeloproliferative neoplasm (MPN), including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis, are described. In certain embodiments, the invention includes therapeutic methods of treating a MPN using a combination of a compound of Formula (I) or Formula (II) with a therapeutic agent selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

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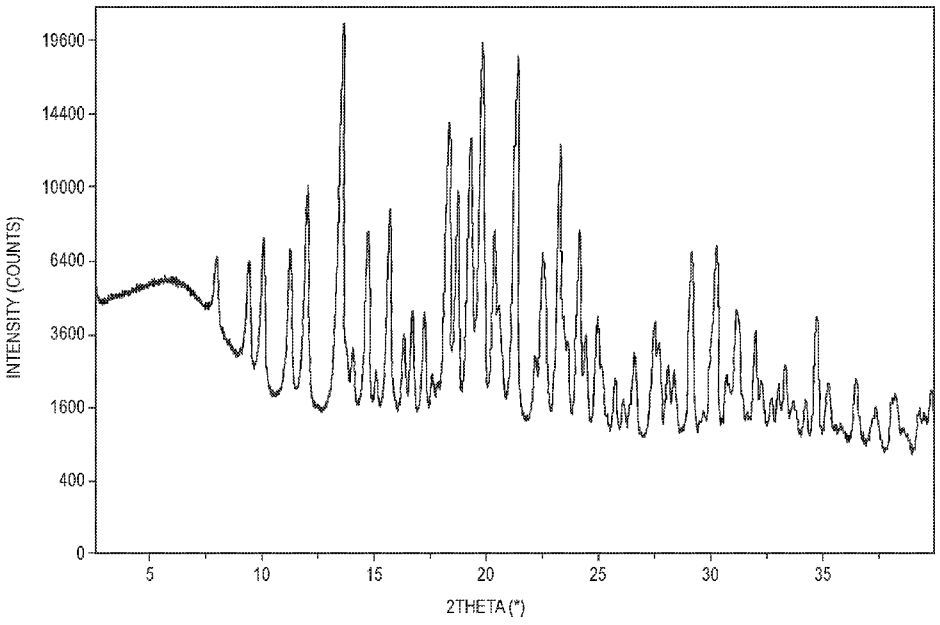


FIG. 1

(57) Abstract: Therapeutic methods and pharmaceutical compositions for treating a myeloproliferative neoplasm (MPN), including polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis, are described. In certain embodiments, the invention includes therapeutic methods of treating a MPN using a combination of a compound of Formula (I) or Formula (II) with a therapeutic agent selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

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METHODS OF TREATING MYELOPROLIFERATIVE NEOPLASMS

FIELD OF THE INVENTION

[0001] Methods of treating a myeloproliferative neoplasm (MPN) using a Mouse double minute 2 homolog (MDM2) inhibitor and a therapeutic agent selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

BACKGROUND OF THE INVENTION

[0002] p53 is a tumor suppressor and transcription factor that responds to cellular stress by activating the transcription of numerous genes involved in cell cycle arrest, apoptosis, senescence, and DNA repair. Unlike normal cells, which have infrequent cause for p53 activation, tumor cells are under constant cellular stress from various insults including hypoxia and pro-apoptotic oncogene activation. Thus, there is a strong selective advantage for inactivation of the p53 pathway in tumors, and it has been proposed that eliminating p53 function may be a prerequisite for tumor survival. In support of this notion, three groups of investigators have used mouse models to demonstrate that absence of p53 function is a continuous requirement for the maintenance of established tumors. When the investigators restored p53 function to tumors with inactivated p53, the tumors regressed.

[0003] p53 is inactivated by mutation and/or loss in 50% of solid tumors and 10% of liquid tumors. Other key members of the p53 pathway are also genetically or epigenetically altered in cancer. MDM2, an oncoprotein, inhibits p53 function, and it is activated by gene amplification at incidence rates that are reported to be as high as 10%. MDM2, in turn, is inhibited by another tumor suppressor, p14ARF. It has been suggested that alterations downstream of p53 may be responsible for at least partially inactivating the p53 pathway in p53 WT tumors (p53 wild type). In support of this concept, some p53WT tumors appear to exhibit reduced apoptotic capacity, although their capacity to undergo cell cycle arrest remains intact. One cancer treatment strategy involves the use of small molecules that bind MDM2 and neutralize its interaction with p53. MDM2 inhibits p53 activity by three mechanisms: 1) acting as an E3 ubiquitin ligase to promote

p53 degradation; 2) binding to and blocking the p53 transcriptional activation domain; and 3) exporting p53 from the nucleus to the cytoplasm. All three of these mechanisms would be blocked by neutralizing the MDM2-p53 interaction. In particular, this therapeutic strategy could be applied to tumors that are p53 WT, and studies with small molecule MDM2 inhibitors have yielded promising reductions in tumor growth both in vitro and in vivo. Further, in patients with p53-inactivated tumors, stabilization of wild type p53 in normal tissues by MDM2 inhibition might allow selective protection of normal tissues from mitotic poisons. As used herein, MDM2 means a human MDM2 protein and p53 means a human p53 protein. It is noted that human MDM2 can also be referred to as HDM2 or hMDM2. Several MDM2 inhibitors are in human clinical trials for the treatment of various cancers.

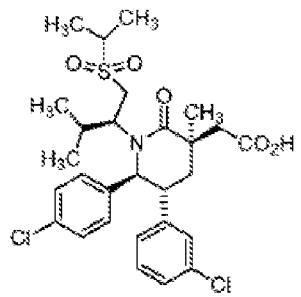
[0004] The myeloproliferative neoplasms (MPN), including but not limited to: polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are clonal hematopoietic stem cell (HSC) disorders characterized by the clonal proliferation of terminally differentiated myeloid cells. Approximately 1%, 4%, and 20% of ET, PV and PMF patients, respectively, progress to a blast phase (BP) termed MPN-BP over a 10-year period from the time of diagnosis. Cervantes F, et al., *Acta Haematol.*1991;85(3):124–127. MPN-BP and *de novo* acute myeloid leukemia (AML) each have distinct mutational patterns and clinical courses. Rampal R, et al., *Proc Natl Acad Sci USA.* 2014; 111(50):E5401-10. Patients with MPN-BP have a particularly dismal prognosis with a median survival of less than 6 months with currently available therapies.

[0005] The present invention relates to methods of treating a myeloproliferative neoplasm in a human subject with a MDM2 inhibitor and a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a Janus kinase (JAK) inhibitor, an isocitrate dehydrogenase (IDH) inhibitor, a programmed death-1 (PD-1) inhibitor, a programmed death-ligand 1(PD-L1) inhibitor, a programmed death-ligand 2 (PD-L2) inhibitor, an interferon, a hosphoinositide 3-kinase (PI3K) inhibitor, a protein kinase B (AKT) inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

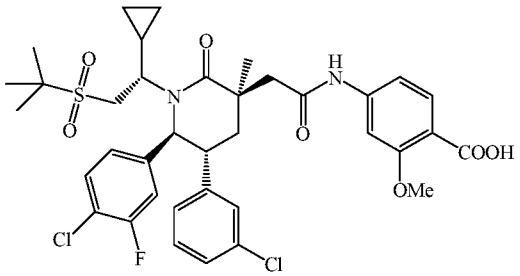
SUMMARY OF THE INVENTION

[0006] The present invention relates to a method of treating a myeloproliferative neoplasm (MPN) comprising the step of administering to a human in need thereof, therapeutically effective amounts of a MDM2 inhibitor in combination with a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0007] In an embodiment, the MDM2 inhibitor is a compound of Formula (I) or a compound of Formula (II):



(I)



(II)

or a pharmaceutically acceptable salt thereof.

[0008] In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0009] In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B,

SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0010] In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof.

[0011] In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride.

[0012] In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof.

[0013] In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof.

[0014] In one embodiment, the anti-PD- L2 antibody is rHIgM12B7A.

[0015] In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof.

[0016] In an embodiment, the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin,

Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof.

[0017] In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof.

[0018] In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof.

[0019] In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof.

[0020] In an embodiment, the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0021] In an embodiment, the interferon is selected from the group consisting of PEGylated rIFN-alpha 2b (PEG-Intron), PEGylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon alpha-n3 (Alferon), albinterferon alpha-2b (Albuferon), IFN alpha-2b XL, BLX-883 (Locteron), DA-3021, AVI-005, belerofon, Cepeginterferon alfa-2b, and combinations thereof.

[0022] In an embodiment, the MPN is thrombocythemia.

[0023] In an embodiment, thrombocythemia is essential thrombocythemia (ET).

[0024] In an embodiment, the MPN is myelofibrosis.

[0025] In an embodiment, myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

[0026] In an embodiment, the MPN is chronic myelogenous leukemia.

[0027] In an embodiment, the MPN is systemic mastocystosis (SM).

[0028] In an embodiment, the MPN is chronic neutrophilic leukemia (CNL).

[0029] In an embodiment, the MPN is myelodysplastic syndrome (MDS).

[0030] In an embodiment, the MPN is mast cell disease (SMCD).

[0031] In an embodiment, the MPN is chronic eosinophilic leukemia.

[0032] In an embodiment, the MPN is chronic myelomonocytic leukemia (CMML).

[0033] In an embodiment, the MPN is atypical chronic myeloid leukemia (aCML).

[0034] In an embodiment, the MPN is juvenile myelomonocytic leukemia (JMML).

[0035] In an embodiment, the MPN is hypereosinophilic syndromes (HES).

[0036] In an embodiment, the compound of Formula (I) or Formula (II) is in a crystalline form.

[0037] In an embodiment, the crystalline form is characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6 ± 0.1.

[0038] In an embodiment, the compound of Formula (I) or Formula (II) is in a free form.

[0039] In an embodiment, the MDM2 inhibitor is a pharmaceutically acceptable salt of a compound of Formula (I) or Formula (II).

[0040] In an embodiment, the compound of Formula (I) or Formula (II) is in an amorphous form.

[0041] In an embodiment, the compound of Formula (I) or Formula (II) is administered once daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

[0042] In an embodiment, the compound of Formula (I) or Formula (II) is administered twice daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

[0043] In an embodiment, the human is treated with the MDM2 inhibitor for a period selected from the group consisting of about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, and about 56 days.

[0044] In an embodiment, the compound of Formula (I) or Formula (II) is orally administered.

[0045] In an embodiment, the MDM2 inhibitor is administered before administration of the therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0046] In an embodiment, the MDM2 inhibitor is administered after administration of the therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0047] In an embodiment, the MDM2 inhibitor is administered concurrently with administration of the therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0048] In an embodiment, the therapeutically effective amount of the MDM2 inhibitor is 100 mg.

BRIEF DESCRIPTION OF THE DRAWINGS

[0049] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0050] FIG. 1 illustrates XRPD Pattern of the compound of Formula (I) in a crystalline anhydrous form.

DETAILED DESCRIPTION OF THE INVENTION

[0051] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

[0052] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0053] The terms "administered in combination with" and "co-administration" as used herein, encompass administration of two or more active pharmaceutical ingredients to a subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more agents are present.

[0054] The term "combination" or "pharmaceutical combination" is defined herein to refer to either a fixed combination in one dosage unit form, a non-fixed combination or a kit of parts for the combined administration where the therapeutic agents may be administered together, independently at the same time or separately within time intervals, which preferably allows that the combination partners show a cooperative, e.g. synergistic effect. Thus, the single compounds

of the pharmaceutical combination of the present disclosure could be administered simultaneously or sequentially.

[0055] Furthermore, the pharmaceutical combination of the present disclosure may be in the form of a fixed combination or in the form of a non-fixed combination.

[0056] The term "effective amount" or "therapeutically effective amount" refers to that amount of an active pharmaceutical ingredient or combination of active pharmaceutical ingredients as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, and other factors which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

[0057] The terms "enantiomerically enriched," "enantiomerically pure," and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (*R*)-enantiomer, such as at least 75% by weight, such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure," or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to the other enantiomer, such as at least 90% by weight, and such as at least 95% by weight. The terms "diastereomerically enriched" and "diastereomerically pure," as used herein, refer to compositions in which the percent by weight of one diastereomer is greater than the amount of that one diastereomer in a

control mixture of diastereomers. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially diastereomerically enriched" or "substantially diastereomerically pure" preparation, which refers to preparations of compositions which have at least 85% by weight of one diastereomer relative to other diastereomers, such as at least 90% by weight, and such as at least 95% by weight.

[0058] In some embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or some enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *Enantiomers, Racemates and Resolutions*, Wiley Interscience, New York (1981); E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York (1994).

[0059] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (*R*)- or an (*S*)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (*R*)- or (*S*)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (*S*)- and 20% (*R*)-, the enantiomeric purity of the compound with respect to the (*S*)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

[0060] The term "fixed combination" means that the therapeutic agents, e.g., the single compounds of the combination, are in the form of a single entity or dosage form.

[0061] The term "IC_{50}" refers to the half maximal inhibitory concentration, *i.e.* inhibition of 50% of the desired activity. The term "EC_{50}" refers to the drug concentration at which one-half the maximum response is achieved.

[0062] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*, having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

[0063] In an embodiment, compounds described herein include of the isomers, stereoisomers, and enantiomers thereof.

[0064] "MPN-BP" refers to blast phase (BP) of the myeloproliferative neoplasms (MPN) described in this disclosure.

[0065] The term "non-fixed combination" means that the therapeutic agents, e.g., the single compounds of the combination, are administered to a patient as separate entities or dosage forms

either simultaneously or sequentially with no specific time limits, wherein preferably such administration provides therapeutically effective levels of the two therapeutic agents in the body of the subject, e.g., a mammal or human in need thereof.

[0066] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic, and absorption delaying agents. The use of such media and agents for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional media or agent is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions. Unless otherwise specified, or clearly indicated by the text, reference to therapeutic agents useful in the pharmaceutical combination of the present disclosure includes both the free base of the compounds, and all pharmaceutically acceptable salts of the compounds.

[0067] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term "cocrystal" refers to a molecular

complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve proton transfer between the cocrystal and the drug, and instead involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and the drug in the crystal structure.

[0068] The terms "QD," "qd," or "q.d." means *quaque die*, once a day, or once daily. The terms "BID," "bid," or "b.i.d." mean *bis in die*, twice a day, or twice daily. The terms "TID," "tid," or "t.i.d." mean *ter in die*, three times a day, or three times daily. The terms "QID," "qid," or "q.i.d." mean *quater in die*, four times a day, or four times daily.

[0069] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

[0070] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

[0071] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

[0072] Compounds of the invention also include crystalline and amorphous forms, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as

well as combinations thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as combinations thereof, unless a particular crystalline or amorphous form is referred to.

Co-administration of compounds

[0073] The present invention relates to pharmaceutical combinations or pharmaceutical compositions that are particularly useful as a medicine. Specifically, the combinations or compositions of the present disclosure can be applied in the treatment of a cancer. In an embodiment, the cancer is a MPN. The present invention also relates to use of pharmaceutical combinations or pharmaceutical compositions of the present disclosure for the preparation of a medicament for the treatment of a cancer, in particular a MPN, and to a method for treating cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of a pharmaceutical combination according to the present disclosure, or the pharmaceutical composition according to the present disclosure.

[0074] In an embodiment, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD).

[0075] In an embodiment, the myelofibrosis is selected from the group consisting of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

[0076] In an embodiment, the primary myelofibrosis (PMF) is selected from the group consisting of prefibrotic/early stage PMF and overt fibrotic stage PMF.

[0077] In an embodiment, the MPN is selected from the group consisting of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia

(JMML), hypereosinophilic syndromes (HES), and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

[0078] An embodiment of the invention is a composition, such as a pharmaceutical composition comprising a combination comprising a MDM2 inhibitor in combination with a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. Another embodiment is a kit containing both components formulated into separate pharmaceutical compositions, which are formulated for co-administration.

[0079] Another embodiment of the invention is a method of for treating a myeloproliferative neoplasm (MPN), wherein the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, thrombocythemia, idiopathic myelofibrosis, chronic myelogenous leukemia, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD) in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination comprising a MDM2 inhibitor in combination with a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. The pharmaceutical composition comprising the combination, and the kit, are both for use in treating such disease or condition.

[0080] In an embodiment, the MDM2 inhibitor is a compound of Formula (I) or Formula (II).

[0081] In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0082] In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B,

SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0083] In an embodiment, the JAK inhibitor is a JAK1 inhibitor.

[0084] In an embodiment, the JAK inhibitor is a JAK2 inhibitor.

[0085] In an embodiment, the JAK inhibitor is a JAK3 inhibitor.

[0086] In an embodiment, the JAK inhibitor is a selective JAK inhibitor.

[0087] In an embodiment, the JAK inhibitor is a pan JAK inhibitor.

[0088] In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof.

[0089] In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride.

[0090] In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof.

[0091] In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof.

[0092] In an embodiment, the anti-PD- L2 antibody is rHIgM12B7A.

[0093] In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof.

[0094] In an embodiment, the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof.

[0095] In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof.

[0096] In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof.

[0097] In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof.

[0098] In an embodiment, the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0099] In an embodiment, the interferon is selected from the group consisting of PEGylated rIFN-alpha 2b (PEG-Intron), PEGylated rIFN-alpha 2a (Pegasys), rIFN-alpha 2b (Intron A), rIFN-alpha 2a (Roferon-A), interferon alpha (MOR-22, OPC-18, Alfaferone, Alfanative, Multiferon, subalin), interferon alfacon-1 (Infergen), interferon alpha-n1 (Wellferon), interferon

alpha-n3 (Alferon), albinterferon alpha-2b (Albuferon), IFN alpha-2b XL, BLX-883 (Locteron), DA-3021, AVI-005, belerofon, Cepeginterferon alfa-2b, and combinations thereof.

[0100] In an embodiment, the nucleoside analog is selected from the group consisting of decitabine, cytarabine, azacitidine, zebularine, and pharmaceutically acceptable salts thereof.

[0101] The combination may be administered by any route known in the art. In an exemplary embodiment, the MDM2 inhibitor and the therapeutic agent are independently administered by oral, intravenous, intramuscular, intraperitoneal, subcutaneous or transdermal means, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In one embodiment, the MDM2 inhibitor is administered orally.

[0102] In an exemplary embodiment, the MDM2 inhibitor is in the form of a pharmaceutically acceptable salt.

[0103] In an exemplary embodiment, the MDM2 inhibitor is administered to the subject before administration of the therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0104] In an exemplary embodiment, the MDM2 inhibitor is administered to the subject after administration of the therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0105] In an exemplary embodiment, the MDM2 inhibitor is administered to the subject concurrently with administration of the therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0106] In an embodiment, the disclosure provides a method of for treating a blast phase myeloproliferative neoplasm (MPN-BP) in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination comprising a MDM2 inhibitor in combination with a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. The pharmaceutical composition comprising the combination, and the kit, are both for use in treating such disease or condition. In an embodiment, the MPN-BP is selected from the group consisting of blast phase polycythemia vera (BP-PV), blast phase myelofibrosis, blast phase primary myelofibrosis, blast phase thrombocythemia, blast phase essential thrombocythemia (BP-ET), blast phase idiopathic myelofibrosis, blast phase systemic mastocystosis (BP-SM), blast phase chronic neutrophilic leukemia (BP-CNL), blast phase myelodysplastic syndrome (BP-MDS), and blast phase systemic mast cell disease (BP-SMCD). In an embodiment, the blast phase myelofibrosis is selected from the group consisting of blast phase primary myelofibrosis (BP-PMF), blast phase post-polycythemia vera myelofibrosis (BP-post-PV MF), and blast phase post-essential thrombocythemia myelofibrosis (BP-post-ET MF). In an embodiment, the blast phase primary myelofibrosis (BP-PMF) is selected from the group consisting of blast phase prefibrotic/early stage PMF and blast phase overt fibrotic stage PMF. In an embodiment, the MPN-BP is selected from the group consisting of blast phase chronic neutrophilic leukemia (BP-CNL), blast phase chronic eosinophilic leukemia, blast phase chronic myelomonocytic leukemia (BP-CMML), blast phase atypical chronic myeloid leukemia (BP-aCML), blast phase juvenile myelomonocytic leukemia (BP-JMML), blast phase hypereosinophilic syndromes (BP-HES), and blast phase myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (BP-MDS/MPN-RS-T). In an embodiment, the MDM2 inhibitor is a compound of Formula (I) or Formula (II). In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of

Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B, SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0107] In an embodiment, the disclosure provides a method of for treating a blast phase myeloproliferative neoplasm (MPN-BP) in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination comprising the compound of Formula (I) in combination with a nucleoside analog, wherein the nucleoside analog is selected from the group consisting of decitabine, cytarabine, azacitidine, zebularine, and pharmaceutically acceptable salts thereof.

[0108] In an embodiment, the disclosure provides a method of for treating a blast phase myeloproliferative neoplasm (MPN-BP) in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination comprising the compound of Formula (I) in combination with decitabine or a pharmaceutically acceptable salt thereof.

[0109] In an embodiment, the disclosure provides a method of for treating a blast phase myeloproliferative neoplasm (MPN-BP) in a subject, comprising co-administering to the subject in need thereof a therapeutically effective amount of a combination comprising the compound of Formula (I) in combination with cytarabine or a pharmaceutically acceptable salt thereof.

[0110] In an embodiment, the MPN in the human subject is characterized by a CALR mutation (calreticulin, located on chromosome 19p13.2), as described in Massie, N. Engl. J. Med. 2013, 25: 2379-2390 and incorporated by reference herein in its entirety.

[0111] In an embodiment, the MPN in the human subject is characterized by an MPL mutation (myeloproliferative leukemia virus oncogene; located on chromosome 1p34), as described in Pikman, Plos Med. 2006; 3(7): e270 and incorporated by reference herein in its entirety.

[0112] In an embodiment, the MPN in the human subject is characterized by a JAK2V617F mutation. The JAK2V617F mutation is a functional mutation promoting cytokine-independent growth of myeloid cells and accounts for a majority of myeloproliferative neoplasms (MPN), as described in Nakatake, Oncogene, 2012, 31, 1323-1333 and incorporated by reference herein in its entirety.

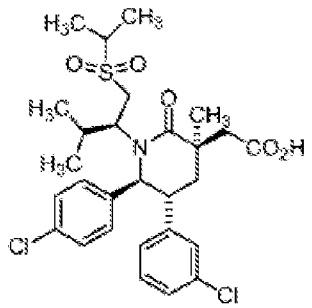
[0113] In an embodiment, the MPN in the human subject is characterized by having one or more mutations selected from the group consisting of JAK2V617F, MPL, CALR, and combinations thereof.

[0114] In an exemplary embodiment, the subject is a mammal, such as a human.

MDM2 inhibitor

[0115] The compound of Formula (I) has the structure and name shown below.

2-((3R,5R,6S)-5-(3-chlorophenyl)-6-(4-chlorophenyl)-1-((S)-1-(isopropylsulfonyl)-3-methylbutan-2-yl)-3-methyl-2-oxopiperidin-3-yl) acetic acid:



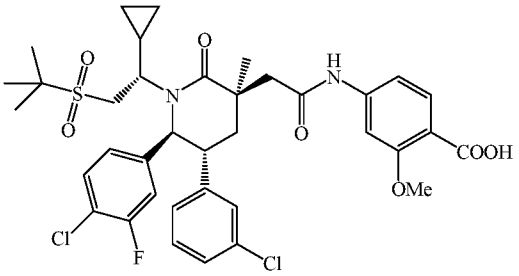
(I)

[0116] The synthesis of the compound of Formula (I) is set forth in International Applications: WO2011/153509 and WO2014/200937; U.S. Patent No. 8,569,341; 9,593,129; 9,296,736; 9,623,018; 9,757,367; 9,801,867; 9;376;386; and 9,855,259, the disclosure of which are incorporated by reference herein in its entirety.

[0117] In an embodiment, the compound of Formula (I) or Formula (II) is in an amorphous form. In an embodiment, the MDM2 inhibitor is the compound of Formula (I) or Formula (II) in a crystalline form. In an embodiment, the MDM2 inhibitor is the compound of Formula (I) in a crystalline anhydrous form. In an embodiment, the MDM2 inhibitor is the compound of Formula (I) in a crystalline anhydrous form characterized by a powder X-ray diffraction pattern comprising peaks at diffraction angle 2 theta degrees at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6. In an embodiment, the MDM2 inhibitor is the compound of Formula (I) in a

crystalline anhydrous form having the X-ray diffraction pattern substantially shown in FIG. 1. The method of making such crystalline form was disclosed in the International Application WO2014200937, the disclosure of which is incorporated herein by reference in its entirety.

[0118] In an embodiment, the MDM2 inhibitor is a compound of Formula (II) having the structure and name shown below.



(II)

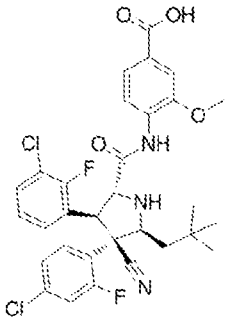
4-(2-((3R,5R,6S)-1-((S)-2-(tert-butylsulfonyl)-1-cyclopropylethyl)-6-(4-chloro-3-fluorophenyl)-5-(3-chlorophenyl)-3-methyl-2-oxopiperidin-3-yl)acetamido)-2-methoxybenzoic acid.

[0119] The synthesis of the compound of Formula (II) is set forth in US Patent No. 8,952,036, the disclosure of which is incorporated by reference herein in its entirety.

RG7388 (Idasanutlin)

[0120] In an embodiment, the MDM2 inhibitor is RG7388. RG7388 has the chemical structure and name shown as:

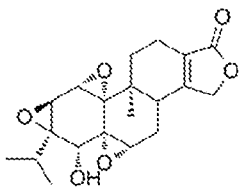
[0121] 4-[[(2R,3S,4R,5S)-3-(3-chloro-2-fluorophenyl)-4-(4-chloro-2-fluorophenyl)-4-cyano-5-(2,2-dimethylpropyl)pyrrolidine-2-carbonyl]amino]-3-methoxybenzoic acid



Triptolide (PG490)

[0122] In an embodiment, the MDM2 inhibitor is triptolide. Triptolide has the chemical structure and name shown as:

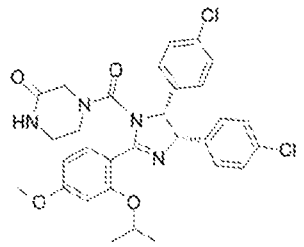
[0123] (5bS,6aS,7aS,8R,8aR,9aS,9bS,10aS,10bS)-8-hydroxy-8a-isopropyl-10b-methyl-2,5,5b,6,6a,8,8a,9a,9b,10b-decahydrotris(oxireno) [2',3':4b,5;2'',3'':6,7;2''',3''':8a,9] phenanthro[1,2-c]furan-3(1H)-one



Nutlin-3a

[0124] In an embodiment, the MDM2 inhibitor is Nutlin-3a. Nutlin-3a has the chemical structure and name shown as:

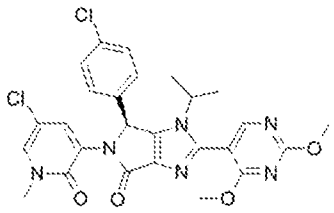
[0125] 4-[(4S,5R)-4,5-bis(4-chlorophenyl)-2-(4-methoxy-2-propan-2-yloxyphenyl)-4,5-dihydroimidazole-1-carbonyl]piperazin-2-one



HDM201

[0126] In an embodiment, the MDM2 inhibitor is HDM201. HDM201 has the chemical structure and name shown as:

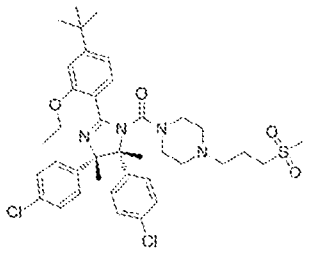
[0127] (4S)-5-(5-chloro-1-methyl-2-oxopyridin-3-yl)-4-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-3-propan-2-yl-4H-pyrrolo[3,4-d]imidazol-6-one



RG7112

[0128] In an embodiment, the MDM2 inhibitor is RG7112. RG7112 has the chemical structure and name shown as:

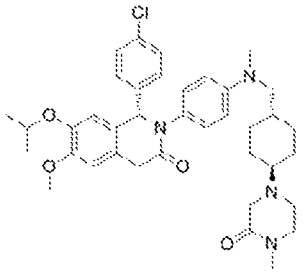
[0129] [(4S,5R)-2-(4-tert-butyl-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethylimidazol-1-yl]-[4-(3-methylsulfonylpropyl)piperazin-1-yl]methanone



CGM097A

[0130] In an embodiment, the MDM2 inhibitor is CGM097A. CGM097A has the chemical structure and name shown as:

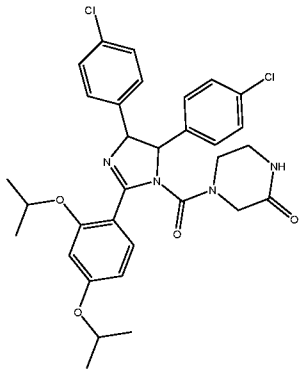
[0131] (1S)-1-(4-chlorophenyl)-6-methoxy-2-[4-[methyl-[[4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl]methyl]amino]phenyl]-7-propan-2-yloxy-1,4-dihydroisoquinolin-3-one



Nutlin-3

[0132] In an embodiment, the MDM2 inhibitor is nutlin-3. Nutlin-3 has the chemical structure and name shown as:

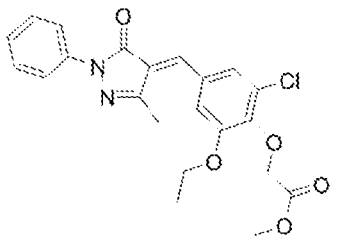
[0133] 4-[4,5-bis(4-chlorophenyl)-2-(4-methoxy-2-propan-2-yloxyphenyl)-4,5-dihydroimidazole-1-carbonyl]piperazin-2-one



SJ-172550

[0134] In an embodiment, the MDM2 inhibitor is SJ-172550. SJ-172550 has the chemical structure and name shown as:

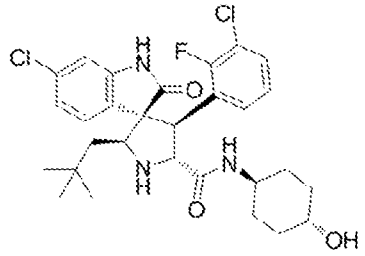
[0135] methyl 2-[2-chloro-6-ethoxy-4-[(3-methyl-5-oxo-1-phenylpyrazol-4-ylidene)methyl]phenoxy]acetate



SAR405838 (MI-77301)

[0136] In an embodiment, the MDM2 inhibitor is SAR405838. SAR405838 has the chemical structure and name shown as:

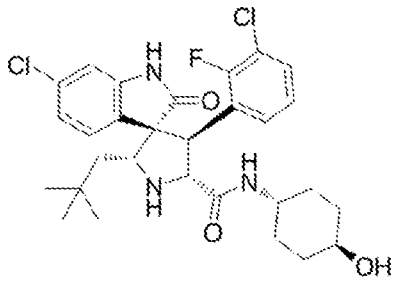
[0137] (2'R,3R,3'S,5'S)-6-chloro-3'-(3-chloro-2-fluorophenyl)-5'-(2,2-dimethylpropyl)-N-(4-hydroxycyclohexyl)-2-oxospiro[1H-indole-3,4'-pyrrolidine]-2'-carboxamide



MI-773

[0138] In an embodiment, the MDM2 inhibitor is MI-773. MI-773 has the chemical structure and name shown as:

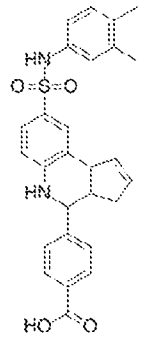
[0139] (2'R,3S,3'S,5'R)-6-chloro-3'-(3-chloro-2-fluorophenyl)-5'-(2,2-dimethylpropyl)-N-(4-hydroxycyclohexyl)-2-oxospiro[1H-indole-3,4'-pyrrolidine]-2'-carboxamide



MX69

[0140] In an embodiment, the MDM2 inhibitor is MX69. MX69 has the chemical structure and name shown as:

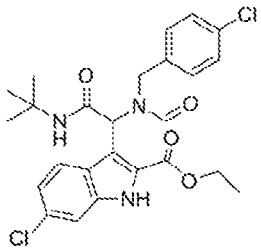
[0141] 4-[8-[(3,4-dimethylphenyl)sulfamoyl]-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolin-4-yl]benzoic acid



YH239-EE

[0142] In an embodiment, the MDM2 inhibitor is YH239-EE. YH239-EE has the chemical structure and name shown as:

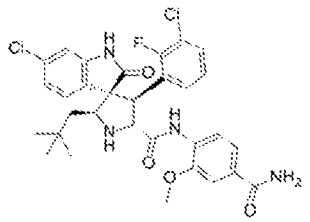
[0143] ethyl 3-[2-(tert-butylamino)-1-[(4-chlorophenyl)methyl-formylamino]-2-oxoethyl]-6-chloro-1H-indole-2-carboxylate



RO8994

[0144] In an embodiment, the MDM2 inhibitor is RO8994. RO8994 has the chemical structure and name shown as:

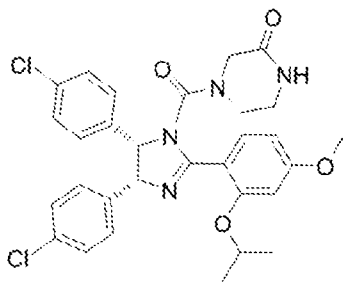
[0145] (2'R,3R,3'S,5'S)-N-(4-carbamoyl-2-methoxyphenyl)-6-chloro-3'-(3-chloro-2-fluorophenyl)-5'-(2,2-dimethylpropyl)-2-oxospiro[1H-indole-3,4'-pyrrolidine]-2'-carboxamide



Nutlin-3b

[0146] In an embodiment, the MDM2 inhibitor is nutlin-3b. Nutlin-3b has the chemical structure and name shown as:

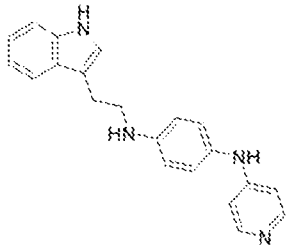
[0147] 4-[(4R,5S)-4,5-bis(4-chlorophenyl)-2-(4-methoxy-2-propan-2-yloxyphenyl)-4,5-dihydroimidazole-1-carbonyl]piperazin-2-one



Serdemetan (JNJ-26854165)

[0148] In an embodiment, the MDM2 inhibitor is Serdemetan. Serdemetan has the chemical structure and name shown as:

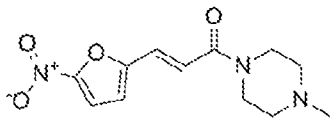
[0149] 1-N-[2-(1H-indol-3-yl)ethyl]-4-N-pyridin-4-ylbenzene-1,4-diamine



NSC59984

[0150] In an embodiment, the MDM2 inhibitor is NSC59984. NSC59984 has the chemical structure and name shown as:

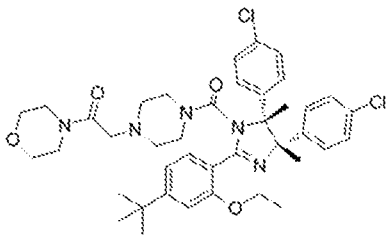
[0151] (E)-1-(4-methylpiperazin-1-yl)-3-(5-nitrofuran-2-yl)prop-2-en-1-one



CHEMBL2386350

[0152] In an embodiment, the MDM2 inhibitor is CHEMBL2386350. CHEMBL2386350 has the chemical structure and name shown as:

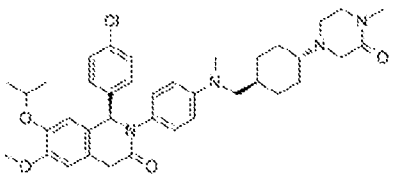
[0153] 2-[4-[(4S,5R)-2-(4-tert-butyl-2-ethoxyphenyl)-4,5-bis(4-chlorophenyl)-4,5-dimethylimidazole-1-carbonyl]piperazin-1-yl]-1-morpholin-4-ylethanone



CGM0970B

[0154] In an embodiment, the MDM2 inhibitor is CGM0970B. CGM0970B has the chemical structure and name shown as:

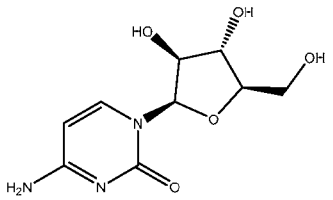
[0155] (1R)-1-(4-chlorophenyl)-6-methoxy-2-[4-[methyl-[[4-(4-methyl-3-oxopiperazin-1-yl)cyclohexyl]methyl]amino]phenyl]-7-propan-2-yloxy-1,4-dihydroisoquinolin-3-one



MK-8242

[0156] In an embodiment, the MDM2 inhibitor is MK-8242. MK-8242 has the chemical structure and name shown as:

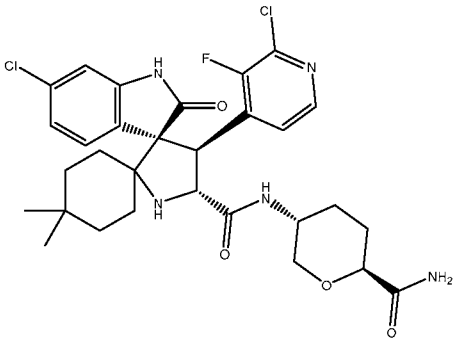
[0157] 4-amino-1-[(2R,3S,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one



DS-3032

[0158] In an embodiment, the MDM2 inhibitor is DS-3032. DS-3032 has the chemical structure and name shown as:

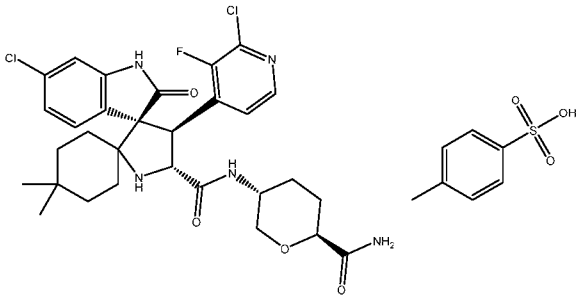
[0159] (3'R,4'S,5'R)-N-((3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl)-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indoline]-5'-carboxamide



DS-3032B

[0160] In an embodiment, the MDM2 inhibitor is DS-3032B. DS-3032B has the chemical structure and name shown as:

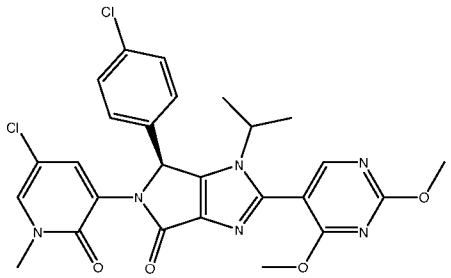
[0161] (3'R,4'S,5'R)-N-((3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl)-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indoline]-5'-carboxamide 4-methylbenzenesulfonate



HDM201

[0162] In an embodiment, the MDM2 inhibitor is HDM201. HDM201 has the chemical structure and name shown as:

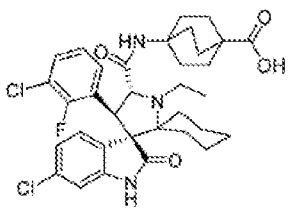
[0163] (4S)-5-(5-chloro-1-methyl-2-oxopyridin-3-yl)-4-(4-chlorophenyl)-2-(2,4-dimethoxypyrimidin-5-yl)-3-propan-2-yl-4H-pyrrolo[3,4-d]imidazol-6-one



APG-115

[0164] In an embodiment, the MDM2 inhibitor is APG-115. APG-115 has the chemical structure and name shown as:

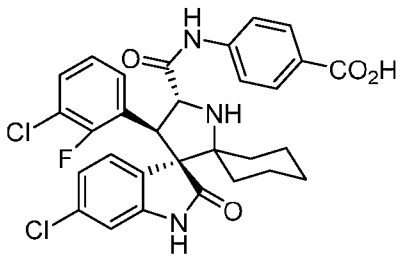
[0165] 4-((3′R,4′S,5′R)-6″-Chloro-4′-(3-chloro-2-fluorophenyl)-1′-ethyl-2″-oxodispiro[cyclohexane-1,2′-pyrrolidine-3′,3″-indoline]-5′-carboxamido)bicyclo[2.2.2]octane-1-carboxylic Acid



MI-1061

[0166] In an embodiment, the MDM2 inhibitor is APG-115. APG-115 has the chemical structure and name shown as:

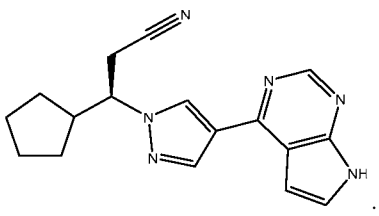
[0167] 4-((3'R,4'S,5'R)-6"-chloro-4'-(3-chloro-2-fluorophenyl)-2"-oxodispiro[cyclohexane-1,2'-pyrrolidine-3',3"-indoline]-5'-carboxamido)benzoic acid



JAK Inhibitor

Ruxolitinib

[0168] In an embodiment, the JAK inhibitor is Ruxolitinib (available from Incyte Corp. and Novartis AG). Ruxolitinib has the chemical structure and name shown as: (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile,



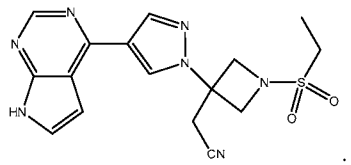
[0169] The preparation of this compound is described in U.S. Patent No. 8,604,043, 7,834,022, 8,486,902, 8,530,485, 7,598,257, 8,541,425, and 8,410,265 the disclosures of which are

incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound selected from the structures disclosed in U.S. Patent No. 8,604,043, 7,834,022, 8,486,902, 8,530,485, 7,598,257, 8,541,425, and 8,410,265, the disclosures of which are incorporated by reference herein.

[0170] In an embodiment, the JAK inhibitor is Ruxolitinib phosphate (available from Incyte Corp. and Novartis AG). In an embodiment, the JAK inhibitor is the phosphate salt of (*R*)-3-(4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-3-cyclopentylpropanenitrile.

Baricitinib

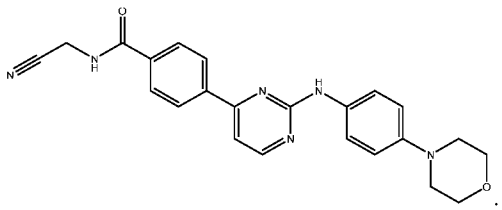
[0171] In an embodiment, the JAK inhibitor is Baricitinib (available from Incyte Corp. and Eli Lilly & Co.). Baricitinib has the chemical structure and name shown as: 2-(3-(4-(7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)-1*H*-pyrazol-1-yl)-1-(ethylsulfonyl)azetidin-3-yl)acetonitrile



[0172] The preparation of this compound is described in U.S. Patent No. 8,158,616 and 8,420,629, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 8,158,616 and 8,420,629, the disclosures of which are incorporated by reference herein.

Momelotinib

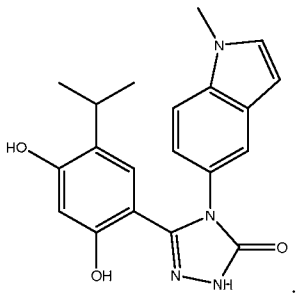
[0173] In an embodiment, the JAK inhibitor is Momelotinib (Gilead Sciences). Momelotinib is also known as CYT-387. Momelotinib has the chemical structure and name shown as: *N*-(cyanomethyl)-4-(2-((4-morpholinophenyl)amino)pyrimidin-4-yl)benzamide



[0174] The preparation of this compound is described in U.S. Patent No. 8,486,941, the disclosure of which is incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 8,486,941, the disclosure of which is incorporated by reference herein.

Ganetespib

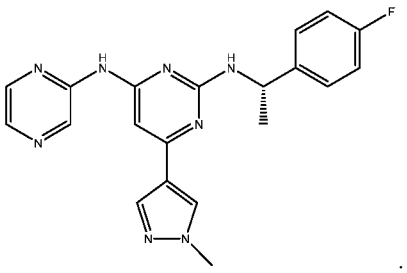
[0175] In an embodiment, the JAK inhibitor is Ganetespib. Ganetespib has the chemical structure and name shown as: 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(1-methyl-1*H*-indol-5-yl)-2,4-dihydro-3*H*-1,2,4-triazol-3-one



[0176] The preparation of this compound is described in U.S. Patent No. 7,825,148 and 8,628,752, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 7,825,148 and 8,628,752, the disclosures of which are incorporated by reference herein.

NS-018

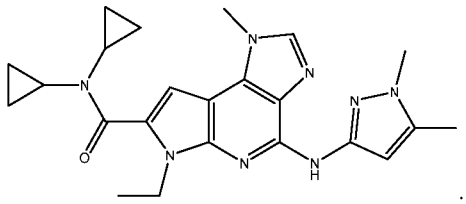
[0177] In an embodiment, the JAK inhibitor is NS-018. NS-018 has the chemical structure and name shown as: (*S*)-N^2-(1-(4-fluorophenyl)ethyl)-6-(1-methyl-1*H*-pyrazol-4-yl)-N^4-(pyrazin-2-yl)pyrimidine-2,4-diamine



[0178] The preparation of this compound is described in U.S. Patent No. 8,673,891 and 8,586,591, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 8,673,891 and 8,586,591, the disclosures of which are incorporated by reference herein.

BMS-911543

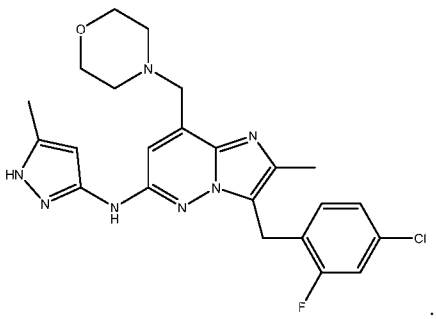
[0179] In an embodiment, the JAK inhibitor is BMS-911543. BMS-911543 has the chemical structure and name shown as: *N*,*N*-dicyclopropyl-4-((1,5-dimethyl-1*H*-pyrazol-3-yl)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine-7-carboxamide



[0180] The preparation of this compound is described in U.S. Patent No. 8,673,933 and 8,202,881, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 8,673,933 and 8,202,881, the disclosures of which are incorporated by reference herein.

Gandotinib (LY2784544)

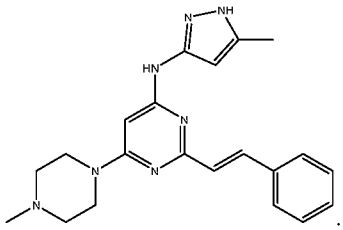
[0181] In an embodiment, the JAK inhibitor is Gandotinib. Gandotinib has the chemical structure and name shown as: 3-(4-chloro-2-fluorobenzyl)-2-methyl-*N*-(5-methyl-1*H*-pyrazol-3-yl)-8-(morpholinomethyl)imidazo[1,2-*b*]pyridazin-6-amine



[0182] The preparation of this compound is described in U.S. Patent No. 7,897,600, the disclosure of which is incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 7,897,600, the disclosure of which is incorporated by reference herein.

ENMD-2076

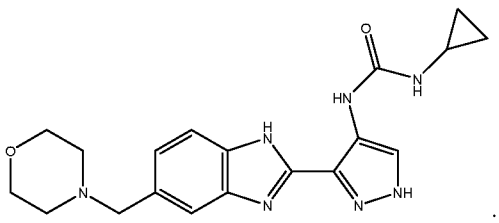
[0183] In an embodiment, the JAK inhibitor is ENMD-2076. ENMD-2076 has the chemical structure and name shown as: (*E*)-*N*-(5-methyl-1*H*-pyrazol-3-yl)-6-(4-methylpiperazin-1-yl)-2-styrylpyrimidin-4-amine



[0184] The preparation of this compound is described in U.S. Patent No. 8,153,630; 7,563,787 and 8,114,870, the disclosures of which are incorporated by reference herein. In an embodiment, the JAK inhibitor is a compound described in U.S. Patent No. 8,153,630; 7,563,787 and 8,114,870, the disclosures of which are incorporated by reference herein.

AT-9283

[0185] In an embodiment, the JAK inhibitor is AT-9283. AT-9283 has the chemical structure and name shown as: 1-cyclopropyl-3-(3-(5-(morpholinomethyl)-1*H*-benzo[*d*]imidazol-2-yl)-1*H*-pyrazol-4-yl)urea

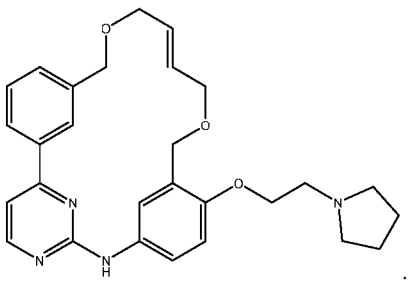


[0186] The preparation of this compound is described in U.S. Patent No. 8,399,442 and 7,977,477, the disclosures of which are incorporated by reference herein. In an embodiment, the

JAK inhibitor is a compound described in U.S. Patent No. 8,399,442 and 7,977,477, the disclosures of which are incorporated by reference herein.

Pacritinib

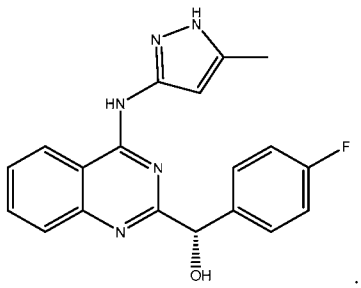
[0187] In an embodiment, the JAK inhibitor is Pacritinib. Pacritinib has the chemical structure and name shown as: 11-(2-pyrrolidin-1-yl-ethoxy)-14,19-dioxa-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene



[0188] In an embodiment, the structure of Pacritinib may be a tautomeric form. The preparation of Pacritinib is described in U.S. Patent No. 8,143,255; 8,153,632 and 8,415,338, the disclosures of which are incorporated by reference herein.

AC-410

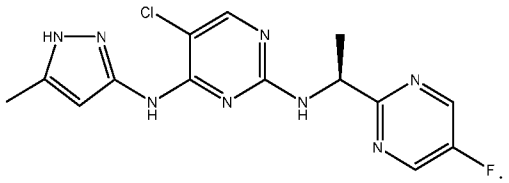
[0189] In an embodiment, the JAK inhibitor is AC-410 (available from Ambit Biosciences). AC-410 has the chemical structure and name shown as: (*S*)-(4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol



[0190] The preparation of racemic (4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol hydrochloride is described in Examples 3 and 12 of U.S. Patent No. 8,349,851, the disclosure of which is incorporated by reference herein.

AZD-1480

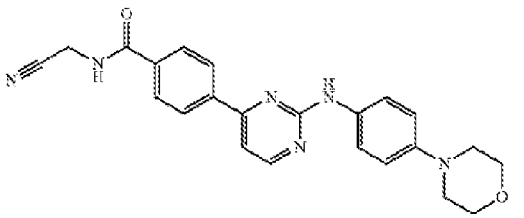
[0191] In an embodiment, the JAK inhibitor is AZD-1480. AZD-1480 has the chemical structure and name shown as: (*S*)-5-chloro-N^2-(1-(5-fluoropyrimidin-2-yl)ethyl)-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine



[0192] The preparation of this compound is described in U.S. Patent No. 8,088,784, the disclosure of which is incorporated by reference herein. In an embodiment, the JAK inhibitor is selected from the compounds described in U.S. Patent No. 8,088,784, the disclosure of which is incorporated by reference herein.

CYT387

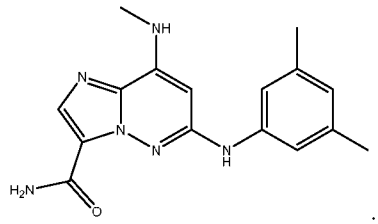
[0193] In an embodiment, the JAK inhibitor is CYT387. CYT387 has the chemical structure and name shown as: N-(cyanomethyl)-4-(2-(4-morpholinophenylamino)pyrimidin-4-yl)benzamide



[0194] The preparation of this compound is described in U.S. Patent No. 9,809,559 and 8,486,941, the disclosures of which are incorporated by reference herein.

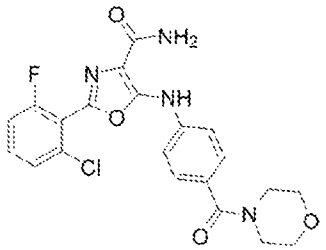
TYK2-IN-2

[0195] In an embodiment, the JAK inhibitor is TYK2-IN-2. TYK2-IN-2 has the chemical structure and name shown as: 6-((3,5-dimethylphenyl)amino)-8-(methylamino)imidazo[1,2-b]pyridazine-3-carboxamide



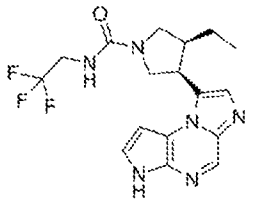
SAR-20347

[0196] In an embodiment, the JAK inhibitor is SAR-20347. SAR-20347 has the chemical structure and name shown as: 2-(2-chloro-6-fluorophenyl)-5-[4-(morpholine-4-carbonyl)anilino]-1,3-oxazole-4-carboxamide



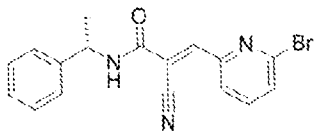
Upadacitinib (ABT-494)

[0197] In an embodiment, the JAK inhibitor is Upadacitinib (ABT-494). Upadacitinib has the chemical structure and name shown as: (3S,4R)-3-ethyl-4-(3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-yl)-N-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide



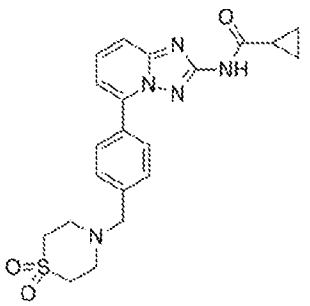
WP1066

[0198] In an embodiment, the JAK inhibitor is WP1066. WP1066 has the chemical structure and name shown as: (E)-3-(6-bromopyridin-2-yl)-2-cyano-N-[(1S)-1-phenylethyl]prop-2-enamide



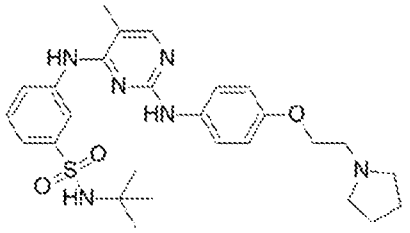
GLPG0634 (Filgotinib)

[0199] In an embodiment, the JAK inhibitor is GLPG0634 (Filgotinib). GLPG0634 has the chemical structure and name shown as: N-[5-[4-[(1,1-dioxo-1,4-thiazinan-4-yl)methyl]phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide



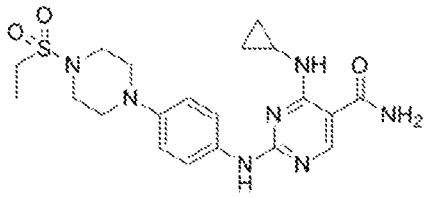
TG101348 (Fedratinib; SAR 302503)

[0200] In an embodiment, the JAK inhibitor is TG101348 (Fedratinib; SAR 302503). TG101348 has the chemical structure and name shown as: N-tert-butyl-3-[[5-methyl-2-[4-(2-pyrrolidin-1-ylethoxy)anilino]pyrimidin-4-yl]amino]benzenesulfonamide



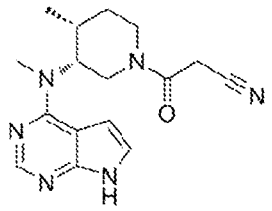
Cerdulatinib (PRT062070; PRT2070)

[0201] In an embodiment, the JAK inhibitor is Cerdulatinib (PRT062070; PRT2070). Cerdulatinib has the chemical structure and name shown as: 4-(cyclopropylamino)-2-[4-(4-ethylsulfonylpiperazin-1-yl)anilino]pyrimidine-5-carboxamide



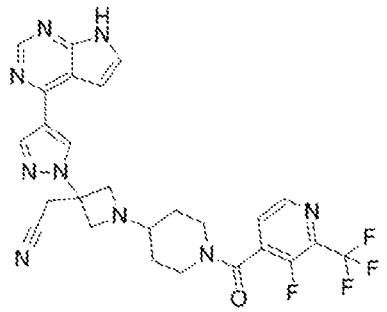
Tofacitinib

[0202] In an embodiment, the JAK inhibitor is Tofacitinib. Tofacitinib has the chemical structure and name shown as: 3-[(3R,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile



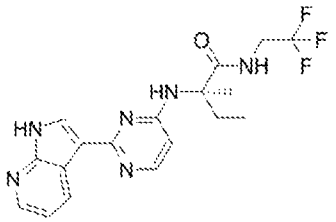
Itacitinib

In an embodiment, the JAK inhibitor is Itacitinib. Itacitinib has the chemical structure and name shown as: 2-[1-[1-[3-fluoro-2-(trifluoromethyl)pyridine-4-carbonyl]piperidin-4-yl]-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]azetidin-3-yl]acetonitrile



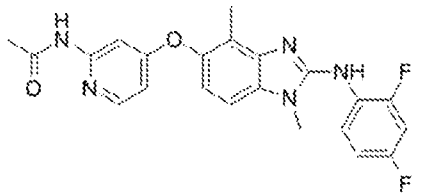
Decernotinib

In an embodiment, the JAK inhibitor is Decernotinib. Decernotinib has the chemical structure and name shown as: (2R)-2-methyl-2-[[2-(1H-pyrrolo[2,3-b]pyridin-3-yl)pyrimidin-4-yl]amino]-N-(2,2,2-trifluoroethyl)butanamide



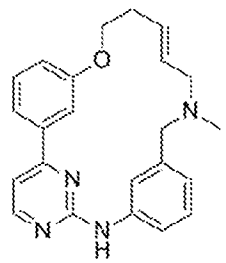
CHZ868

[0203] In an embodiment, the JAK inhibitor is CHZ868. CHZ868 has the chemical structure and name shown as: N-[4-[2-(2,4-difluoroanilino)-1,4-dimethylbenzimidazol-5-yl]oxypyridin-2-yl]acetamide



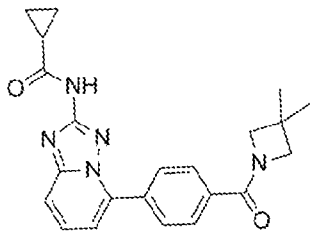
SB1317

[0204] In an embodiment, the JAK inhibitor is SB1317. SB1317 has the chemical structure and name shown as: (E)-6-methyl-12-oxa-3,6-diaza-2(4,2)-pyrimidina-1,4(1,3)-dibenzenacyclododecaphan-8-ene



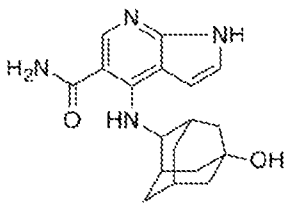
Solcitinib

[0205] In an embodiment, the JAK inhibitor is Solcitinib. Solcitinib has the chemical structure and name shown as: N-[5-[4-(3,3-dimethylazetidine-1-carbonyl)phenyl]-[1,2,4]triazolo[1,5-a]pyridin-2-yl]cyclopropanecarboxamide



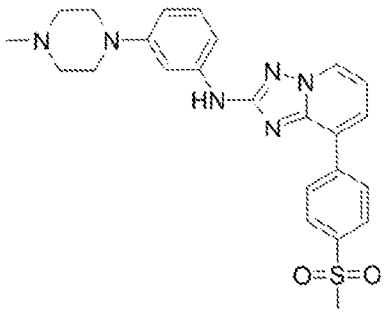
Peficitinib

[0206] In an embodiment, the JAK inhibitor is Peficitinib. Peficitinib has the chemical structure and name shown as: 4-[[(1R,3S)-5-hydroxy-2-adamantyl]amino]-1H-pyrrolo[2,3-b]pyridine-5-carboxamide



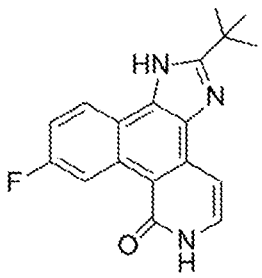
CEP-33779

[0207] In an embodiment, the JAK inhibitor is CEP-33779. CEP-33779 has the chemical structure and name shown as: N-[3-(4-methylpiperazin-1-yl)phenyl]-8-(4-methylsulfonylphenyl)-[1,2,4]triazolo[1,5-a]pyridin-2-amine



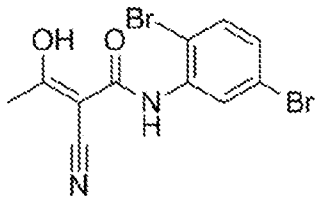
Pyridone 6

[0208] In an embodiment, the JAK inhibitor is Pyridone 6. Pyridone 6 has the chemical structure and name shown as: 2-(tert-butyl)-9-fluoro-3H-benzo[h]imidazo[4,5-f]isoquinolin-7-ol



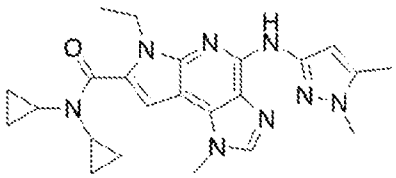
LFM-A13

[0209] In an embodiment, the JAK inhibitor is LFM-A13. LFM-A13 has the chemical structure and name shown as: (Z)-2-cyano-N-(2,5-dibromophenyl)-3-hydroxybut-2-enamide



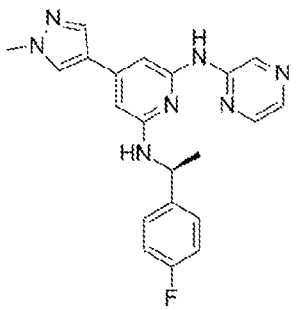
BMS-911543

[0210] In an embodiment, the JAK inhibitor is BMS-911543. BMS-911543 has the chemical structure and name shown as: (Z)-N,N-dicyclopropyl-4-((1,5-dimethyl-1,2-dihydro-3H-pyrazol-3-ylidene)amino)-6-ethyl-1-methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide



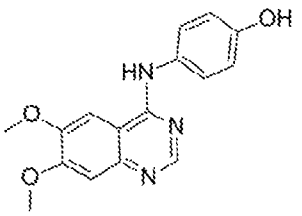
NS-018

[0211] In an embodiment, the JAK inhibitor is NS-018. NS-018 has the chemical structure and name shown as: 6-N-[(1S)-1-(4-fluorophenyl)ethyl]-4-(1-methylpyrazol-4-yl)-2-N-pyrazin-2-ylpyridine-2,6-diamine



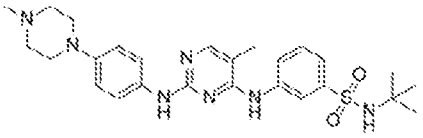
JANEX-1

[0212] In an embodiment, the JAK inhibitor is JANEX-1. JANEX-1 has the chemical structure and name shown as: 4-[(6,7-dimethoxyquinazolin-4-yl)amino]phenol



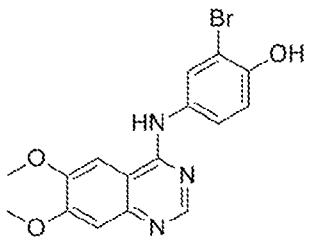
TG101209

[0213] In an embodiment, the JAK inhibitor is TG101209. TG101209 has the chemical structure and name shown as: N-tert-butyl-3-[[5-methyl-2-[4-(4-methylpiperazin-1-yl)anilino]pyrimidin-4-yl]amino]benzenesulfonamide



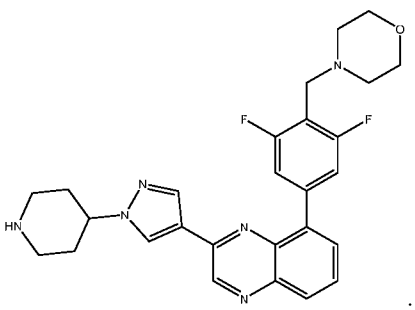
WHI-P154

[0214] In an embodiment, the JAK inhibitor is WHI-P154. WHI-P154 has the chemical structure and name shown as: 2-bromo-4-[(6,7-dimethoxyquinazolin-4-yl)amino]phenol



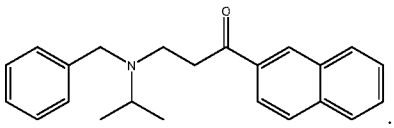
NVP-BSK805

[0215] In an embodiment, the JAK inhibitor is NVP-BSK805. NVP-BSK805 has the chemical structure and name shown as: 4-[[2,6-difluoro-4-[3-(1-piperidin-4-ylpyrazol-4-yl)quinoxalin-5-yl]phenyl]methyl]morpholine



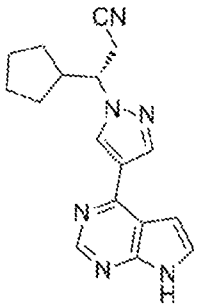
ZM39923

[0216] In an embodiment, the JAK inhibitor is ZM39923. ZM39923 has the chemical structure and name shown as: 3-[benzyl(propan-2-yl)amino]-1-naphthalen-2-ylpropan-1-one



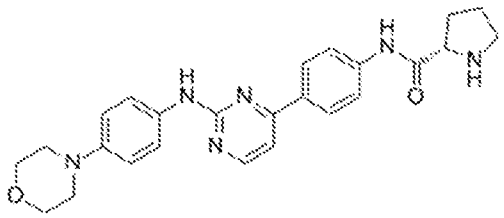
Ruxolitinib-S

[0217] In an embodiment, the JAK inhibitor is Ruxolitinib-S. Ruxolitinib-S has the chemical structure and name shown as: (3S)-3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)pyrazol-1-yl]propanenitrile



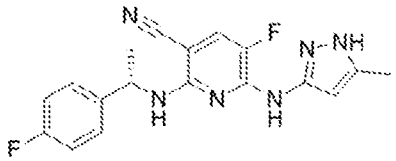
XL019

[0218] In an embodiment, the JAK inhibitor is XL019. XL019 has the chemical structure and name shown as: (2S)-N-[4-[2-(4-morpholin-4-ylanilino)pyrimidin-4-yl]phenyl]pyrrolidine-2-carboxamide



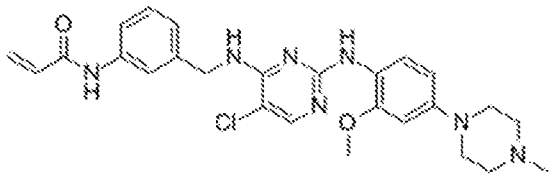
AZ960

[0219] In an embodiment, the JAK inhibitor is AZ960. AZ960 has the chemical structure and name shown as: 5-fluoro-2-[[(1S)-1-(4-fluorophenyl)ethyl]amino]-6-[(5-methyl-1H-pyrazol-3-yl)amino]pyridine-3-carbonitrile



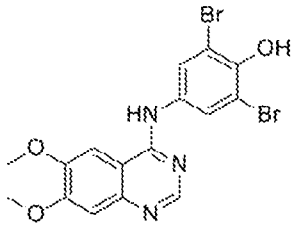
JAK3-IN-1

[0220] In an embodiment, the JAK inhibitor is JAK3-IN-1. JAK3-IN-1 has the chemical structure and name shown as: N-[3-[[[5-chloro-2-[2-methoxy-4-(4-methylpiperazin-1-yl)anilino]pyrimidin-4-yl]amino]methyl]phenyl]prop-2-enamide



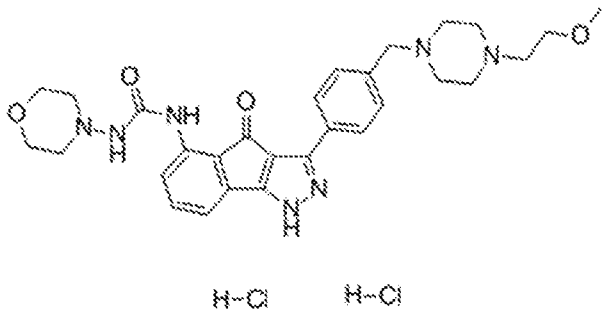
WHI-P97

[0221] In an embodiment, the JAK inhibitor is WHI-P97. WHI-P97 has the chemical structure and name shown as: 2,6-dibromo-4-[(6,7-dimethoxyquinazolin-4-yl)amino]phenol



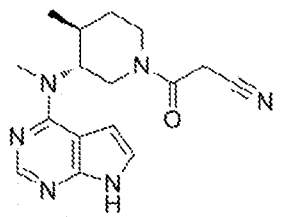
RGB-286638

[0222] In an embodiment, the JAK inhibitor is RGB-286638. RGB-286638 has the chemical structure and name shown as: 1-[3-[4-[[4-(2-methoxyethyl)piperazin-1-yl]methyl]phenyl]-4-oxo-1H-indeno[1,2-c]pyrazol-5-yl]-3-morpholin-4-ylurea;dihydrochloride



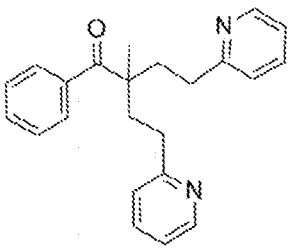
Tofacitinib(3R,4S)

[0223] In an embodiment, the JAK inhibitor is Tofacitinib(3R,4S). Tofacitinib(3R,4S) has the chemical structure and name shown as: 3-[(3R,4S)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile



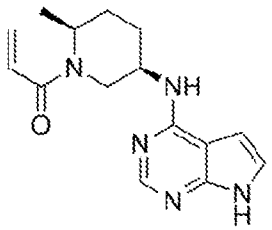
NSC42834

[0224] In an embodiment, the JAK inhibitor is NSC42834. NSC42834 has the chemical structure and name shown as: 2-methyl-1-phenyl-4-pyridin-2-yl-2-(2-pyridin-2-ylethyl)butan-1-one



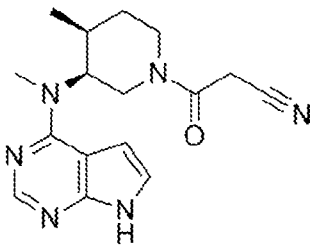
PF-06651600

[0225] In an embodiment, the JAK inhibitor is PF-06651600. PF-06651600 has the chemical structure and name shown as: benzyl 2-(hydroxymethyl)-5-[(2-methylpropan-2-yl)oxycarbonylamino]piperidine-1-carboxylate



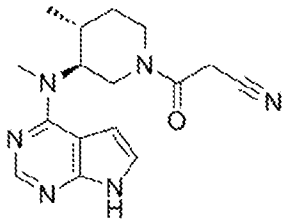
Tofacitinib(3S,4S)

[0226] In an embodiment, the JAK inhibitor is Tofacitinib(3S,4S). Tofacitinib(3S,4S) has the chemical structure and name shown as: 3-[(3S,4S)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile



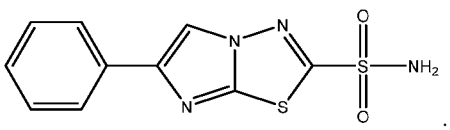
Tofacitinib(3S,4R)

[0227] In an embodiment, the JAK inhibitor is Tofacitinib(3S,4R). Tofacitinib(3S,4R) has the chemical structure and name shown as: 3-[(3S,4R)-4-methyl-3-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]piperidin-1-yl]-3-oxopropanenitrile



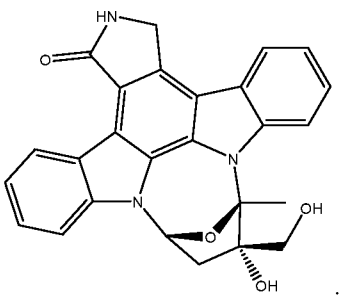
AEG3482

[0228] In an embodiment, the JAK inhibitor is AEG3482. AEG3482 has the chemical structure and name shown as: 6-phenylimidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide



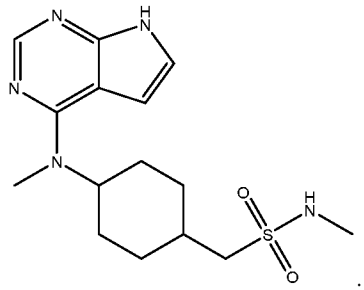
Lestaurtinib (CEP-701)

[0229] In an embodiment, the JAK inhibitor is Lestaurtinib (CEP-701). Lestaurtinib has the chemical structure and name shown as: (5R,7S,8S)-7-hydroxy-7-(hydroxymethyl)-8-methyl-5,6,7,8,13,14-hexahydro-15H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[b,h]cycloocta[jkl]cyclopenta[e]-as-indacen-15-one

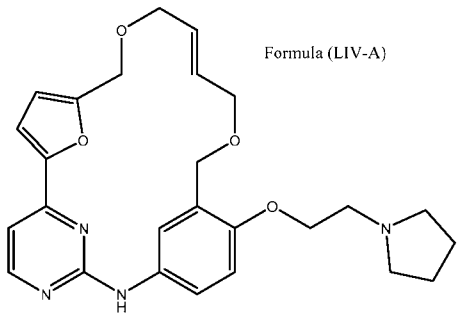


Oclacitinib

[0230] In an embodiment, the JAK inhibitor is Oclacitinib. Oclacitinib has the chemical structure and name shown as: N-methyl-1-[4-[methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclohexyl]methanesulfonamide



[0231] In an embodiment, the JAK inhibitor is (*E*)-4-(2-(pyrrolidin-1-yl)ethoxy)-6,11-dioxa-3-aza-2(4,2)-pyrimidina-1(2,5)-furana-4(1,3)-benzenacyclododecaphan-8-ene. In an embodiment, the JAK inhibitor is (9E)-15-(2-(pyrrolidin-1-yl)ethoxy)-7,12,25-trioxa-19,21,24-triaza-tetracyclo[18.3.1.1(2,5).1(14,18)]hexacosa-1(24),2,4,9,14(26),15,17,20,22-nonaene. In an embodiment, the JAK inhibitor is a compound of Formula (LIV-A):



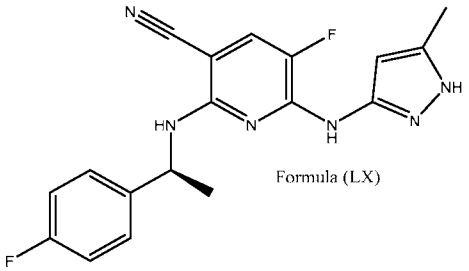
Formula (LIV-A)

or a pharmaceutically acceptable salt thereof. The preparation and properties of this JAK inhibitor are known to those of ordinary skill in the art, and for example are described in: Madan (2012) J. Immunol. 189, 4123-4134 and William (2012) J. Med. Chem. 55, 2623-2640.

[0232] In an embodiment, the JAK inhibitor is (*R*)-(4-fluorophenyl)(4-((5-methyl-1*H*-pyrazol-3-yl)amino)quinazolin-2-yl)methanol, which is also known in the art to be active as a JAK inhibitor. In an embodiment, the JAK inhibitor is racemic (4-fluorophenyl)(4-((5-methyl-1*H*-

pyrazol-3-yl)amino)quinazolin-2-yl)methanol, which is also known in the art to be active as a JAK inhibitor.

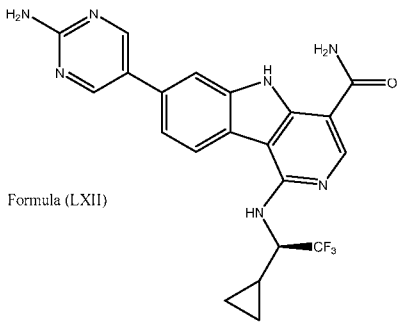
[0233] In an embodiment, the JAK inhibitor is (*S*)-5-fluoro-2-((1-(4-fluorophenyl)ethyl)amino)-6-((5-methyl-1*H*-pyrazol-3-yl)amino)nicotinonitrile. In an embodiment, the JAK inhibitor is a compound of Formula (LX):



Formula (LX)

or a pharmaceutically acceptable salt thereof. The preparation of this compound is described in U.S. Patent No. 8,324,252, the disclosure of which is incorporated by reference herein. In an embodiment, the JAK inhibitor is selected from the compounds described in U.S. Patent No. 8,324,252, the disclosure of which is incorporated by reference herein.

[0234] In an embodiment, the JAK inhibitor is ((*R*)-7-(2-aminopyrimidin-5-yl)-1-((1-cyclopropyl-2,2,2-trifluoroethyl)amino)-5*H*-pyrido[4,3-*b*]indole-4-carboxamide, which is also named 7-(2-aminopyrimidin-5-yl)-1-{[(1*R*)-1-cyclopropyl-2,2,2-trifluoroethyl]amino}-5*H*-pyrido[4,3-*b*]indole-4-carboxamide. In an embodiment, the JAK inhibitor is a compound of Formula (LXII):



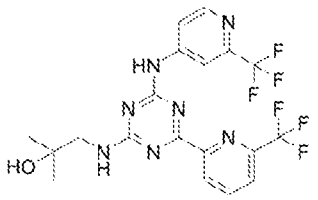
Formula (LXII)

or a pharmaceutically acceptable salt thereof. The preparation of this compound is known to those of ordinary skill in the art, and is described in Lim (2011) J. Med. Chem. *54,* 7334-7349, the disclosure of which is incorporated by reference herein.

IDH Inhibitors

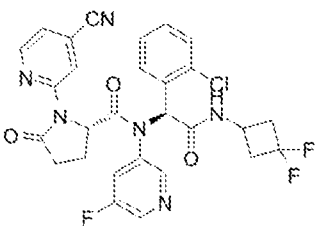
Enasidenib

[0235] In an embodiment, the IDH inhibitor is Enasidenib. Enasidenib has the chemical structure and name shown as: 2-methyl-1-[[4-[6-(trifluoromethyl)pyridin-2-yl]-6-[[2-(trifluoromethyl)pyridin-4-yl]amino]-1,3,5-triazin-2-yl]amino]propan-2-ol



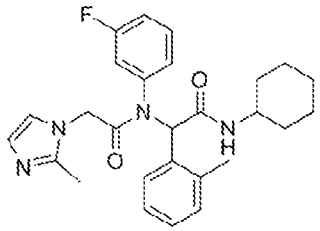
Ivosidenib (AG-120)

[0236] In an embodiment, the IDH inhibitor is Ivosidenib. Ivosidenib has the chemical structure and name shown as: (2S)-N-[(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl]-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide



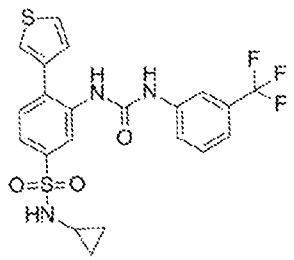
AGI-5198 (IDH-C35)

[0237] In an embodiment, the IDH inhibitor is AGI-5198. AGI-5198 has the chemical structure and name shown as: N-cyclohexyl-2-(3-fluoro-N-[2-(2-methylimidazol-1-yl)acetyl]anilino)-2-(2-methylphenyl)acetamide



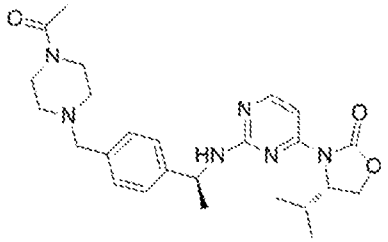
AGI-6780

[0238] In an embodiment, the IDH inhibitor is AGI-6780. AGI-6780 has the chemical structure and name shown as: 1-[5-(cyclopropylsulfamoyl)-2-thiophen-3-ylphenyl]-3-[3-(trifluoromethyl)phenyl]urea



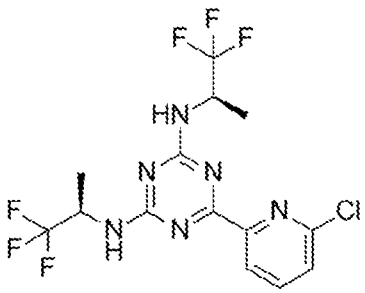
CHEMBL3682093

[0239] In an embodiment, the IDH inhibitor is CHEMBL3682093. CHEMBL3682093 has the chemical structure and name shown as: (4S)-3-[2-[[(1S)-1-[4-[(4-acetylpiperazin-1-yl)methyl]phenyl]ethyl]amino]pyrimidin-4-yl]-4-propan-2-yl-1,3-oxazolidin-2-one



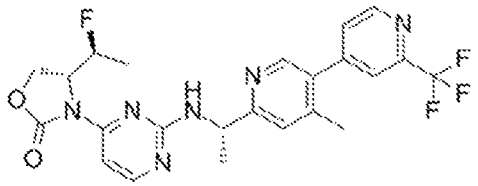
Vorasidenib (AG-881)

[0240] In an embodiment, the IDH inhibitor is Vorasidenib. Vorasidenib has the chemical structure and name shown as: 6-(6-chloropyridin-2-yl)-2-N,4-N-bis[(2R)-1,1,1-trifluoropropan-2-yl]-1,3,5-triazine-2,4-diamine



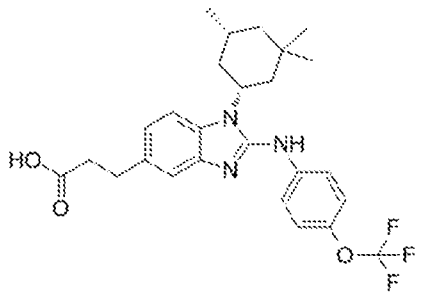
IDH-305

[0241] In an embodiment, the IDH inhibitor is IDH-305. IDH-305 has the chemical structure and name shown as: (4R)-4-[(1S)-1-fluoroethyl]-3-[2-[[(1S)-1-[4-methyl-5-[2-(trifluoromethyl)pyridin-4-yl]pyridin-2-yl]ethyl]amino]pyrimidin-4-yl]-1,3-oxazolidin-2-one



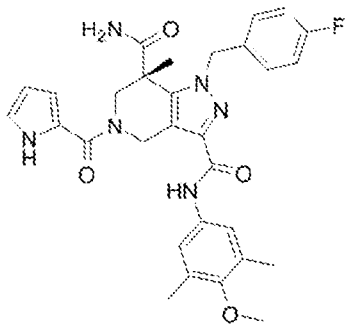
BAY-1436032

[0242] In an embodiment, the IDH inhibitor is BAY-1436032. BAY-1436032 has the chemical structure and name shown as: 3-[2-[4-(trifluoromethoxy)anilino]-1-[(1R,5R)-3,3,5-trimethylcyclohexyl]benzimidazol-5-yl]propanoic acid



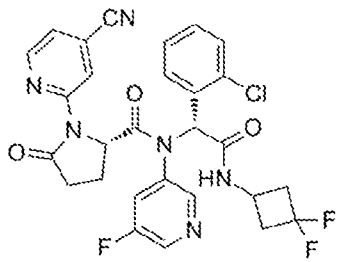
GSK864

[0243] In an embodiment, the IDH inhibitor is GSK864. GSK864 has the chemical structure and name shown as: (7S)-1-[(4-fluorophenyl)methyl]-3-N-(4-methoxy-3,5-dimethylphenyl)-7-methyl-5-(1H-pyrrole-2-carbonyl)-4,6-dihydropyrazolo[4,3-c]pyridine-3,7-dicarboxamide



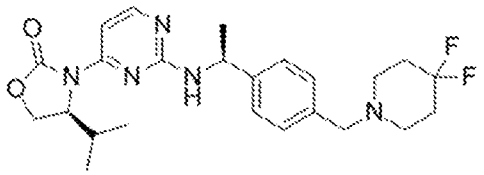
(R,S)-Ivosidenib

[0244] In an embodiment, the IDH inhibitor is (R,S)-Ivosidenib. (R,S)-Ivosidenib has the chemical structure and name shown as: (2R)-N-[(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl]-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide



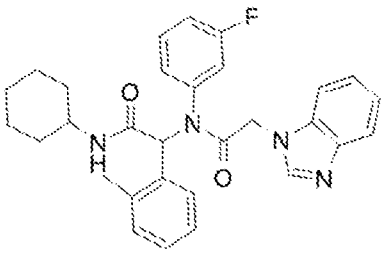
IDH1-IN-2

[0245] In an embodiment, the IDH inhibitor is IDH1-IN-2. IDH1-IN-2 has the chemical structure and name shown as: (4S)-3-[2-[[(1S)-1-[4-[(4,4-difluoropiperidin-1-yl)methyl]phenyl]ethyl]amino]pyrimidin-4-yl]-4-propan-2-yl-1,3-oxazolidin-2-one



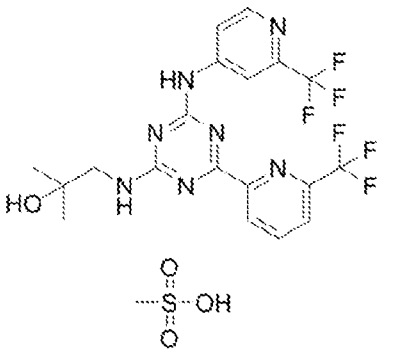
IDH1-IN-1

[0246] In an embodiment, the IDH inhibitor is IDH1-IN-1. IDH1-IN-1 has the chemical structure and name shown as: 2-(N-[2-(benzimidazol-1-yl)acetyl]-3-fluoroanilino)-N-cyclohexyl-2-(2-methylphenyl)acetamide



Enasidenib mesylate

[0247] In an embodiment, the IDH inhibitor is Enasidenib mesylate. Enasidenib mesylate has the chemical structure and name shown as: 2-methyl-1-[[4-[6-(trifluoromethyl)pyridin-2-yl]-6-[[2-(trifluoromethyl)pyridin-4-yl]amino]-1,3,5-triazin-2-yl]amino]propan-2-ol methanesulfonic acid



PD-1 Inhibitors

[0248] The PD-1 inhibitor may be any PD-1 inhibitor or PD-1 blocker known in the art. In particular, it is one of the PD-1 inhibitors or blockers described in more detail in the following paragraphs. The terms "inhibitor" and "blocker" are used interchangeably herein in reference to PD-1 inhibitors. For avoidance of doubt, references herein to a PD-1 inhibitor that is an antibody may refer to a compound or antigen-binding fragments, variants, conjugates, or biosimilars thereof. For avoidance of doubt, references herein to a PD-1 inhibitor may also refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

[0249] In some embodiments, the compositions and methods described include a PD-1 inhibitor. In some embodiments, the PD-1 inhibitor is a small molecule. In a preferred embodiment, the PD-1 inhibitor is an antibody, a fragment thereof, including Fab fragments, or a single-chain variable fragment (scFv). In some embodiments the PD-1 inhibitor is a polyclonal antibody. In a preferred embodiment, the PD-1 inhibitor is a monoclonal antibody. In some embodiments, the PD-1 inhibitor competes for binding with PD-1, and/or binds to an epitope on PD-1. In an embodiment, the antibody competes for binding with PD-1, and/or binds to an epitope on PD-1. In some embodiments, the PD-1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition

or a method and is further combined with a BTK inhibitor and/or a JAK-2 inhibitor. In some embodiments, a PD-1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, a PD-1 inhibitor is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, a PD-1 inhibitor is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, an anti-PD-1 monoclonal antibody is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, the compositions described herein provide a combination of a PD-1 inhibitor with a BTK inhibitor, or methods of using a combination of a PD-1 inhibitor with a BTK inhibitor. In some embodiments, the PD-1 inhibitors provided herein are selective for PD-1, in that the compounds bind or interact with PD-1 at substantially lower concentrations than they bind or interact with other receptors.

[0250] In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds human PD-1 with a K_D of about 100 pM or lower, binds human PD-1 with a K_D of about 90 pM or lower, binds human PD-1 with a K_D of about 80 pM or lower, binds human PD-1 with a K_D of about 70 pM or lower, binds human PD-1 with a K_D of about 60 pM or lower, binds human PD-1 with a K_D of about 50 pM or lower, binds human PD-1 with a K_D of about 40 pM or lower, or binds human PD-1 with a K_D of about 30 pM or lower.

[0251] In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds to human PD-1 with a k_{assoc} of about 7.5×10^5 l/M·s or faster, binds to human PD-1 with a k_{assoc} of about 7.5×10^5 l/M·s or faster, binds to human PD-1 with a k_{assoc} of about 8×10^5 l/M·s or faster, binds to human PD-1 with a k_{assoc} of about 8.5×10^5 l/M·s or faster, binds to human PD-1 with a k_{assoc} of about 9×10^5 l/M·s or faster, binds to human PD-1 with a k_{assoc} of about 9.5×10^5 l/M·s or faster, or binds to human PD-1 with a k_{assoc} of about 1×10^6 l/M·s or faster.

[0252] In some embodiments, the compositions and methods described include a PD-1 inhibitor that binds to human PD-1 with a k_{dissoc} of about 2×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.1×10^{-5} l/s or slower , binds to human PD-1 with a k_{dissoc} of about 2.2×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.3×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.4×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.5×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.6×10^{-5} l/s or slower or binds to human PD-1 with a k_{dissoc} of about 2.7×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.8×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.9×10^{-5} l/s or slower, or binds to human PD-1 with a k_{dissoc} of about 3×10^{-5} l/s or slower.

[0253] In some embodiments, the compositions and methods described include a PD-1 inhibitor that blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 10 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 9 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 8 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 7 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 6 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 5 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 4 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 3 nM or lower, blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 2 nM or lower, or blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 1 nM or lower.

[0254] In an embodiment, an anti-PD-1 antibody comprises nivolumab, produced by Bristol-Myers Squibb Co., or antigen-binding fragments, conjugates, or variants thereof. Nivolumab is referred to as 5C4 in International Patent Publication No. WO 2006/121168. Nivolumab is assigned CAS registry number 946414-94-4 and is also known to those of ordinary skill in the art as BMS-936558, MDX-1106 or ONO-4538. Nivolumab is a fully human IgG4 antibody blocking the PD-1 receptor. The clinical safety and efficacy of nivolumab in various forms of cancer has been described in Wang, *Cancer Immunol Res.* **2014,** 2, 846-56; Page, *Ann. Rev.*

Med., **2014,** *65,* 185-202; and Weber, *J. Clin. Oncology*, **2013,** *31,* 4311-4318. The nivolumab monoclonal antibody includes a heavy chain given by SEQ ID NO:1 and a light chain given by SEQ ID NO:2. In an embodiment, the anti-PD-1 antibody is an immunoglobulin G4 kappa, anti-(human CD274) antibody. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively, or antigen binding fragments, Fab fragments, single-chain variable fragments (scFv), variants, or conjugates thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:1 and SEQ ID NO:2, respectively.

[0255] In other embodiments, the anti-PD-1 antibody comprises the heavy and light chain CDRs or VRs of nivolumab. In one embodiment, the antibody V_H region comprises the sequence shown in SEQ ID NO: 3, and the antibody V_L region comprises the sequence shown in SEQ ID NO:4. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:3 and SEQ ID NO:4,

respectively. In an alternative embodiment, the antibody comprises V_H and/or V_L regions having the amino acid sequences set forth in SEQ ID NO:3 and/or SEQ ID NO:4, respectively.

[0256] In another embodiment, the anti-PD-1 antibody comprises the heavy chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively, or conservative amino acid substitutions thereof, and the light chain CDR1, CDR2 and CDR3 domains having the sequences set forth in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively, or conservative amino acid substitutions thereof.

[0257] In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 95% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 94% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 90% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 88% identical to the sequences shown in SEQ ID NO:5, SEQ ID NO:6, and SEQ ID NO:7, respectively. In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as the aforementioned antibodies.

[0258] In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 95% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 91% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 90% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In an embodiment, an anti-PD-1 antibody comprises CDR1, CDR2 and CDR3 domains that are each at least 85% identical to the sequences shown in SEQ ID NO:8, SEQ ID NO:9, and SEQ ID NO:10, respectively. In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as the aforementioned antibodies.

[0259] In an embodiment, the anti-PD-1 antibody is an antibody disclosed and/or prepared according to U.S. Patent No. 8,008,449 or U.S. Patent Application Publication Nos. 2009/0217401 A1 or 2013/0133091 A1, the disclosures of which are specifically incorporated by reference herein. For example, in an embodiment, the monoclonal antibody includes 5C4 (referred to herein as nivolumab), 17D8, 2D3, 4H1, 4A11, 7D3, and 5F4, described in U.S. Patent No. 8,008,449, the disclosures of which are hereby incorporated by reference. The PD-1 antibodies 17D8, 2D3, 4H1, 5C4, and 4A11, are all directed against human PD-1, bind specifically to PD-1 and do not bind to other members of the CD28 family. The sequences and CDR regions for these antibodies are provided in U.S. Patent No. 8,008,449, in particular Figure 1 through Figure 12; all of which are incorporated by reference herein in their entireties.

[0260] The anti-PD-1 antibody nivolumab may be prepared by the following procedure, as described in U.S. Patent No. 8,008,449. The antibody nivolumab may be produced in this manner, or by other known means given the disclosure of the amino acid sequences herein.

[0261] In another embodiment, the anti-PD-1 antibody comprises pembrolizumab, which is commercially available from Merck, or antigen-binding fragments, conjugates, or variants thereof. Pembrolizumab is referred to as h409A11 in International Patent Publication No. WO 2008/156712 A1, U.S. Patent No. 8,354,509 and U.S. Patent Application Publication Nos. US 2010/0266617 A1, US 2013/0108651 A1, and US 2013/0109843 A2. Pembrolizumab has an immunoglobulin G4, anti-(human protein PDCD1 (programmed cell death 1)) (human-Mus musculus monoclonal heavy chain), disulfide with human-Mus musculus monoclonal light chain, dimer structure. The structure of pembrolizumab may also be described as immunoglobulin G4, anti-(human programmed cell death 1); humanized mouse monoclonal [228-L-proline(H10-S>P)]γ4 heavy chain (134-218')-disulfide with humanized mouse monoclonal κ light chain dimer (226-226'':229-229'')-bisdisulfide. Pembrolizumab is assigned CAS registry number 1374853-91-4 and is also known as lambrolizumab, MK-3475, and SCH-900475. The clinical safety and efficacy of pembrolizumab in various forms of cancer is described in Fuerst, *Oncology Times,* **2014,** *36,* 35-36; Robert, *Lancet,* **2014,** *384,* 1109-17; and Thomas, *Exp. Opin. Biol. Ther.*, **2014,** *14,* 1061-1064. In an embodiment, the pembrolizumab monoclonal antibody includes a heavy chain given by SEQ ID NO:12 and a light chain given by SEQ ID NO:14, and also shown below with disulfide and glycosylation information:

Heavy chain

QVQLVQSGVEVKKPGASVKVSCKASGYTFTNYYMYWVRQAPGQGLEWMGG 50
INPSNGGTNFNEKFKNRVTLTTDSSTTTAYMELKSLQFDDTAVYYCARRD 100
YRFDMGFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVK 150
DYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTKT 200
YTCNVDHKPSNTKVDKRVESKYGPPCPPCPAPEFLGGPSVFLFPPKPKDT 250
LMISRTPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTY 300
RVVSVLTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVYT 350
LPPSQEEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS 400
DGSFFLYSRLTVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK 447

Light chain

EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRL 50′
LIYLASYLESGVPARFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPL 100′
TFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKV 150′
QWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEV 200′
THQGLSSPVTKSFNRGEC 218′

Disulfide bridges

22-96	22′′-96′′	23′-92′	23′′′-92′′′
134-218′	134′′-218′′′	138′-198′	138′′′-198′′′
147-203	147′′-203′′	226-226′′	229-229′′
261-321	261′′-321′′	367-425	367′′-425′′

Glycosylation sites (N)

Asn-297

[0262] In an embodiment, an anti-PD-1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises

heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:12 and SEQ ID NO:14, respectively, or antigen binding fragments and variants thereof.

[0263] In other embodiments, the anti-PD-1 antibody comprises the heavy and light chain CDRs or VRs of pembrolizumab. In an embodiment, the antibody V_H region comprises the sequence of residues 20 to 446 of SEQ ID NO:11, and the antibody V_L region comprises the sequence shown in SEQ ID NO:14. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 99% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 98% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 97% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 96% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively. In an embodiment, an anti-PD-1 antibody comprises V_H and V_L regions that are each at least 95% identical to the sequences of residues 20 to 446 of SEQ ID NO:11 and the sequence shown in SEQ ID NO:14, respectively.

[0264] In an embodiment, the anti-PD-1 antibody comprises a heavy chain comprising amino acid residues 20 to 446 of SEQ ID NO:11 and a light chain comprising amino acid residues of 20-237 of SEQ ID NO:13.

[0265] In an embodiment, the anti-PD-1 antibody is an isolated antibody or antibody fragment which binds to human PD-1 comprising three light chain CDRs of SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, or conservative amino acid substitutions thereof, and three heavy

chain CDRs of SEQ ID NO:18, SEQ ID NO:19 and SEQ ID NO:20, or conservative amino acid substitutions thereof.

[0266] In an embodiment, an anti-PD-1 antibody comprises a heavy chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 95% identical to the sequences shown in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively. In an embodiment, an anti-PD-1 antibody comprises a heavy chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 90% identical to the sequences shown in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively. In an embodiment, an anti-PD-1 antibody comprises a heavy chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 85% identical to the sequences shown in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively. In an embodiment, an anti-PD-1 antibody comprises a heavy chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 80% identical to the sequences shown in SEQ ID NO:15, SEQ ID NO:16, and SEQ ID NO:17, respectively. In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as the aforementioned antibodies.

[0267] In an embodiment, an anti-PD-1 antibody comprises a light chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 95% identical to the sequences shown in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively. In an embodiment, an anti-PD-1 antibody comprises a light chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 90% identical to the sequences shown in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively. In an embodiment, an anti-PD-1 antibody comprises a light chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 85% identical to the sequences shown in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively. In an embodiment, an anti-PD-1 antibody comprises a light chain that comprises CDR1, CDR2 and CDR3 domains that are each at least 80% identical to the sequences shown in SEQ ID NO:18, SEQ ID NO:19, and SEQ ID NO:20, respectively. In another embodiment, the antibody competes for binding with, and/or binds to the same epitope on PD-1 as the aforementioned antibodies.

[0268] In an embodiment, the anti-PD-1 antibody is an antibody disclosed in U.S. Patent No. 8,354,509 or U.S. Patent Application Publication Nos. 2010/0266617 A1, 2013/0108651 A1, 2013/0109843 A2, the disclosures of which are specifically incorporated by reference herein.

[0269] In an embodiment, the anti-PD-1 antibody is pidilizumab, which is also known as CT-011 (CureTech Ltd.), and which is disclosed in U.S. Patent No. 8,686,119 B2, the disclosures of which are specifically incorporated by reference herein. The efficacy of pidilizumab in the treatment of cancers, such as hematological malignancies, is described in Berger, *Clin. Cancer Res.* **2008,** *14,* 3044-51. The pidilizumab monoclonal antibody includes a heavy chain given by SEQ ID NO:21 and a light chain given by SEQ ID NO:22. Pidilizumab has intra-heavy chain disulfide linkages at 22-96, 144-200, 261-321, 367-425, 22''-96'', 144''-200'', 261''-321'', and 367''-425''; intra-light chain disulfide linkages at 23'-87', 133'-193', 23'''-87''', and 133'''-193'''; inter-heavy-light chain disulfide linkages at 220-213' and 220''-213''', inter-heavy-heavy chain disulfide linkages at 226-226'' 229-229''; and N-glycosylation sites (H CH_2 84.4) at 297, 297''.

[0270] In an embodiment, the anti-PD-1 antibody is an immunoglobulin G1 kappa, anti-(human CD274) humanized monoclonal antibody. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively. In an embodiment, an anti-PD-1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:21 and SEQ ID NO:22, respectively.

[0271] In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:23 and SEQ ID NO:24, respectively.

[0272] In another embodiment, anti-PD-1 antibodies and other PD-1 inhibitors include those described in U.S. Patent Nos. 8,287,856, 8,580,247, and 8,168,757 and U.S. Patent Application Publication Nos. 2009/0028857 A1, 2010/0285013 A1, 2013/0022600 A1, and 2011/0008369 A1, the teachings of which are hereby incorporated by reference. In another embodiment, antibodies that compete with any of these antibodies for binding to PD-1 are also included. In another embodiment, the anti-PD-1 antibody is an antibody disclosed in U.S. Patent No. 8,735,553 B1, the disclosures of which are incorporated herein by reference.

[0273] In an embodiment, the anti-PD-1 antibody is a commercially-available monoclonal antibody, such as anti-m-PD-1 clones J43 (Cat # BE0033-2) and RMP1-14 (Cat # BE0146) (Bio X Cell, Inc., West Lebanon, NH, USA). A number of commercially-available anti-PD-1 antibodies are known to one of ordinary skill in the art.

[0274] Monoclonal antibodies that inhibit or block PD-1 can be prepared by procedures known to those of ordinary knowledge and skill in the art, *e.g.*, by injecting test subjects with PD-1 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the

DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, myeloma cells, or other suitable cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The details of recombinant production of specific antibodies may be found in the references cited in the foregoing, the disclosures of which are incorporated by reference herein. Monoclonal antibodies that inhibit PD-1 can be prepared by standard molecular biology methods using the sequences provided herein by reverse translation and insertion into appropriate DNA or RNA vectors.

[0275] The anti-PD-1 antibody sequences discussed and referenced in the foregoing embodiments are summarized in Table 1.

TABLE 1. Anti-PD-1 antibody amino acid sequences.

Identifier	Amino Acid Sequence
SEQ ID NO:1	nivolumab heavy chain
SEQ ID NO:2	nivolumab light chain
SEQ ID NO:3	nivolumab variable heavy chain
SEQ ID NO:4	nivolumab variable light chain
SEQ ID NO:5	nivolumab heavy chain CDR1
SEQ ID NO:6	nivolumab heavy chain CDR2
SEQ ID NO:7	nivolumab heavy chain CDR3
SEQ ID NO:8	nivolumab light chain CDR1
SEQ ID NO:9	nivolumab light chain CDR2
SEQ ID NO:10	nivolumab light chain CDR3
SEQ ID NO:11	pembrolizumab heavy chain
SEQ ID NO:12	pembrolizumab heavy chain
SEQ ID NO:13	pembrolizumab variable light chain

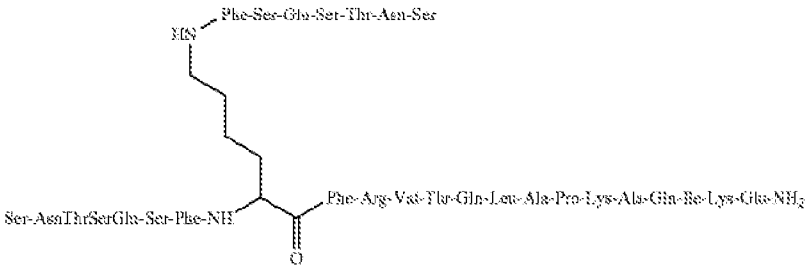
Identifier	Amino Acid Sequence
SEQ ID NO:14	pembrolizumab light chain
SEQ ID NO:15	pembrolizumab light chain CDR1
SEQ ID NO:16	pembrolizumab light chain CDR2
SEQ ID NO:17	pembrolizumab light chain CDR3
SEQ ID NO:18	pembrolizumab heavy chain CDR1
SEQ ID NO:19	pembrolizumab heavy chain CDR2
SEQ ID NO:20	pembrolizumab heavy chain CDR3
SEQ ID NO:21	pidilizumab heavy chain
SEQ ID NO:22	pidilizumab light chain
SEQ ID NO:23	pidilizumab variable heavy chain
SEQ ID NO:24	pidilizumab variable light chain

[0276] The PD-1 inhibitor may also be a small molecule or peptide, or a peptide derivative, such as those described in U.S. Patent No. 8,907,053; 9,096,642; and 9,044,442 and U.S. Patent Application Publication No. 2015/0087581; 1,2,4 oxadiazole compounds and derivatives such as those described in U.S. Patent Application Publication No. 2015/0073024; cyclic peptidomimetic compounds and derivatives such as those described in U.S. Patent Application Publication No. 2015/0073042; cyclic compounds and derivatives such as those described in U.S. Patent Application Publication No. 2015/0125491; 1,3,4 oxadiazole and 1,3,4 thiadiazole compounds and derivatives such as those described in International Patent Application Publication No. WO 2015/033301; peptide-based compounds and derivatives such as those described in International Patent Application Publication Nos. WO 2015/036927 and WO 2015/04490, or a macrocyclic peptide-based compounds and derivatives such as those described in U.S. Patent Application

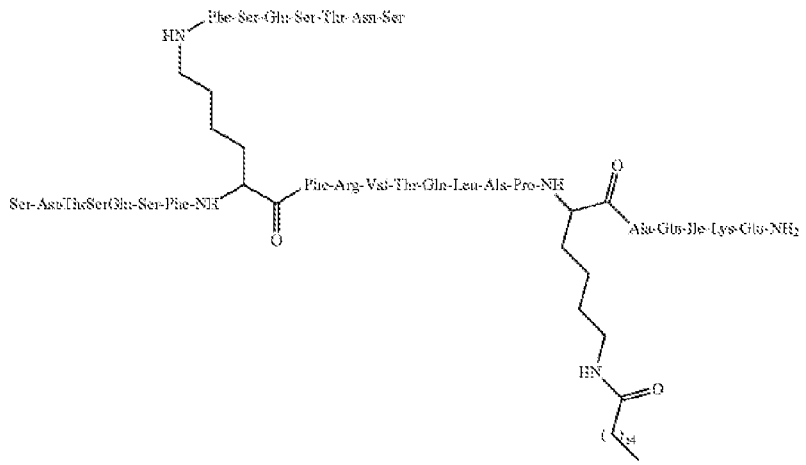
Publication No. 2014/0294898; the disclosures of each of which are hereby incorporated by reference in their entireties.

[0277] In an embodiment, the PD-1 inhibitor is AUNP-12.

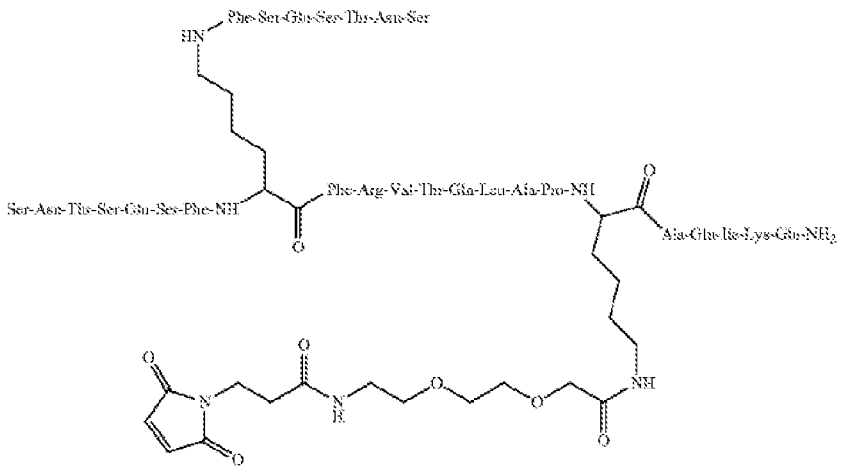
[0278] In an embodiment, the PD-1 inhibitor is a compound selected from the group consisting of:



(SEQ ID NO:26-28),



(SEQ ID NO:29-32),



(SEQ ID NO:33-36),

and
SEQ ID NO:37-38, wherein the branched groups are given by SEQ ID NO:25,
and pharmaceutically acceptable salts, solvates, hydrates, cocrystals, or prodrugs thereof.

[0279] In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and combinations thereof. In an embodiment the PD-1 inhibitor is nivolumab. In an embodiment the PD-1 inhibitor is pembrolizumab. In an embodiment the PD-1 inhibitor is Pidilizumab. In an embodiment the PD-1 inhibitor is AMP-224.

PD-L1 and PD-L2 Inhibitors

[0280] The PD-L1 or PD-L2 inhibitor may be any PD-L1 or PD-L2 inhibitor or blocker known in the art. In particular, it is one of the PD-L1 or PD-L2 inhibitors or blockers described in more detail in the following paragraphs. The terms "inhibitor" and "blocker" are used interchangeably herein in reference to PD-L1 and PD-L2 inhibitors. For avoidance of doubt, references herein to a PD-L1 or PD-L2 inhibitor that is an antibody may refer to a compound or antigen-binding fragments, variants, conjugates, or biosimilars thereof. For avoidance of doubt, references herein to a PD-L1 or PD-L2 inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

[0281] In some embodiments, the compositions and methods include a PD-L1 or PD-L2 inhibitor. In some embodiments, the PD-L1 and PD-L2 inhibitor is a small molecule. In some embodiments, the PD-L1 or PD-L2 inhibitor is an anti-PD-L1 or anti-PD-L2 antibody, a fragment thereof, including Fab fragments or single-chain variable fragments (scFv). In an aspect of the invention, the anti-PD-1 antibody or fragment thereof in any of the aforementioned embodiments is replaced by, or combined with, an anti-PD-Ll or anti-PD-L2 antibody or fragment thereof. In an embodiment, the antibody competes for binding with, and/or binds to an epitope on PD-L1 and/or PD-L2. In some embodiments, the PD-L1 or PD-L2 inhibitor is a monoclonal antibody. In some embodiments the PD-L1 or PD-L2 inhibitor is a polyclonal antibody. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some

embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a BTK inhibitor. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a PI3K inhibitor. In some embodiments, a PD-L1 inhibitor is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, an anti-PD-L1 monoclonal antibody is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, a PD-L2 inhibitor is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, an anti-PD-L2 monoclonal antibody is included in a composition or a method and is further combined with a JAK-2 inhibitor. In some embodiments, both a PD-1 inhibitor and a PD-L1 inhibitor are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, both an anti-PD-1 monoclonal antibody and an anti-PD-L1 monoclonal antibody are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, both a PD-1 inhibitor and a PD-L2 inhibitor are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor. In some embodiments, both an anti-PD-1 monoclonal antibody and an anti-PD-L2 monoclonal antibody

are included in a composition or method and are further combined with a BTK inhibitor, a PI3K inhibitor, and/or a JAK-2 inhibitor.

[0282] In some embodiments, the compositions described herein provide a combination of a PD-L1 and/or PD-L2 inhibitor with a BTK inhibitor, or methods of using a combination of a PD-L1 and/or PD-L2 inhibitor with a BTK inhibitor. In some embodiments, the PD-L1 inhibitors provided herein are selective for PD-L1, in that the compounds bind or interact with PD-L1 at substantially lower concentrations than they bind or interact with other receptors, including the PD-L2 receptor. In certain embodiments, the compounds bind to the PD-L2 receptor at a binding constant that is at least about a 2-fold higher concentration, about a 3-fold higher concentration, about a 5-fold higher concentration, about a 10-fold higher concentration, about a 20-fold higher concentration, about a 30-fold higher concentration, about a 50-fold higher concentration, about a 100-fold higher concentration, about a 200-fold higher concentration, about a 300-fold higher concentration, or about a 500-fold higher concentration than to the PD-L1 receptor.

[0283] Without being bound by any theory, it is believed that tumor cells express PD-L1, and that T cells express PD-1. However, PD-L1 expression by tumor cells is not required for efficacy of PD-1 or PD-L1 inhibitors or blockers. In an embodiment, the tumor cells express PD-L1. In another embodiment, the tumor cells do not express PD-L1. In some embodiments, the methods and compositions described herein include a combination of a PD-1 and a PD-L1 antibody, such as those described herein, in combination with a BTK inhibitor. The administration of a combination of a PD-1 and a PD-L1 antibody and a BTK inhibitor may be simultaneous or sequential.

[0284] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds human PD-L1 and/or PD-L2 with a K_D of about 100 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 90 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 80 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 70 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 60 pM or lower, a K_D of about 50 pM or lower, binds human PD-L1 and/or PD-L2 with a K_D of about 40 pM or lower, or binds human PD-L1 and/or PD-L2 with a KD of about 30 pM or lower,

[0285] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 7.5×10^5 l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 8×10^5 l/M·s or faster, binds to human PD-L1and/ or PD-L2 with a k_{assoc} of about 8.5×10^5 l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 9×10^5 l/M·s or faster, binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 9.5×10^5 l/M·s and/or faster, or binds to human PD-L1 and/or PD-L2 with a k_{assoc} of about 1×10^6 l/M·s or faster.

[0286] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that binds to human PD-L1 or PD-L2 with a k_{dissoc} of about 2×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.1×10^{-5} l/s or slower , binds to human PD-1 with a k_{dissoc} of about 2.2×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.3×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.4×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.5×10^{-5} l/s or slower, binds to human PD-1 with a k_{dissoc} of about 2.6×10^{-5} l/s or slower, binds to human PD-L1 or PD-L2 with a k_{dissoc} of about 2.7×10^{-5} l/s or slower, or binds to human PD-L1 or PD-L2 with a k_{dissoc} of about 3×10^{-5} l/s or slower.

[0287] In some embodiments, the compositions and methods described include a PD-L1 and/or PD-L2 inhibitor that blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 10 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 9 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 8 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 7 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 6 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 5 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 4 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 3 nM or lower; blocks or inhibits binding of human PD-Ll or human PD-L2 to human PD-1 with an IC_{50} of about 2 nM or lower; or blocks human PD-1, or blocks binding of human PD-L1 or human PD-L2 to human PD-l with an IC_{50} of about 1 nM or lower.

[0288] In an embodiment, the anti-PD-L1 antibody is durvalumab, which is also known as MEDI4736, produced by Medimmune, LLC, Gaithersburg, Maryland, a subsidiary of AstraZeneca plc., or antigen-binding fragments, conjugates, or variants thereof. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein. The clinical efficacy of durvalumab (MEDI4736, SEQ ID NO:39 and SEQ ID NO:40) has been described in: Page, *Ann. Rev. Med.*, **2014,** *65,* 185-202; Brahmer, *J. Clin. Oncol.* **2014,** *32,* 5s (supplement, abstract 8021); and McDermott, *Cancer Treatment Rev.*, **2014,** *40,* 1056-64. The durvalumab (MEDI4736) monoclonal antibody includes a V_H region given by SEQ ID NO:41 (corresponding to SEQ ID NO:72 in U.S. Patent No. 8,779,108) and a V_L region given by SEQ ID NO:42 (corresponding to SEQ ID NO:77 in U.S. Patent No. 8,779,108). The durvalumab monoclonal antibody includes disulfide linkages at 22-96, 22''-96'', 23'-89', 23'''-89''', 135'-195', 135'''-195''', 148-204, 148''-204'', 215'-224, 215'''-224'', 230-230'', 233-233'', 265-325, 265''-325'', 371-429, and 371''-429'; and N-glycosylation sites at Asn-301 and Asn-301''.

[0289] In an embodiment, the anti-PD-L1 antibody is an immunoglobulin G1, anti-(human CD antigen CD274) (human monoclonal heavy chain), disulfide with human monoclonal κ-chain, dimer. In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chains of durvalumab (MEDI4736). In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:39 and SEQ ID NO:40, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:39 and SEQ ID NO:40, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:39 and SEQ ID NO:40, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:39 and SEQ ID NO:40, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:39 and SEQ ID NO:40, respectively. In an embodiment, an anti-PD-L1

antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:39 and SEQ ID NO:40, respectively.

[0290] In an embodiment, the anti-PD-L1 antibody comprises V_H and V_L regions having the sequences shown in SEQ ID NO:41 (corresponding to SEQ ID NO:72 in U.S. Patent No. 8,779,108) and SEQ ID NO:42 (corresponding to SEQ ID NO:77 in U.S. Patent No. 8,779,108), respectively, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein, including antigen binding fragments, conjugates, and variants thereof. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:41 and SEQ ID NO:42, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:41 and SEQ ID NO:42, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:41 and SEQ ID NO:42, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:41 and SEQ ID NO:42, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:41 and SEQ ID NO:42, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 90% identical to the sequences shown in SEQ ID NO:41 and SEQ ID NO:42, respectively.

[0291] In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a V_H CDR1 having the amino acid sequence of SEQ ID NO:43 (corresponding to SEQ ID NO:23 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR2 having the amino acid sequence of SEQ ID NO:44 (corresponding to SEQ ID NO:24 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR3 having the amino acid sequence of SEQ ID NO:45 (corresponding to SEQ ID NO:25 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR1 having the amino acid sequence of SEQ ID NO:46 (corresponding to SEQ ID NO:28 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR2 having the amino acid sequence of SEQ ID NO:47 (corresponding to SEQ ID NO:29 in U.S. Patent No. 8,779,108) or

conservative amino acid substitutions thereof, and a V_L CDR3 having the amino acid sequence of SEQ ID NO:48 (corresponding to SEQ ID NO:30 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

[0292] In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a V_H CDR1 having the amino acid sequence of SEQ ID NO:49 (corresponding to SEQ ID NO:3 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR2 having the amino acid sequence of SEQ ID NO:50 (corresponding to SEQ ID NO:4 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR3 having the amino acid sequence of SEQ ID NO:51 (corresponding to SEQ ID NO:5 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR1 having the amino acid sequence of SEQ ID NO:52 (corresponding to SEQ ID NO:8 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR2 having the amino acid sequence of SEQ ID NO:53 (corresponding to SEQ ID NO:9 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, and a V_L CDR3 having the amino acid sequence of SEQ ID NO:54 (corresponding to SEQ ID NO:10 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559 A1, the disclosures of which are specifically incorporated by reference herein.

[0293] In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a V_H CDR1 having the amino acid sequence of SEQ ID NO:55 (corresponding to SEQ ID NO:13 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR2 having the amino acid sequence of SEQ ID NO:56 (corresponding to SEQ ID NO:14 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR3 having the amino acid sequence of SEQ ID NO:57 (corresponding to SEQ ID NO:15 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR1 having the amino acid sequence of SEQ ID NO:58 (corresponding to SEQ ID NO:18 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR2 having the amino acid sequence of SEQ ID NO:59 (corresponding to SEQ ID NO:19 in U.S. Patent No. 8,779,108) or

conservative amino acid substitutions thereof, and a V_L CDR3 having the amino acid sequence of SEQ ID NO:60 (corresponding to SEQ ID NO:20 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

[0294] In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a V_H CDR1 having the amino acid sequence of SEQ ID NO:61 (corresponding to SEQ ID NO:63 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR2 having the amino acid sequence of SEQ ID NO:62 (corresponding to SEQ ID NO:64 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR3 having the amino acid sequence of SEQ ID NO:63 (corresponding to SEQ ID NO:65 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR1 having the amino acid sequence of SEQ ID NO:64 (corresponding to SEQ ID NO:68 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR2 having the amino acid sequence of SEQ ID NO:65 (corresponding to SEQ ID NO:69 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, and a V_L CDR3 having the amino acid sequence of SEQ ID NO:66 (corresponding to SEQ ID NO:70 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

[0295] In another embodiment, the anti-PD-L1 antibody comprises an amino acid sequence comprising a V_H CDR1 having the amino acid sequence of SEQ ID NO:67 (corresponding to SEQ ID NO:73 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR2 having the amino acid sequence of SEQ ID NO:68 (corresponding to SEQ ID NO:74 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_H CDR3 having the amino acid sequence of SEQ ID NO:69 (corresponding to SEQ ID NO:75 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR1 having the amino acid sequence of SEQ ID NO:70 (corresponding to SEQ ID NO:78 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, a V_L CDR2 having the amino acid sequence of SEQ ID NO:71 (corresponding to SEQ ID NO:79 in U.S. Patent No. 8,779,108) or

conservative amino acid substitutions thereof, and a V_L CDR3 having the amino acid sequence of SEQ ID NO:72 (corresponding to SEQ ID NO:80 in U.S. Patent No. 8,779,108) or conservative amino acid substitutions thereof, as described in U.S. Patent No. 8,779,108 or U.S. Patent Application Publication No. 2013/0034559, the disclosures of which are specifically incorporated by reference herein.

[0296] In an embodiment, the anti-PD-L1 antibody is atezolizumab, also known as MPDL3280A or RG7446, produced by Genentech, Inc., a subsidiary of Roche, or antigen-binding fragments, conjugates, or variants thereof. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent No. 8,217,149, the disclosure of which is specifically incorporated by reference herein. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent Application Publication Nos. 2010/0203056 A1, 2013/0045200 A1, 2013/0045201 A1, 2013/0045202 A1, or 2014/0065135 A1, the disclosures of which are specifically incorporated by reference herein. The atezolizumab monoclonal antibody includes a heavy chain given by SEQ ID NO:73 and a light chain given by SEQ ID NO:74.

[0297] In an embodiment, the anti-PD-L1 antibody is an immunoglobulin G1 kappa, anti-(human PD-L1) humanized monoclonal antibody. In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chains of atezolizumab (MPDL3280A). In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:73 and SEQ ID NO:74, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:73 and SEQ ID NO:74, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:73 and SEQ ID NO:74, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:73 and SEQ ID NO:74, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:73 and SEQ ID NO:74, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:73 and SEQ ID NO:74, respectively.

[0298] In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chain CDRs or VRs of atezolizumab (MPDL3280A). In an embodiment, the anti-PD-L1 antibody V_H region comprises the sequence shown in SEQ ID NO:75 (corresponding to SEQ ID NO:20 in U.S. Patent No. 8,217,149), and the anti-PD-L1 antibody V_L region comprises the sequence shown in SEQ ID NO:76 (corresponding to SEQ ID NO:21 in U.S. Patent No. 8,217,149). In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:75 and SEQ ID NO:76, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:75 and SEQ ID NO:76, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:75 and SEQ ID NO:76, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:75 and SEQ ID NO:76, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:75 and SEQ ID NO:76, respectively.

[0299] In an embodiment, the anti-PD-L1 antibody is avelumab, also known as MSB0010718C, produced by Merck KGaA/EMD Serono, or antigen-binding fragments, conjugates, or variants thereof. In an embodiment, the anti-PD-L1 antibody is an antibody disclosed in U.S. Patent Application Publication No. US 2014/0341917 A1, the disclosure of which is specifically incorporated by reference herein. The avelumab monoclonal antibody includes a heavy chain of SEQ ID NO:83 and a light chain of SEQ ID NO:84.

[0300] In an embodiment, the anti-PD-L1 antibody is an immunoglobulin G1 lambda-1, anti-(human PD-L1) human monoclonal antibody. In an embodiment, the anti-PD-L1 antibody comprises the heavy and light chains of avelumab (MSB0010718C). In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains having the sequences shown in SEQ ID NO:83 and SEQ ID NO:84, respectively, or antigen binding fragments, variants, or conjugates thereof. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 99% identical to the sequences shown in SEQ ID NO:83 and SEQ ID NO:84, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 98% identical to the sequences shown in SEQ ID NO:83 and SEQ ID NO:84,

respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 97% identical to the sequences shown in SEQ ID NO:83 and SEQ ID NO:84, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 96% identical to the sequences shown in SEQ ID NO:83 and SEQ ID NO:84, respectively. In an embodiment, an anti-PD-L1 antibody comprises heavy and light chains that are each at least 95% identical to the sequences shown in SEQ ID NO:83 and SEQ ID NO:84, respectively.

[0301] In an embodiment, the anti-PD-L1 antibody V_H region comprises the sequence given in SEQ ID NO:85 (corresponding to SEQ ID NO:24 in U.S. Patent Application Publication No. 2014/0341917), and the anti-PD-L1 antibody V_L region comprises the sequence given in SEQ ID NO:86 (corresponding to SEQ ID NO:25 in U.S. Patent Application Publication No. 2014/0341917). In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 99% identical to the sequences shown in SEQ ID NO:85 and SEQ ID NO:86, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 98% identical to the sequences shown in SEQ ID NO:85 and SEQ ID NO:86, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 97% identical to the sequences shown in SEQ ID NO:85 and SEQ ID NO:86, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 96% identical to the sequences shown in SEQ ID NO:85 and SEQ ID NO:86, respectively. In an embodiment, an anti-PD-L1 antibody comprises V_H and V_L regions that are each at least 95% identical to the sequences shown in SEQ ID NO:85 and SEQ ID NO:86, respectively.

[0302] In an embodiment, the anti-PD-L1 antibody comprises a heavy chain variable region (V_H) polypeptide that comprises an HVR-H1, HVR-H2 and HVR-H3 sequence, wherein the HVR-H1 sequence is given by SEQ ID NO:87 (corresponding to SEQ ID NO:15 in U.S. Patent Application Publication No. 2014/0341917) or conservative amino acid substitutions thereof, the HVR-H2 sequence is given by SEQ ID NO:88 (corresponding to SEQ ID NO:16 in U.S. Patent Application Publication No. 2014/0341917) or conservative amino acid substitutions thereof, and the HVR-H3 sequence is given by SEQ ID NO:89 (corresponding to SEQ ID NO:17 in U.S. Patent Application Publication No. 2014/0341917) or conservative amino acid substitutions

thereof, and the anti-PD-L1 antibody also comprises a light chain variable region (V_L) polypeptide that comprises an HVR-L1, HVR-L2 and HVR-L3 sequence wherein the HVR-L1 sequence is given by SEQ ID NO:90 (corresponding to SEQ ID NO:18 in U.S. Patent Application Publication No. 2014/0341917) or conservative amino acid substitutions thereof, the HVR-L2 sequence is given by SEQ ID NO:91 (corresponding to SEQ ID NO:19 in U.S. Patent Application Publication No. 2014/0341917) or conservative amino acid substitutions thereof, and the HVR-L3 sequence is SEQ ID NO:92 (corresponding to SEQ ID NO:20 in U.S. Patent Application Publication No. 2014/0341917) or conservative amino acid substitutions thereof.

[0303] In an embodiment, the anti-PD-L1 antibody is MDX-1105, also known as BMS-935559, which is disclosed in U.S. Patent No. 7,943,743, the disclosures of which are specifically incorporated by reference herein. In an embodiment, the anti-PD-L1 antibody is selected from the anti-PD-L1 antibodies disclosed in U.S. Patent No. 7,943,743 which is specifically incorporated by reference herein.

[0304] In an embodiment, the anti-PD-L1 antibody is a commercially-available monoclonal antibody, such as INVIVOMAB anti-m-PD-L1 clone 10F.9G2 (BioXCell). A number of commercially-available anti-PD-L1 antibodies are known to one of ordinary skill in the art.

[0305] In an embodiment, the anti-PD-L2 antibody is a commercially-available monoclonal antibody, such as BIOLEGEND 24F.10C12 Mouse IgG2a, κ isotype (Biolegend), anti-PD-L2 antibody (Sigma-Aldrich), or other commercially-available anti-PD-L2 antibodies known to one of ordinary skill in the art.

[0306] Monoclonal antibodies that inhibit PD-L1 and/or PD-L2 can be prepared by procedures known to those of ordinary knowledge and skill in the art, e.g. by injecting test subjects with PD-L1 or PD-L2 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, myeloma cells,

or other suitable cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The details of recombinant production of specific antibodies may be found in the references cited in the foregoing, the disclosures of which are incorporated by reference herein. Monoclonal antibodies that inhibit PD-1 can be prepared by standard molecular biology methods using the sequences provided herein by reverse translation and insertion into appropriate DNA or RNA vectors.

[0307] The anti-PD-L1 antibody sequences referenced in the foregoing embodiments are summarized in Table 2.

TABLE 2. Anti-PD-L1 antibody amino acid sequences.

Identifier	Amino Acid Sequence
SEQ ID NO:39	durvalumab (MEDI4736)heavy chain
SEQ ID NO:40	durvalumab(MEDI4736) light chain
SEQ ID NO:41	durvalumab(MEDI4736) variable heavy chain
SEQ ID NO:42	durvalumab(MEDI4736) variable light chain
SEQ ID NO:43	durvalumab(MEDI4736) heavy chain CDR1
SEQ ID NO:44	durvalumab(MEDI4736) heavy chain CDR2
SEQ ID NO:45	durvalumab(MEDI4736) heavy chain CDR3
SEQ ID NO:46	durvalumab(MEDI4736) light chain CDR1
SEQ ID NO:47	durvalumab(MEDI4736) light chain CDR2
SEQ ID NO:48	durvalumab(MEDI4736) light chain CDR3
SEQ ID NO:49	Durvalumab alternative heavy chain CDR15
SEQ ID NO:50	Durvalumab alternative heavy chain CDR2
SEQ ID NO:51	Durvalumab alternative heavy chain CDR3
SEQ ID NO:52	Durvalumab alternative light chain CDR1

Identifier	Amino Acid Sequence
SEQ ID NO:53	Durvalumab alternative light chain CDR2
SEQ ID NO:54	Durvalumab alternative light chain CDR3
SEQ ID NO:55	Durvalumab alternative heavy chain CDR1
SEQ ID NO:56	Durvalumab alternative heavy chain CDR2
SEQ ID NO:57	Durvalumab alternative heavy chain CDR3
SEQ ID NO:58	Durvalumab alternative light chain CDR1
SEQ ID NO:59	Durvalumab alternative light chain CDR2
SEQ ID NO:60	Durvalumab alternative light chain CDR3
SEQ ID NO:61	Durvalumab alternative heavy chain CDR1
SEQ ID NO:62	Durvalumab alternative heavy chain CDR2
SEQ ID NO:63	Durvalumab alternative heavy chain CDR3
SEQ ID NO:64	Durvalumab alternative light chain CDR1
SEQ ID NO:65	Durvalumab alternative light chain CDR2
SEQ ID NO:66	Durvalumab alternative light chain CDR3
SEQ ID NO:67	Durvalumab alternative heavy chain CDR1
SEQ ID NO:68	Durvalumab alternative heavy chain CDR2
SEQ ID NO:69	Durvalumab alternative heavy chain CDR3
SEQ ID NO:70	Durvalumab alternative light chain CDR1
SEQ ID NO:71	Durvalumab alternative light chain CDR2
SEQ ID NO:72	Durvalumab alternative light chain CDR3
SEQ ID NO:73	atezolizumab (MPDL3280A) heavy chain

Identifier	Amino Acid Sequence
SEQ ID NO:74	Atezolizumab (MPDL3280A) light chain
SEQ ID NO:75	atezolizumab (MPDL3280A) variable heavy chain
SEQ ID NO:76	atezolizumab (MPDL3280A) variable light chain
SEQ ID NO:77	atezolizumab (MPDL3280A) heavy chain HVR-H1
SEQ ID NO:78	atezolizumab (MPDL3280A) heavy chain HVR-H2
SEQ ID NO:79	atezolizumab (MPDL3280A) heavy chain HVR-H3
SEQ ID NO:80	atezolizumab (MPDL3280A) heavy chain HVR-L1
SEQ ID NO:81	atezolizumab (MPDL3280A) heavy chain HVR-L2
SEQ ID NO:82	atezolizumab (MPDL3280A) heavy chain HVR-L3
SEQ ID NO:83	avelumab (MSB0010718C) heavy chain
SEQ ID NO:84	avelumab (MSB0010718C) light chain
SEQ ID NO:85	avelumab (MSB0010718C) variable heavy chain
SEQ ID NO:86	avelumab (MSB0010718C) variable light chain
SEQ ID NO:87	avelumab (MSB0010718C) heavy chain HVR-H1
SEQ ID NO:88	avelumab (MSB0010718C) heavy chain HVR-H2
SEQ ID NO:89	avelumab (MSB0010718C) heavy chain HVR-H3
SEQ ID NO:90	avelumab (MSB0010718C) heavy chain HVR-L1
SEQ ID NO:91	avelumab (MSB0010718C) heavy chain HVR-L2
SEQ ID NO:92	avelumab (MSB0010718C) heavy chain HVR-L3

[0308] In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559 and combinations thereof. In an embodiment, the anti-PD-L1 inhibitor is durvalumab (MEDI4736). In an embodiment, the anti-PD-L1 inhibitor is BMS-936559 (also known as MDX-1105-01). In an embodiment, the anti-PD-L1 inhibitor is Atezolizumab. In an embodiment, the anti-PD-L1 inhibitor is Avelumab.

[0309] In an embodiment, the PD-L2 inhibitor is an anti-PD-L2 antibody. In one embodiment, the anti-PD- L2 antibody is rHIgM12B7A.

Interferon (IFN)

[0310] IFNs are initially identified for their ability to induce cellular resistance to viral infection, and function as potent mediators in the host defense mechanism and homeostasis, modulating both the innate and adaptive immune responses. IFNs are small, inducible 20-25 K, usually glycosylated proteins that are produced by vertebrate cells in response to various biological stimuli. Mechanistically, IFNs mediate their biological activities by binding to receptors present on the surface of target cells. Specific ligand-receptor interactions trigger intracellular signaling cascade downstream, resulting in the synthesis of proteins that mediate pleiotropic activities. IFNs are classified into three groups: type I, type II or type III, based on their structure, physicochemical properties and biological activities. In mammals, eight families of type I IFN have been described. These are: IFN-α, IFN-β, IFN-δ, IFN-ε, IFN-κ, IFN-ω and IFN-tau (IFN-τ). In an embodiment, the IFNs of the present invention are interferon alpha or alpha interferon (IFN-α). In an embodiment, the IFNs of the present invention are glycosylated. In an embodiment, the IFNs of the present invention are PEGylated.

[0311] In some embodiments, the interferon is administered in a dose selected from the group consisting of about 1 million international units (MU) to about 800 MU, from about 1 MU to about 10 MU, from about 20 MU to about 40 MU, from about 2 MU to about 15 MU, from about 5 MU to about 25 MU, from about 50 MU to about 100 MU, from about 150 MU to about 250 MU, from about 300 MU to about 400 MU, and from about 500 MU to about 600 MU.

[0312] In some embodiments, the interferon is administered in a dose selected from the group consisting of from about 0.1 μg/day to about 1 mg/day, from about 10 μg/day to about 200 μg/day, from about 20 μg/day to about 150 μg/day, from about 0.1 μg/day to about 125 μg/day, from about 1 μg/day to about 20 μg/day, and about 4.5 μg/day to about 30 μg/day.

[0313] In some embodiments, the interferon is administered in a dose selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30 MU/m^2.

[0314] In some embodiments, the interferon is PEGylated.

[0315] In some embodiments, the interferon is glycosylated.

rIFN-alpha 2b

[0316] In an embodiment, the IFN is recombinant interferon alpha-2b (rIFN-alpha2b). In an embodiment, the IFN is recombinant interferon alpha-2b with the trade name Intron A from Merck Sharp & Dohme Limited. rIFN-alpha 2b is a type I interferon consisting of 165 amino acid residues with arginine in position 23. This protein is produced by recombinant DNA technology and resembles interferon secreted by leukocytes. In an embodiment, the IFN is an interferon having the sequence set forth in SEQ ID NO: 93 or fragment, variant, conjugates or biosimilar thereof.

PEGylated rIFN-alpha 2b

[0317] In an embodiment, the IFN is PEGylated rIFN-alpha 2b. In an embodiment, the IFN is PEGylated rIFN-alpha 2b with the trade name PEG- Intron from Merck Sharp & Dohme Limited. PEGylated rIFN-alpha 2b is derived from recombinant human interferon's alfa-2b moiety. It binds to and activates human type 1 interferon receptors causing them to dimerize.

rIFN-alpha 2a

[0318] In an embodiment, the IFN is recombinant interferon alpha-2a (rIFN-alpha2a). In an embodiment, the IFN is recombinant interferon alpha-2a with the trade name Roferon-A from Hoffmann La Roche. rIFN-alpha 2ab is a type I interferon consisting of 165 amino acid residues with lysine in position 23. This protein is produced by recombinant DNA technology and

resembles interferon secreted by leukocytes. In an embodiment, the IFN is an interferon having the sequence set forth in SEQ ID NO: 94 or fragment, variant, conjugates or biosimilar thereof.

PEGylated rIFN-alpha 2a

[0319] In an embodiment, the IFN is PEGylated rIFN-alpha 2a. In an embodiment, the IFN is PEGylated rIFN-alpha 2a with the trade name Pegasys from Hoffmann La Roche. PEGylated rIFN-alpha 2a is derived from recombinant human interferon's alfa-2a moiety. It binds to and activates human type 1 interferon receptors causing them to dimerize.

Interferon alpha

[0320] In an embodiment, the IFN is interferon alpha, also named as natural alpha interferon. Interferon alfa contains several naturally occurring IFN-α subtypes and is purified by affinity chromatography. Interferon alpha proteins are mainly involved in innate immune response against viral infection. They come in 13 subtypes that are called IFN-α 1, IFN-α 2, IFN-α 4, IFN-α 5, IFN-α 6, IFN-α 7, IFN-α 8, IFN-α 10, IFN-α 13, IFN-α 14, IFN-α 16, IFN-α 17, IFN-α 21. In an embodiment, the IFN is interferon alpha with the trade name Multiferon from Swedish Orphan Biovitrim. Multiferon consists of the 6 major subtypes are IFN-α1, IFN-α2, IFN-α8, IFN-α10, IFN-α14 and IFN-α21. Of these, IFN-α2 and IFN-α14 are glycosylated. In an embodiment, the IFN is interferon alpha selected from the group consisting of IFN-α 1, IFN-α 2, IFN-α 4, IFN-α 5, IFN-α 6, IFN-α 7, IFN-α 8, IFN-α 10, IFN-α 13, IFN-α 14, IFN-α 16, IFN-α 17, IFN-α 21, and combinations thereof. In an embodiment, the IFN is interferon alpha selected from the group consisting of IFN-α1, IFN-α2, IFN-α8, IFN-α10, IFN-α14, IFN-α21, and combinations thereof. In an embodiment, the IFN is IFN-α1. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 95 or fragment, variant, conjugates or biosimilar thereof.

[0321] In an embodiment, the IFN is IFN-α2. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 96 or fragment, variant, conjugates or biosimilar thereof.

[0322] In an embodiment, the IFN is IFN-α8. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 97 or fragment, variant, conjugates or biosimilar thereof.

[0323] In an embodiment, the IFN is IFN-α10. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 98 or fragment, variant, conjugates or biosimilar thereof.

[0324] In an embodiment, the IFN is IFN-α14. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 99 or fragment, variant, conjugates or biosimilar thereof.

[0325] In an embodiment, the IFN is IFN-α21. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 100 or fragment, variant, conjugates or biosimilar thereof.

interferon alfacon-1

[0326] In an embodiment, the IFN is interferon alfacon-1. Interferon alfacon-1 is a recombinant non-naturally occurring type-I interferon. The 166-amino acid sequence of Interferon alfacon-1 was derived by scanning the sequences of several natural interferon alpha subtypes and assigning the most frequently observed amino acid in each corresponding position. Four additional amino acid changes were made to facilitate the molecular construction, and a corresponding synthetic DNA sequence was constructed using chemical synthesis methodology. Interferon alfacon-1 differs from interferon alfa-2b at 20/166 amino acids (88% homology), and comparison with interferon-beta shows identity at over 30% of the amino acid positions. In an embodiment, the IFN is interferon alfacon-1 under the trade name Infergen from Three Rivers Pharmaceuticals LLC. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 101 or fragment, variant, conjugates or biosimilar thereof.

Interferon alfa-n1

[0327] In an embodiment, the IFN is interferon alfa-n1, also named as interferon alpha-2, or interferon alpha-A. Interferon alfa-n1 is a purified, natural (n is for natural) glycosylated human interferon alpha protein having 166 residues. In an embodiment, the IFN is interferon alfa-n1 under the trade name Wellferon from The Wellcome Foundation Ltd. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 102 or fragment, variant, conjugates or biosimilar thereof.

Interferon alfa-n3

[0328] In an embodiment, the IFN is interferon alfa-n3. Interferon alfa-n3 is a purified, natural (n is for natural) human interferon alpha proteins (consists of 3 forms or polymorphisms including interferon alfa- 2a, 2b and 2c, set forth in SEQ ID Nos: 103-106 respectively), having 166 residues, and some are glycosylated. In an embodiment, the IFN is interferon alfa-n3 under the trade name Alferon from Hemispherx Biopharma. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 103 or fragment, variant, conjugates or biosimilar thereof. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 104 or fragment, variant, conjugates or biosimilar thereof. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 105 or fragment, variant, conjugates or biosimilar thereof. In an embodiment, the IFN an interferon having the sequence set forth in SEQ ID NO: 106 or fragment, variant, conjugates or biosimilar thereof.

Albinterferon alpha-2b

[0329] In an embodiment, the IFN is albinterferon alpha-2b, also referred as Albumin-interferon alpha or alb-IFN. Albumin-interferon alpha (Albuferon) is a novel, long-acting form of interferon alpha. In an embodiment, the IFN is albinterferon alpha-2b under the trade name Albuferon from Human Genome Sciences.

IFN alpha-2b XL

[0330] In an embodiment, the IFN is IFN alpha-2b XL, referred as interferon alpha-2b controlled-release from Avadel Pharmaceuticals.

BLX-883

[0331] In an embodiment, the IFN is BLX-883, also referred as Locteron. BLX-883 is a form of alfa interferon from Biolex Therapeutics, and has been under clinical investigation (NCT00863239, NCT00953589, and NCT00593151).

AVI-005

[0332] In an embodiment, the IFN is AVI-005. AVI-005 is a form of glycosylated interferon alpha-2b from AviGenics Inc.

Belerofon

[0333] In an embodiment, the IFN is belerofon. Belerofon is a form of long-lasting human interferon alpha from Nautilus Biotech.

Cepeginterferon alfa-2b

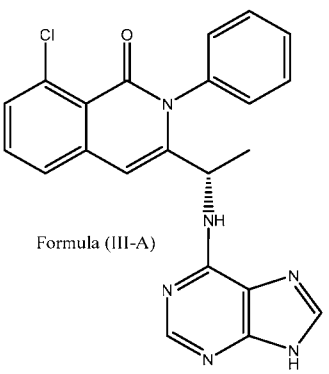
[0334] In an embodiment, the IFN is Cepeginterferon alfa-2b. Cepeginterferon alfa-2b is a long-acting PEGylated interferon alfa 2b that is developed by Biocad and is under clinical investigation (NCT01889433).

PI3K Inhibitors

[0335] The PI3K inhibitor may be any PI3K inhibitor known in the art. In particular, it is one of the PI3K inhibitors described in more detail in the following paragraphs. Preferably, it is a PI3K inhibitor selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor. In one specific embodiment, it is a PI3K-δ inhibitor. For avoidance of doubt, references herein to a PI3K inhibitor may refer to a compound or a pharmaceutically acceptable salt, ester, solvate, hydrate, cocrystal, or prodrug thereof.

[0336] In an embodiment, the PI3K inhibitor, which is preferably selected from the group consisting of a PI3K-γ inhibitor, a PI3K-δ inhibitor, and a PI3K-γ,δ inhibitor, is a compound selected from the structures disclosed in U.S. Patent No. 8,193,182 and 8,569,323, and U.S. Patent Application Publication No. 2012/0184568, 2013/0344061, and 2013/0267521, the disclosures of which are incorporated by reference herein.

[0337] In an embodiment, the PI3K-γ,δ inhibitor is a compound of Formula (III-A):

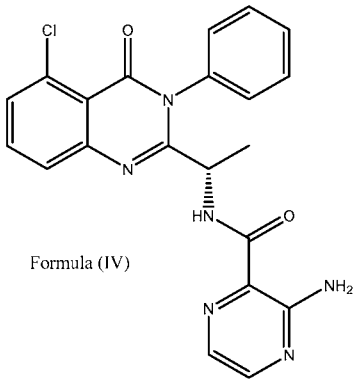


Formula (III-A)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. Formula

(III-A) is also known as IPI-145 or duvelisib (Infinity Pharmaceuticals) and has been studied at doses of 5 mg and 25 mg in clinical trials, including those described in Flinn, *Blood,* **2014,** *124,* 802, and O'Brien, *Blood,* **2014,** *124,* 3334.

[0338] In an embodiment, the PI3K inhibitor is a compound of Formula (IV):



Formula (IV)

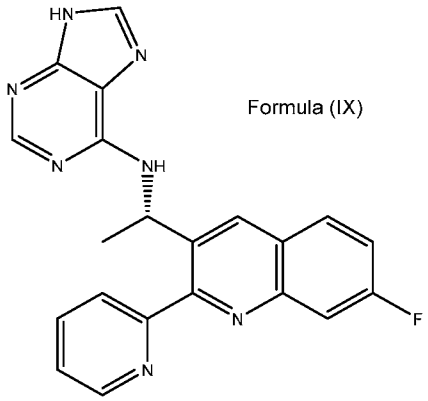
or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0339] In a preferred embodiment, the PI3K inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2*H*)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0340] In an embodiment, the PI3K inhibitor is (*S*)-3-amino-N-(1-(5-chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)ethyl)pyrazine-2-carboxamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0341] In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is a compound selected from the structures disclosed in U.S. Patent No. 8,193,199, 8,586,739, and 8,901,135, the disclosure of each of which is incorporated by reference herein.

[0342] In an embodiment, the PI3K-δ inhibitor is a compound of Formula (IX):

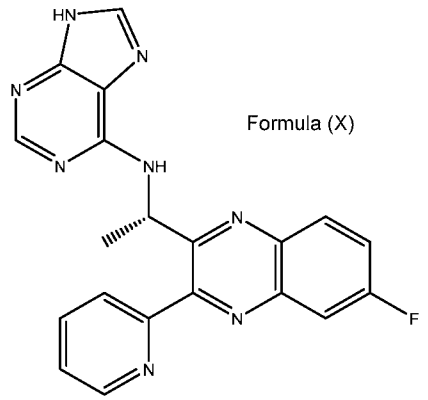


Formula (IX)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0343] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(7-fluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0344] In an embodiment, the PI3K-δ inhibitor is a compound of Formula (X):

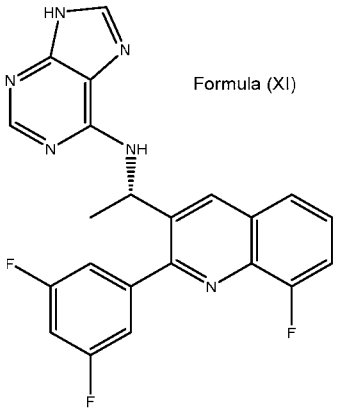


Formula (X)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0345] In an embodiment, the PI3K inhibitor or PI3K-δ inhibitor is (*S*)-*N*-(1-(6-fluoro-3-(pyridin-2-yl)quinoxalin-2-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0346] In an embodiment, the PI3K-δ inhibitor is a compound of Formula (XI):

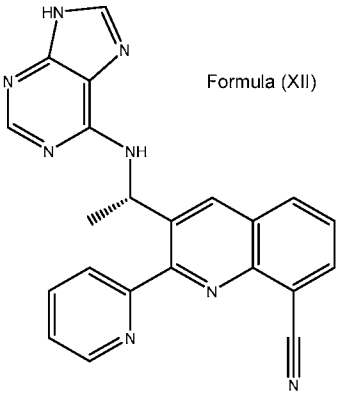


Formula (XI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0347] In an embodiment, the PI3K-δ inhibitor is (*S*)-*N*-(1-(2-(3,5-difluorophenyl)-8-fluoroquinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically-acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0348] In an embodiment, the PI3K-δ inhibitor is a compound of Formula (XII):

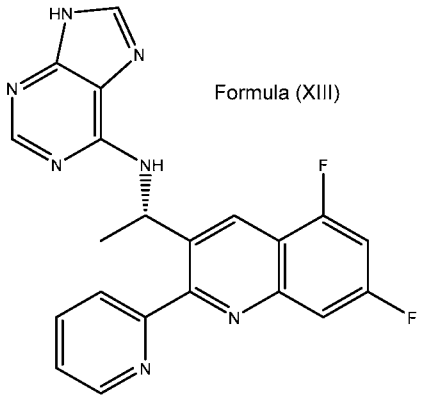


Formula (XII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0349] In an embodiment, the PI3K-δ inhibitor is (*S*)-3-(1-((9*H*-purin-6-yl)amino)ethyl)-2-(pyridin-2-yl)quinoline-8-carbonitrile or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0350] In an embodiment, the PI3K-δ inhibitor is a compound of Formula (XIII):

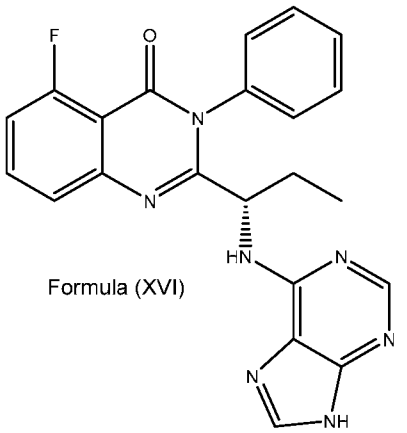


Formula (XIII)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

[0351] In an embodiment, the PI3K-δ inhibitor is (*S*)-*N*-(1-(5,7-difluoro-2-(pyridin-2-yl)quinolin-3-yl)ethyl)-9*H*-purin-6-amine or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0352] In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is idelalisib. In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is the compound of Formula (XVI):



Formula (XVI)

or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

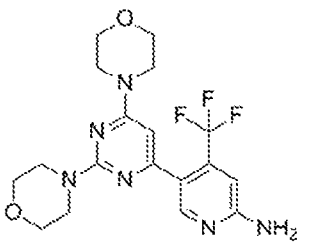
[0353] In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is (*S*)-2-(1-((9*H*-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3*H*)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[0354] In an embodiment, the PI3K inhibitor (which may be a PI3K-γ inhibitor, PI3K-δ inhibitor, or PI3K-γ,δ inhibitor) is 4(3*H*)-quinazolinone, 5-fluoro-3-phenyl-2-[(1*S*)-1-(9*H*-purin-6-ylamino)propyl]-5-fluoro-3-phenyl-2-{(1*S*)-1-[(7*H*-purin-6-yl)amino]propyl}quinazolin-4(3*H*)-one or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof

[0355] Other PI3K inhibitors suitable for use in the described combination with a BTK inhibitor also include, but are not limited to, those described in, for example, U.S. Patent No. 8,193,182 and U.S. Published Application No. 2013/0267521; 2013/0053362; 2013/0029984; 2013/0029982; 2012/0184568; and 2012/0059000, the disclosures of each of which are incorporated by reference in their entireties.

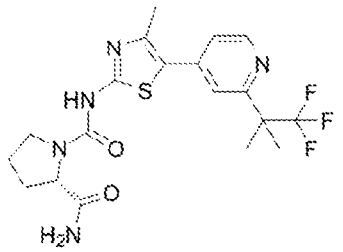
Buparlisib

[0356] In an embodiment, the PI3K inhibitor is Buparlisib. Buparlisib has the chemical structure and name shown as: 5-(2,6-dimorpholin-4-ylpyrimidin-4-yl)-4-(trifluoromethyl)pyridin-2-amine



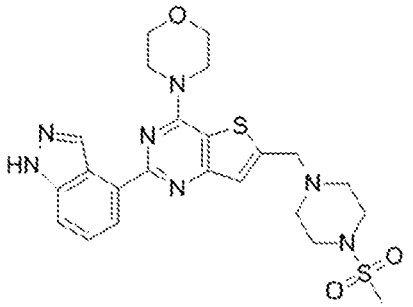
Alpelisib

[0357] In an embodiment, the PI3K inhibitor is Alpelisib. Alpelisib has the chemical structure and name shown as: (2S)-1-N-[4-methyl-5-[2-(1,1,1-trifluoro-2-methylpropan-2-yl)pyridin-4-yl]-1,3-thiazol-2-yl]pyrrolidine-1,2-dicarboxamide



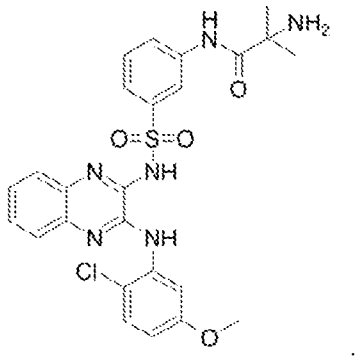
Pictilisib

[0358] In an embodiment, the PI3K inhibitor is Pictilisib. Pictilisib has the chemical structure and name shown as: 4-[2-(1H-indazol-4-yl)-6-[(4-methylsulfonylpiperazin-1-yl)methyl]thieno[3,2-d]pyrimidin-4-yl]morpholine



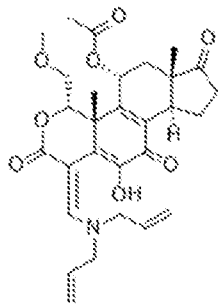
Pilaralisib

[0359] In an embodiment, the PI3K inhibitor is Pilaralisib. Pilaralisib has the chemical structure and name shown as: 2-amino-N-[3-[[3-(2-chloro-5-methoxyanilino)quinoxalin-2-yl]sulfamoyl]phenyl]-2-methylpropanamide



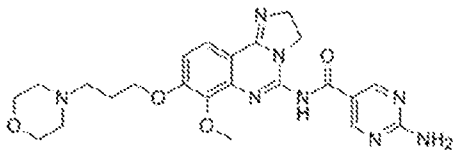
Sonolisib

[0360] In an embodiment, the PI3K inhibitor is Sonolisib. Sonolisib has the chemical structure and name shown as: (4S,4aR,5R,6aS,9aR,E)-1-((diallylamino)methylene)-11-hydroxy-4-(methoxymethyl)-4a,6a-dimethyl-2,7,10-trioxo-1,2,4,4a,5,6,6a,7,8,9,9a,10-dodecahydroindeno[4,5-h]isochromen-5-yl acetate



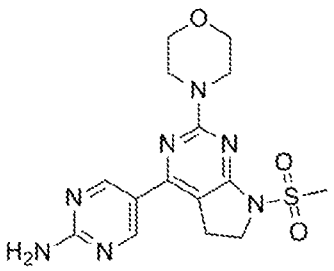
Copanlisib

[0361] In an embodiment, the PI3K inhibitor is Copanlisib. Copanlisib has the chemical structure and name shown as: 2-amino-N-(7-methoxy-8-(3-morpholinopropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl)pyrimidine-5-carboxamide



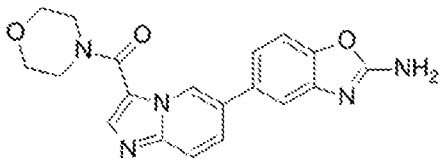
CH5132799

[0362] In an embodiment, the PI3K inhibitor is CH5132799. CH5132799 has the chemical structure and name shown as: 5-(7-methylsulfonyl-2-morpholin-4-yl-5,6-dihydropyrrolo[2,3-d]pyrimidin-4-yl)pyrimidin-2-amine



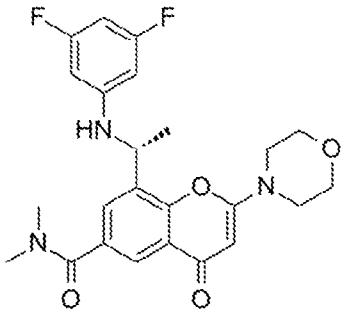
Serabelisib

[0363] In an embodiment, the PI3K inhibitor is Serabelisib. Serabelisib has the chemical structure and name shown as: [6-(2-amino-1,3-benzoxazol-5-yl)imidazo[1,2-a]pyridin-3-yl]-morpholin-4-ylmethanone



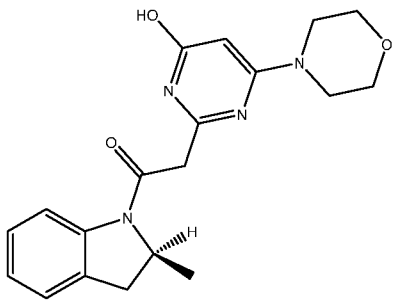
AZD8186

[0364] In an embodiment, the PI3K inhibitor is AZD8186. AZD8186 has the chemical structure and name shown as: 8-[(1R)-1-(3,5-difluoroanilino)ethyl]-N,N-dimethyl-2-morpholin-4-yl-4-oxochromene-6-carboxamide



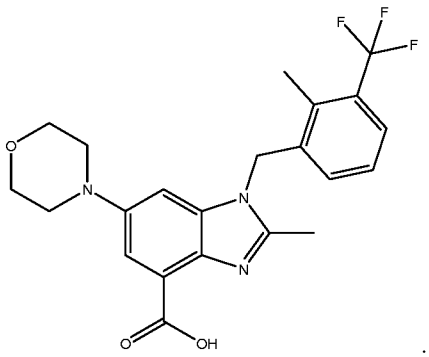
SAR260301

[0365] In an embodiment, the PI3K inhibitor is SAR260301. SAR260301 has the chemical structure and name shown as: (S)-2-(2-(2-methylindolin-1-yl)-2-oxoethyl)-6-morpholinopyrimidin-4(3H)-one



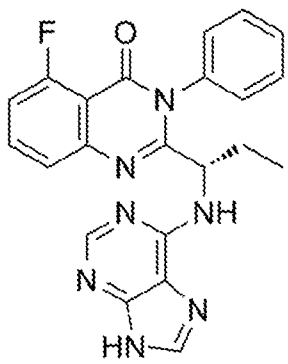
GSK2636771

[0366] In an embodiment, the PI3K inhibitor is GSK2636771. GSK2636771 has the chemical structure and name shown as: 2-methyl-1-(2-methyl-3-(trifluoromethyl)benzyl)-6-morpholino-1H-benzo[d]imidazole-4-carboxylic acid



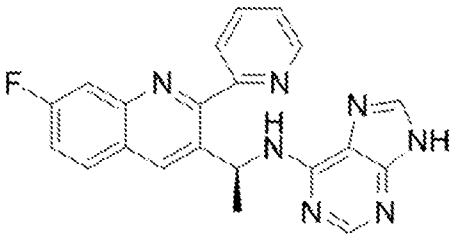
Idelalisib

[0367] In an embodiment, the PI3K inhibitor is Idelalisib. Idelalisib has the chemical structure and name shown as: (S)-2-(1-((9H-purin-6-yl)amino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one



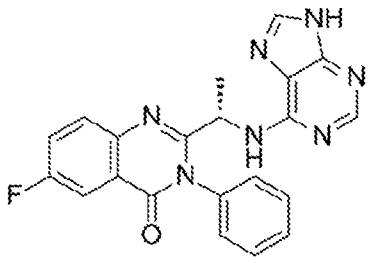
AMG319

[0368] In an embodiment, the PI3K inhibitor is AMG319. AMG319 has the chemical structure and name shown as: N-[(1S)-1-(7-fluoro-2-pyridin-2-ylquinolin-3-yl)ethyl]-7H-purin-6-amine



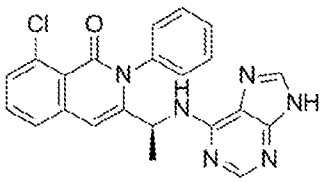
Acalisib

[0369] In an embodiment, the PI3K inhibitor is Acalisib. Acalisib has the chemical structure and name shown as: 6-fluoro-3-phenyl-2-[(1S)-1-(7H-purin-6-ylamino)ethyl]quinazolin-4-one



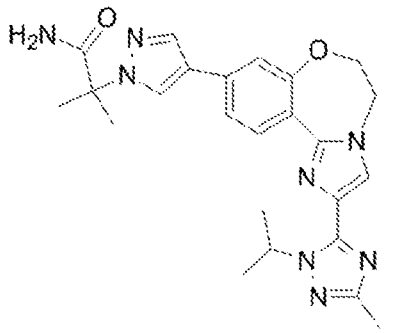
Duvelisib

[0370] In an embodiment, the PI3K inhibitor is Duvelisib. Duvelisib has the chemical structure and name shown as: 8-chloro-2-phenyl-3-[(1S)-1-(7H-purin-6-ylamino)ethyl]isoquinolin-1-one



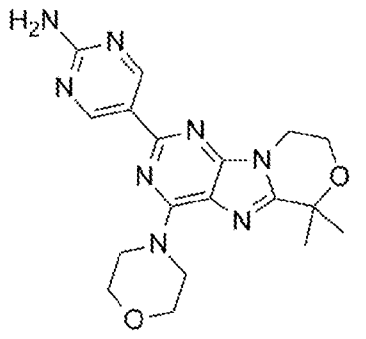
Taselisib

[0371] In an embodiment, the PI3K inhibitor is Taselisib. Taselisib has the chemical structure and name shown as: 2-methyl-2-[4-[2-(5-methyl-2-propan-2-yl-1,2,4-triazol-3-yl)-5,6-dihydroimidazo[1,2-d][1,4]benzoxazepin-9-yl]pyrazol-1-yl]propanamide



GDC-0084

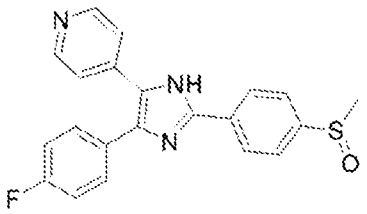
[0372] In an embodiment, the PI3K inhibitor is GDC-0084. GDC-0084 has the chemical structure and name shown as: 5-(6,6-dimethyl-4-morpholin-4-yl-8,9-dihydropurino[8,9-c][1,4]oxazin-2-yl)pyrimidin-2-amine



AKT Inhibitors

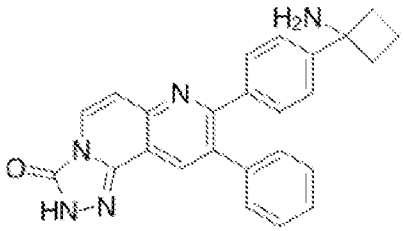
SB-203580

[0373] In an embodiment, the AKT inhibitor is SB-203580. SB-203580 has the chemical structure and name shown as: 4-[4-(4-fluorophenyl)-2-(4-methylsulfinylphenyl)-1H-imidazol-5-yl]pyridine



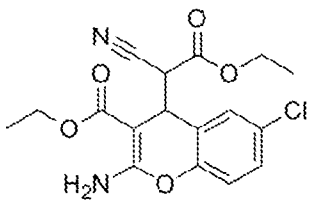
MK-2206

[0374] In an embodiment, the AKT inhibitor is MK-2206. MK-2206 has the chemical structure and name shown as: 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-2H-[1,2,4]triazolo[3,4-f][1,6]naphthyridin-3-one



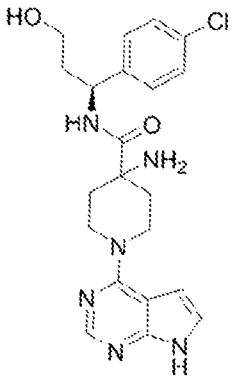
SC79

[0375] In an embodiment, the AKT inhibitor is SC79. SC79 has the chemical structure and name shown as: ethyl 2-amino-6-chloro-4-(1-cyano-2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate



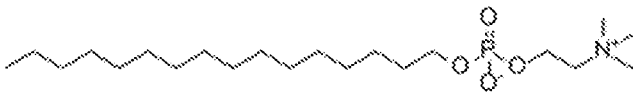
AZD5363

[0376] In an embodiment, the AKT inhibitor is AZD5363. AZD5363 has the chemical structure and name shown as: 4-amino-N-[(1S)-1-(4-chlorophenyl)-3-hydroxypropyl]-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidine-4-carboxamide



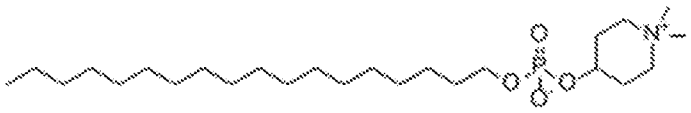
Miltefosine

[0377] In an embodiment, the AKT inhibitor is Miltefosine. Miltefosine has the chemical structure and name shown as: hexadecyl 2-(trimethylazaniumyl)ethyl phosphate



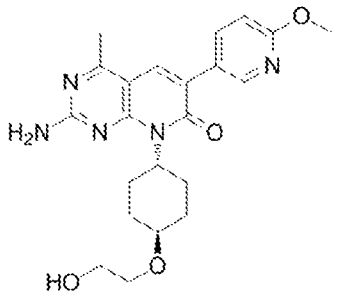
Perifosine

[0378] In an embodiment, the AKT inhibitor is Perifosine. Perifosine has the chemical structure and name shown as: (1,1-dimethylpiperidin-1-ium-4-yl) octadecyl phosphate



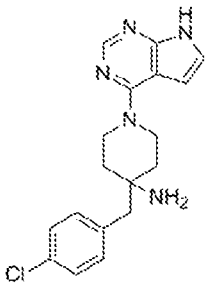
PF-04691502

[0379] In an embodiment, the AKT inhibitor is PF-04691502. PF-04691502 has the chemical structure and name shown as: 2-amino-8-[4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxypyridin-3-yl)-4-methylpyrido[2,3-d]pyrimidin-7-one



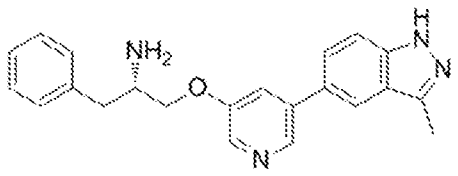
CCT128930

[0380] In an embodiment, the AKT inhibitor is CCT128930. CCT128930 has the chemical structure and name shown as: 4-[(4-chlorophenyl)methyl]-1-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperidin-4-amine



A-674563

[0381] In an embodiment, the AKT inhibitor is A-674563. A-674563 has the chemical structure and name shown as: (2S)-1-[5-(3-methyl-2H-indazol-5-yl)pyridin-3-yl]oxy-3-phenylpropan-2-amine

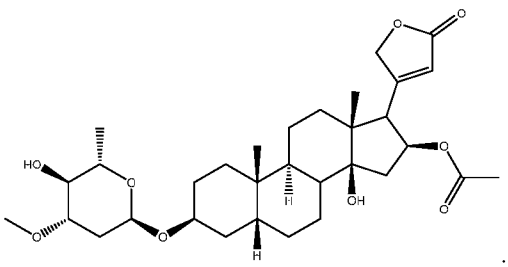


RX-0201 (Archexin)

[0382] In an embodiment, the AKT inhibitor is RX-0201 (Archexin). In an embodiment, the AKT inhibitor is an oligodeoxynucleotide with the sequence of 5′ gctgcatgatctccttggcg 3′.

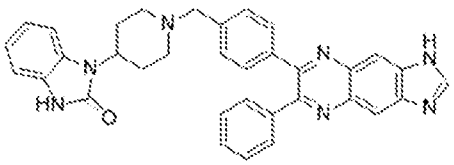
PBI-05204 (Oleandrin)

[0383] In an embodiment, the AKT inhibitor is PBI-05204 (Oleandrin). PBI-05204 has the chemical structure and name shown as: [(3S,5R,8R,9S,10S,13R,14S,16S,17R)-14-hydroxy-3-[(2R,4S,5S,6S)-5-hydroxy-4-methoxy-6-methyloxan-2-yl]oxy-10,13-dimethyl-17-(5-oxo-2H-furan-3-yl)-1,2,3,4,5,6,7,8,9,11,12,15,16,17-tetradecahydrocyclopenta[a]phenanthren-16-yl] acetate



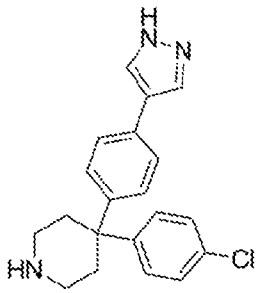
AKT inhibitor VIII

[0384] In an embodiment, the AKT inhibitor is AKT inhibitor VIII. AKT inhibitor VIII has the chemical structure and name shown as: 3-[1-[[4-(7-phenyl-3H-imidazo[4,5-g]quinoxalin-6-yl)phenyl]methyl]piperidin-4-yl]-1H-benzimidazol-2-one



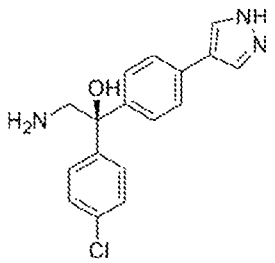
AT7867

[0385] In an embodiment, the AKT inhibitor is AT7867. AT7867 has the chemical structure and name shown as: 4-(4-chlorophenyl)-4-[4-(1H-pyrazol-4-yl)phenyl]piperidine



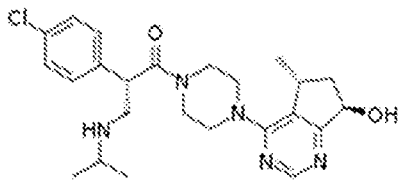
AT13148

[0386] In an embodiment, the AKT inhibitor is AT13148. AT13148 has the chemical structure and name shown as: (1S)-2-amino-1-(4-chlorophenyl)-1-[4-(1H-pyrazol-4-yl)phenyl]ethanol



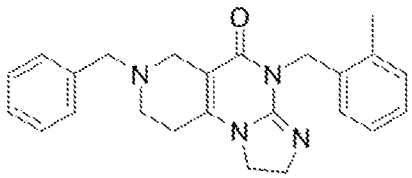
GDC-0068 (lpatasertib)

[0387] In an embodiment, the AKT inhibitor is GDC-0068 (lpatasertib). GDC-0068 has the chemical structure and name shown as: (S)-2-(4-Chlorophenyl)-1-(4-((5R,7R)-7-hydroxy-5-methyl-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino)propan-1-one



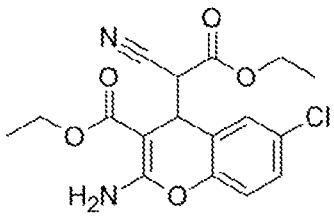
TIC10

[0388] In an embodiment, the AKT inhibitor is TIC10. TIC10 has the chemical structure and name shown as: 7-benzyl-4-(2-methylbenzyl)-1,2,6,7,8,9-hexahydroimidazo[1,2-a]pyrido[3,4-e]pyrimidin-5(4H)-one



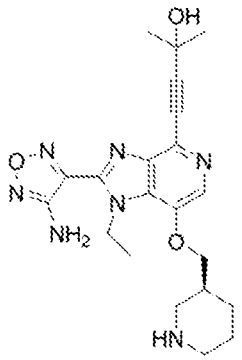
SC79

[0389] In an embodiment, the AKT inhibitor is SC79. SC79 has the chemical structure and name shown as: ethyl 2-amino-6-chloro-4-(1-cyano-2-ethoxy-2-oxoethyl)-4H-chromene-3-carboxylate



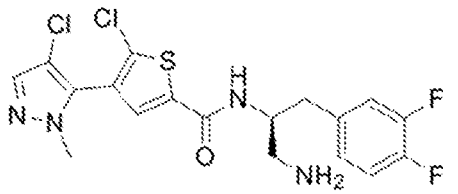
GSK690693

[0390] In an embodiment, the AKT inhibitor is GSK690693. GSK690693 has the chemical structure and name shown as: 4-[2-(4-amino-1,2,5-oxadiazol-3-yl)-1-ethyl-7-[[(3S)-piperidin-3-yl]methoxy]imidazo[4,5-c]pyridin-4-yl]-2-methylbut-3-yn-2-ol



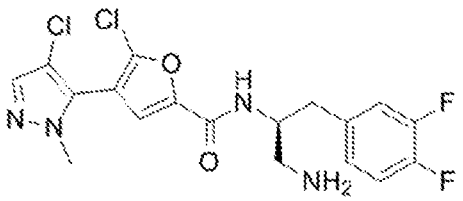
GSK2110183

[0391] In an embodiment, the AKT inhibitor is GSK2110183. GSK2110183 has the chemical structure and name shown as: N-[(2S)-1-amino-3-(3,4-difluorophenyl)propan-2-yl]-5-chloro-4-(4-chloro-2-methylpyrazol-3-yl)thiophene-2-carboxamide



GSK2141795

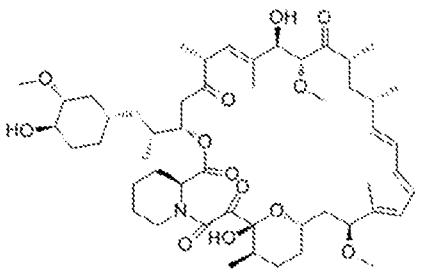
In an embodiment, the AKT inhibitor is GSK2141795. GSK2141795 has the chemical structure and name shown as: N-[(2S)-1-amino-3-(3,4-difluorophenyl)propan-2-yl]-5-chloro-4-(4-chloro-2-methylpyrazol-3-yl)furan-2-carboxamide



mTOR Inhibitor

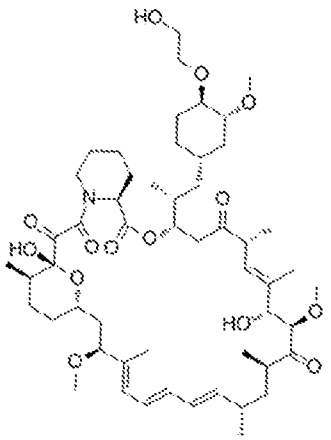
Sirolimus

[0392] In an embodiment, the mTOR inhibitor is Sirolimus. Sirolimus has the chemical structure and name shown as:
(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4H,6H,31H)-pentone



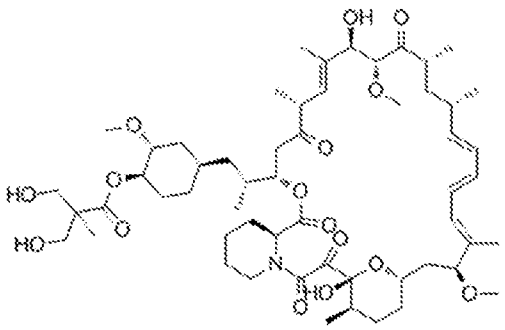
Everolimus

[0393] In an embodiment, the mTOR inhibitor is Everolimus. Everolimus has the chemical structure and name shown as:
(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18- dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.04,9]hexatriaconta16,24,26,28-tetraene-2,3,10,14,20-pentaone



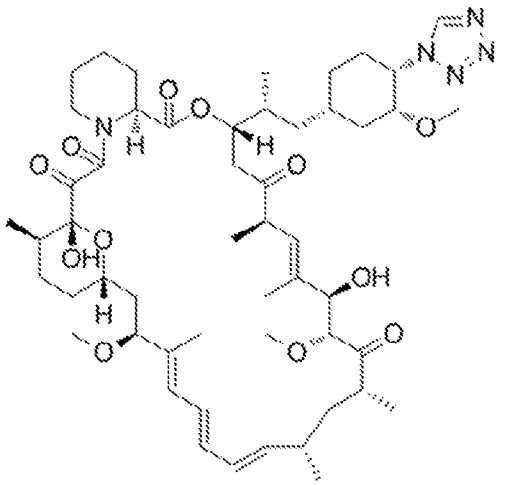
Temsirolimus

[0394] In an embodiment, the mTOR inhibitor is Temsirolimus. Temsirolimus has the chemical structure and name shown as: (1R,2R,4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetracosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxycyclohexyl 3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate



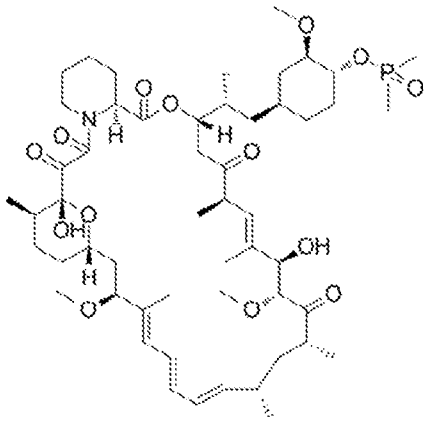
Zotarolimus

[0395] In an embodiment, the mTOR inhibitor is Zotarolimus. Zotarolimus has the chemical structure and name shown as:
(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-3-{(1R)-2-[(1S,3R,4S)-3-methoxy-4-(1H-tetrazol-1-yl)cyclohexyl]-1-methylethyl}-6,8,12,14,20,26-hexamethyl-4,9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-heptadecahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontine-1,5,11,28,29(6H,31H)-pentone



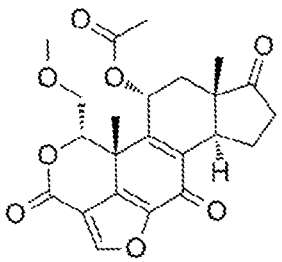
Deforolimus

[0396] In an embodiment, the mTOR inhibitor is Deforolimus. Deforolimus has the chemical structure and name shown as: (1R,2R,4S)-4-[(2R)-2-[(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28Z,30S,32S,35R)-1,18-dihydroxy-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-2,3,10,14,20-pentaoxo-11,36-dioxa-4-azatricyclo[30.3.1.04,9]hexatriaconta-16,24,26,28-tetraen-12-yl]propyl]-2-methoxycyclohexyl dimethylphosphinate



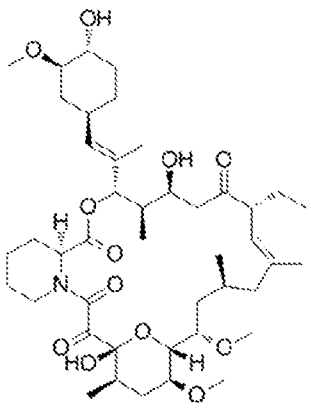
Wortmannin

In an embodiment, the mTOR inhibitor is Wortmannin. Wortmannin has the chemical structure and name shown as: (1S,6bR,9aS,11R,11bR)-1-(methoxymethyl)-9a,11b-dimethyl-3,6,9-trioxo-3,6,6b,7,8,9,9a,10,11,11b-decahydro-1H-furo[4,3,2-de]indeno[4,5-h]isochromen-11-yl acetate



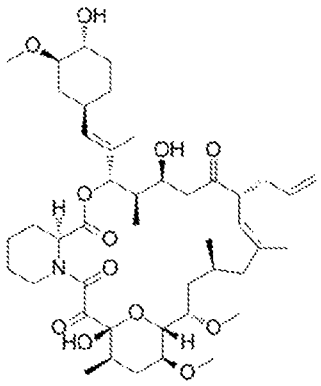
Ascomycin

[0397] In an embodiment, the mTOR inhibitor is Ascomycin. Ascomycin has the chemical structure and name shown as: (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)-8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-15,19-epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone



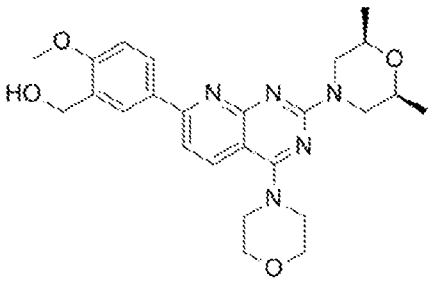
Tacrolimus

[0398] In an embodiment, the mTOR inhibitor is Tacrolimus. Tacrolimus has the chemical structure and name shown as: [3S [3R*[E(1S*,3S*,4S*)], 4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]] - 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone



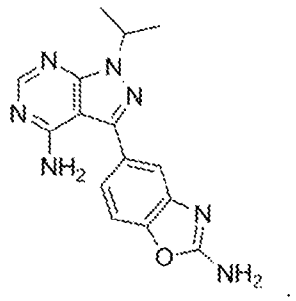
KU-0063794

[0399] In an embodiment, the mTOR inhibitor is KU-0063794. KU-0063794 has the chemical structure and name shown as: [5-[2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-4-morpholin-4-ylpyrido[2,3-d]pyrimidin-7-yl]-2-methoxyphenyl]methanol



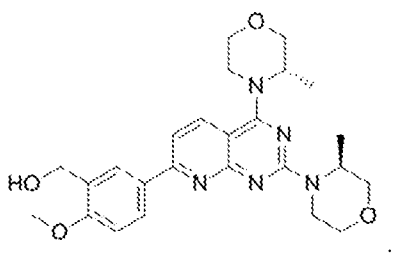
Sapanisertib

[0400] In an embodiment, the mTOR inhibitor is Sapanisertib. Sapanisertib has the chemical structure and name shown as: 5-(4-amino-1-propan-2-ylpyrazolo[3,4-d]pyrimidin-3-yl)-1,3-benzoxazol-2-amine



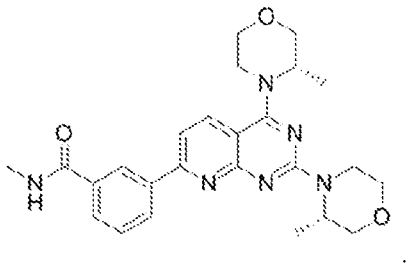
AZD8055

[0401] In an embodiment, the mTOR inhibitor is AZD8055. AZD8055 has the chemical structure and name shown as: [5-[2,4-bis[(3S)-3-methylmorpholin-4-yl]pyrido[2,3-d]pyrimidin-7-yl]-2-methoxyphenyl]methanol



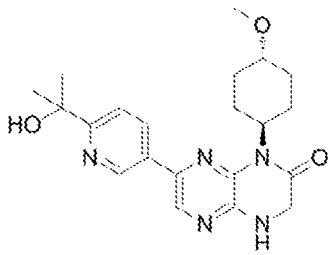
Vistusertib

[0402] In an embodiment, the mTOR inhibitor is Vistusertib. Vistusertib has the chemical structure and name shown as: 3-[2,4-bis[(3S)-3-methylmorpholin-4-yl]pyrido[2,3-d]pyrimidin-7-yl]-N-methylbenzamide



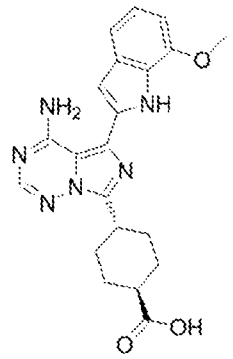
CC-223

[0403] In an embodiment, the mTOR inhibitor is CC-223. CC-223 has the chemical structure and name shown as: 3-[6-(2-hydroxypropan-2-yl)pyridin-3-yl]-5-(4-methoxycyclohexyl)-7,8-dihydropyrazino[2,3-b]pyrazin-6-one



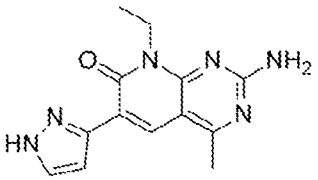
OSI-027

[0404] In an embodiment, the mTOR inhibitor is OSI-027. OSI-027 has the chemical structure and name shown as: 4-(4-amino-5-(7-methoxy-1H-indol-2-yl)imidazo[5,1-f][1,2,4]triazin-7-yl)cyclohexanecarboxylic acid



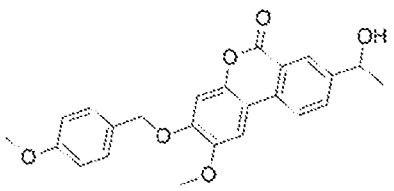
Voxtalisib

[0405] In an embodiment, the mTOR inhibitor is Voxtalisib. Voxtalisib has the chemical structure and name shown as: N-[4-[[3-(3,5-dimethoxyanilino)quinoxalin-2-yl]sulfamoyl]phenyl]-3-methoxy-4-methylbenzamide



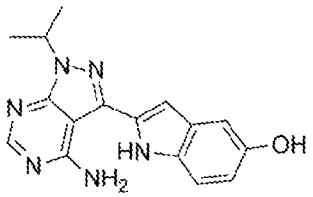
Palomid 529

[0406] In an embodiment, the mTOR inhibitor is Palomid 529. Palomid 529 has the chemical structure and name shown as: 8-(1-hydroxyethyl)-2-methoxy-3-[(4-methoxyphenyl)methoxy]benzo[c]chromen-6-one



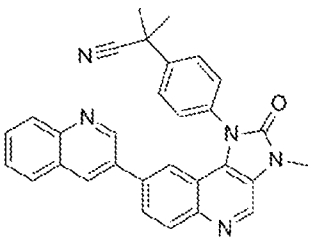
PP 242

[0407] In an embodiment, the mTOR inhibitor is PP 242. PP 242 has the chemical structure and name shown as: (2E)-2-(4-amino-1-propan-2-yl-2H-pyrazolo[3,4-d]pyrimidin-3-ylidene)indol-5-ol



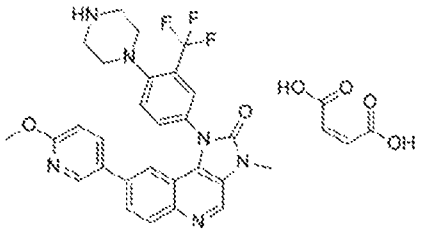
Dactolisib

[0408] In an embodiment, the mTOR inhibitor is Dactolisib. Dactolisib has the chemical structure and name shown as: 2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-ylimidazo[4,5-c]quinolin-1-yl)phenyl]propanenitrile



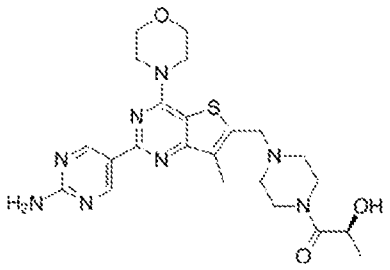
BGT226

[0409] In an embodiment, the mTOR inhibitor is BGT226. BGT226 has the chemical structure and name shown as: (Z)-but-2-enedioic acid; 8-(6-methoxypyridin-3-yl)-3-methyl-1-[4-piperazin-1-yl-3-(trifluoromethyl)phenyl]imidazo[4,5-c]quinolin-2-one



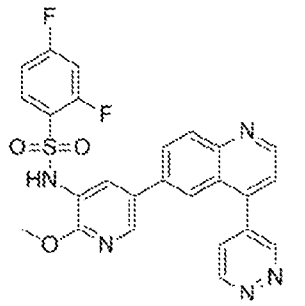
Apitolisib

[0410] In an embodiment, the mTOR inhibitor is Apitolisib. Apitolisib has the chemical structure and name shown as: (2S)-1-[4-[[2-(2-aminopyrimidin-5-yl)-7-methyl-4-morpholin-4-ylthieno[3,2-d]pyrimidin-6-yl]methyl]piperazin-1-yl]-2-hydroxypropan-1-one



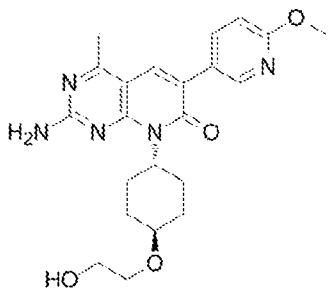
Omipalisib

[0411] In an embodiment, the mTOR inhibitor is Omipalisib. Omipalisib has the chemical structure and name shown as: 2,4-difluoro-N-[2-methoxy-5-(4-pyridazin-4-ylquinolin-6-yl)pyridin-3-yl]benzenesulfonamide



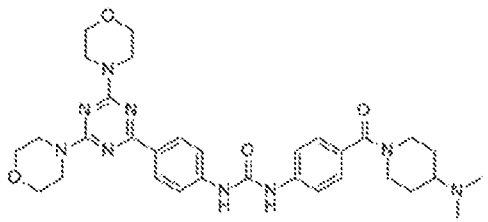
PF-04691502

[0412] In an embodiment, the mTOR inhibitor is PF-04691502. PF-04691502 has the chemical structure and name shown as: 2-amino-8-[4-(2-hydroxyethoxy)cyclohexyl]-6-(6-methoxypyridin-3-yl)-4-methylpyrido[2,3-d]pyrimidin-7-one



Gedatolisib

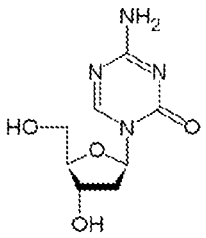
[0413] In an embodiment, the mTOR inhibitor is Gedatolisib. Gedatolisib has the chemical structure and name shown as: 1-[4-[4-(dimethylamino)piperidine-1-carbonyl]phenyl]-3-[4-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)phenyl]urea



Nucleoside analogs

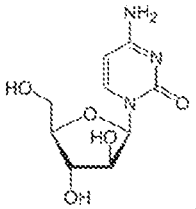
Decitabine

[0414] In an embodiment, the nucleoside analog is decitabine. decitabine has the chemical structure and name shown as: 4-amino-1-[(2R,4S,5R)-4-hydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2-one



Cytarabine

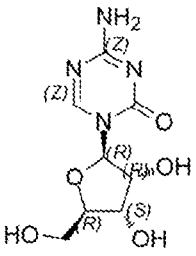
[0415] In an embodiment, the nucleoside analog is cytarabine. Cytarabine has the chemical structure and name shown as: 4-amino-1-[(2R,3S,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one



[0416]

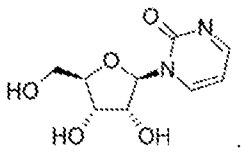
Azacitidine

[0417] In an embodiment, the nucleoside analog is azacitidine. Azacitidine has the chemical structure and name shown as: 4-amino-1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]-1,3,5-triazin-2-one



Zebularine

[0418] In an embodiment, the nucleoside analog is zebularine. Zebularine has the chemical structure and name shown as: 1-[(2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)oxolan-2-yl]pyrimidin-2-one



Pharmaceutical Compositions

[0419] In some embodiments, the invention provides pharmaceutical compositions comprising a combination comprising a MDM2 inhibitor and a therapeutic agent for treating a myeloproliferative neoplasm (MPN), wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In an embodiment, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD). In an embodiment, the myelofibrosis is selected from the group consisting of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF). In an embodiment, the primary myelofibrosis (PMF) is selected from the group consisting of prefibrotic/early stage PMF and overt fibrotic stage PMF. In an embodiment, the MPN is selected from the group consisting of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), hypereosinophilic syndromes (HES), and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

[0420] In an embodiment, the MDM2 inhibitor is a compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof.

[0421] In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0422] In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B, SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof.

[0423] In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof.

[0424] In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride.

[0425] In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof.

[0426] In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof.

[0427] In an embodiment, the anti-PD- L2 antibody is rHIgM12B7A.

[0428] In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof.

[0429] In an embodiment, the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof.

[0430] In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof.

[0431] In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof.

[0432] In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof.

[0433] In an embodiment, the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0434] In an embodiment, thrombocythemia is essential thrombocythemia (ET).

[0435] In an embodiment, myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia

myelofibrosis (post-ET MF).

Polycythemia Vera

[0436] In some embodiments, the invention provides pharmaceutical compositions comprising a combination of the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and a therapeutic agent for treating polycythemia vera, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, a mTOR inhibitor, and combinations thereof; wherein the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof; wherein , the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof; wherein the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof; wherein the anti-PD- L2 inhibitor is rHIgM12B7A; wherein the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof; wherein the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof; wherein the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable

salts thereof; wherein the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof; wherein the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

Essential Thrombocythemia (ET)

[0437] In some embodiments, the invention provides pharmaceutical compositions comprising a combination of the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and a therapeutic agent for treating essential thrombocythemia, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, a mTOR inhibitor, and combinations thereof; wherein the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof; wherein , the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof; wherein the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof; wherein the anti-PD- L2 inhibitor is rHIgM12B7A; wherein the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and

pharmaceutically acceptable salts thereof; wherein the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof; wherein the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof; wherein the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof; wherein the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

Myelofibrosis

[0438] In some embodiments, the invention provides pharmaceutical compositions comprising a combination of the compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and a therapeutic agent for treating myelofibrosis, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, a mTOR inhibitor, and combinations thereof; wherein the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically

acceptable salts thereof; wherein , the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof; wherein the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof; wherein the anti-PD- L2 inhibitor is rHIgM12B7A; wherein the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof; wherein the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof; wherein the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof; wherein the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof; wherein the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0439] In an embodiment, myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

[0440] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a MDM2 inhibitor and a therapeutically effective amount of a therapeutic agent, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an

IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants.

[0441] In selected embodiments, the concentration of a MDM2 inhibitor and a therapeutic agent provided in the pharmaceutical compositions of the invention is independently less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0442] In selected embodiments, the concentration of a MDM2 inhibitor and a therapeutic agent provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a

PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0443] In selected embodiments, the concentration of a MDM2 inhibitor and a therapeutic agent is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0444] In selected embodiments, the concentration of a MDM2 inhibitor and a therapeutic agent is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0445] In selected embodiments, the amount of a MDM2 inhibitor and a therapeutic agent is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0446] In selected embodiments, the amount of a MDM2 inhibitor and a therapeutic agent is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0447] A MDM2 inhibitor is effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently ranging from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

Pharmaceutical Compositions for Oral Administration

[0448] In selected embodiments, the invention provides a pharmaceutical composition for oral administration a combination comprising a MDM2 inhibitor and a therapeutic agent, and a pharmaceutical excipient suitable for oral administration, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0449] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) a combination comprising an effective amount of a MDM2 inhibitor and a therapeutic agent, in combination with (ii) a pharmaceutical excipient suitable for oral administration, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In selected embodiments, the composition further contains (iii) an effective amount of at least one additional active ingredient.

[0450] In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing

agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

[0451] The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

[0452] A combination of a MDM2 inhibitor with a therapeutic agent can be further combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules,

and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

[0453] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and combinations thereof.

[0454] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and combinations thereof.

[0455] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or combinations thereof.

[0456] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or combinations thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or combinations thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

[0457] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

[0458] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

[0459] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and combinations thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

[0460] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils,

while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

[0461] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and combinations thereof.

[0462] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and combinations thereof.

[0463] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate,

stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and combinations thereof.

[0464] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and combinations thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

[0465] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol,

polyglyceryl-10 oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

[0466] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and combinations thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and combinations thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

[0467] In an embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use, such as for compositions for injection. A solubilizer may also be added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

[0468] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, *N*-

alkylpyrrolidone, *N*-hydroxyalkylpyrrolidone, *N*-alkylpiperidone, *N*-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, epsilon-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

[0469] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

[0470] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present, the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

[0471] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and combinations thereof.

[0472] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, *p*-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Examples may include, but are not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

[0473] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, *p*-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

[0474] In selected embodiments, the invention provides a pharmaceutical composition for injection comprising a combination comprising a MDM2 inhibitor and a therapeutic agent, and a pharmaceutical excipient suitable for injection, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0475] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

[0476] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable combinations thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

[0477] Sterile injectable solutions are prepared by incorporating a MDM2 inhibitor and a therapeutic agent in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0478] Administration of a combination comprising a MDM2 inhibitor and a therapeutic agent can be effected by any method that enables delivery of the compounds to the site of action, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intra-arterial, subcutaneous, intramuscular, intravascular, or infusion), topical (*e.g.*, transdermal application), via local delivery by catheter or stent.

[0479] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

[0480] The invention also provides kits. The kits include a MDM2 inhibitor and a therapeutic agent, either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving *in vivo* models and studies based on human clinical trials. The kit may further contain another active pharmaceutical ingredient. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer. In an embodiment, the invention provides a kit comprising a combination comprising a MDM2 inhibitor and a therapeutic agent for use in the treatment of a MPN,

wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In an embodiment, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD). In an embodiment, the myelofibrosis is selected from the group consisting of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF). In an embodiment, the primary myelofibrosis (PMF) is selected from the group consisting of prefibrotic/early stage PMF and overt fibrotic stage PMF. In an embodiment, the MPN is selected from the group consisting of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), hypereosinophilic syndromes (HES), and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)..

Dosages and Dosing Regimens

[0481] The amount of a MDM2 inhibitor and a therapeutic agent administered will be independently dependent on the human being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

[0482] In some embodiments, a MDM2 inhibitor and a therapeutic agent are independently administered in a single dose, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. Typically, such administration will be by injection - *e.g.*, intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of a MDM2 inhibitor and a therapeutic agent may also be used for treatment of an acute condition, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0483] In some embodiments, a MDM2 inhibitor and a therapeutic agent are independently administered in multiple doses for treating a MPN, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In an embodiment, a MDM2 inhibitor and a JAK inhibitor are independently administered in multiple doses by injection - *e.g.*, intravenous injection. In an embodiment, dosing may be once, twice, three times, four times, five times, six times, or more than six times per day. In an embodiment, dosing may be selected from the group consisting of once a day, twice a day, three times a day, four times a day, five times a day, six times a day, once every other day, once weekly, twice weekly, three times weekly, four times weekly, biweekly, and monthly. In some embodiments a MDM2 inhibitor and a therapeutic agent are independently administered three times a week, including every Monday, Wednesday, and Friday, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0484] Administration of a MDM2 inhibitor and a therapeutic agent may independently continue as long as necessary, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2

inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In some embodiments, the MDM2 inhibitor and the therapeutic agent are independently administered for more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31 or more days. In some embodiments, the MDM2 inhibitor and the therapeutic agent are independently administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, the MDM2 inhibitor and the therapeutic agent are independently administered for about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, or about 56 days. In some embodiments, the MDM2 inhibitor and the therapeutic agent are independently administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects. In another embodiment, the administration of the MDM2 inhibitor and the therapeutic agent independently continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, three months, four months, five months, six months, seven months, eight months, nine months, ten months, eleven months or one year. In some embodiments, the administration continues for more than about one year, two years, three years, four years, or five years. In some embodiments, continuous dosing is achieved and maintained as long as necessary.

[0485] In some embodiments, an effective dosage of the MDM2 inhibitor and the therapeutic agent is independently in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10 mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof. In some embodiments, an effective

dosage of the MDM2 inhibitor and the therapeutic agent is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In some embodiments, an effective dosage of a MDM2 inhibitor or a JAK inhibitor is 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0486] In some embodiments, an effective dosage of the MDM2 inhibitor or the therapeutic agent is independently in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a MDM2 inhibitor or a JAK inhibitor is about 0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

[0487] In some embodiments, a MDM2 inhibitor or a pharmaceutically acceptable salt thereof is administered at a dosage of 10 to 500 mg BID, including a dosage of 15 mg, 25 mg, 30 mg, 50

mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg BID.

[0488] In some embodiments, a MDM2 inhibitor or a pharmaceutically acceptable salt thereof is administered at a dosage of 10 to 500 mg QD, including a dosage of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg QD.

[0489] In some embodiments, the interferon is administered in a dose selected from the group consisting of about 1 million international units (MU) to about 800 MU, from about 1 MU to about 10 MU, from about 20 MU to about 40 MU, from about 2 MU to about 15 MU, from about 5 MU to about 25 MU, from about 50 MU to about 100 MU, from about 150 MU to about 250 MU, from about 300 MU to about 400 MU, and from about 500 MU to about 600 MU.

[0490] In some embodiments, the interferon is administered in a dose selected from the group consisting of from about 0.1 μg/day to about 1 mg/day, from about 10 μg/day to about 200 μg/day, from about 20 μg/day to about 150 μg/day, from about 0.1 μg/day to about 125 μg/day, from about 1 μg/day to about 20 μg/day, and about 4.5 μg/day to about 30 μg/day.

[0491] In some embodiments, the interferon is administered in a dose selected from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, and 30 MU/m^2.

[0492] An effective amount of the MDM2 inhibitor or the therapeutic agent may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including buccal, sublingual, and transdermal routes, by intra-arterial injection, intravenously, parenterally, intramuscularly, subcutaneously or orally.

[0493] In some embodiments, the MDM2 inhibitor and the therapeutic agent are independently administered to a subject intermittently, known as intermittent administration. By "intermittent administration", it is meant a period of administration of a therapeutically effective dose of a MDM2 inhibitor and/or the therapeutic agent, followed by a time period of discontinuance, which is then followed by another administration period and so on. In each administration period, the dosing frequency can be independently select from three times daily, twice daily,

daily, once weekly, twice weekly, three times weekly, four times weekly, five times weekly, six times weekly or monthly. In an embodiment, the MDM2 inhibitor is the compound of Formula (I) or Formula (II). In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B, SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride. In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof. In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof. In an embodiment, the anti-PD- L2 antibody is rHIgM12B7A. In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof. In an embodiment, the mTOR

inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof. In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof. In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof. In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof. In an embodiment, the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0494] By "period of discontinuance" or "discontinuance period" or "rest period", it is meant to the length of time when discontinuing of the administration of the MDM2 inhibitor and/or the therapeutic agent. The time period of discontinuance may be longer or shorter than the administration period or the same as the administration period. For example, where the administration period comprises three times daily, twice daily, daily, once weekly, twice weekly, three times weekly, four times weekly, five times weekly, six times weekly or monthly dosing, the discontinuance period may be at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, one month, two months, three months, four months or more days. During the discontinuance period, other therapeutic agents other than a MDM2 inhibitor and the therapeutic agent may be administered.

[0495] In an embodiment, the MDM2 inhibitor and the therapeutic agent are independently administered to a human subject in need thereof for treating a myeloproliferative neoplasm (MPN) for a first administration period, then followed by a discontinuance period, then followed

by a second administration period, and so on. In an embodiment, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD). In an embodiment, the myelofibrosis is selected from the group consisting of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF). In an embodiment, the primary myelofibrosis (PMF) is selected from the group consisting of prefibrotic/early stage PMF and overt fibrotic stage PMF. In an embodiment, the MPN is selected from the group consisting of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), hypereosinophilic syndromes (HES), and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). The first administration period, the second administration period, and the discontinuance period are independently selected from the group consisting of more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, one month, two months, three months, four months and more days, in which the MDM2 inhibitor and the therapeutic agent are independently administered to a subject three times daily, twice daily, daily, once weekly, twice weekly, three times weekly, four times weekly, five times weekly, six times weekly or monthly. In an embodiment, the first administration period is at same length as the second administration period. In an embodiment, the first administration period is shorter than the second administration period. In an embodiment, the first administration period is longer than the second administration period. In an embodiment, the first administration period and the second administration period are about three weeks, in which the MDM2 inhibitor and the therapeutic agent are independently administered to a subject daily; and the discontinuance is about two weeks. In an embodiment, the first administration period and the second administration period are about three weeks, in which the MDM2 inhibitor and the therapeutic agent are independently administered to a subject weekly; and the discontinuance is about two weeks. In an embodiment, the first administration period and the second administration period are about four weeks, in which the MDM2 inhibitor and the therapeutic agent are independently administered to a subject daily; and the discontinuance is about two weeks. In an embodiment,

the first administration period and the second administration period are about four weeks, in which the MDM2 inhibitor and the therapeutic agent are independently administered to a subject weekly; and the discontinuance is about two weeks. In an embodiment, the MDM2 inhibitor is the compound of Formula (I) or Formula (II). In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B, SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride. In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof. In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof. In an embodiment, the anti-PD- L2 antibody is rHIgM12B7A. In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-

0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof. In an embodiment, the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof. In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof. In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof. In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof. In an embodiment, the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0496] In an embodiment, the MDM2 inhibitor is administered to a human intermittently; while the therapeutic agent is administered to a human non-intermittently. In an embodiment, the therapeutic agent is administered to a human intermittently; while the MDM2 inhibitor is administered to a human non-intermittently. In an embodiment, both the MDM2 inhibitor and the therapeutic agent are administered to a human intermittently. In an embodiment, both the MDM2 inhibitor and the therapeutic agent are administered to a human non-intermittently.

Methods of Treating a Myeloproliferative Neoplasm (MPN)

[0497] In an embodiment, the invention relates to a method of treating a MPN in a human that comprises the step of administering to said human a therapeutically effective amount of a MDM2 inhibitor and a therapeutic agent in a dosage independently selected from the group consisting of

15 mg QD, 25 mg QD, 30 mg QD, 50 mg QD, 60 mg QD, 75 mg QD, 100 mg QD, 120 mg QD, 150 mg QD, 175 mg QD, 200 mg QD, 225 mg QD, 240 mg QD, 250 mg QD, 275 mg QD, 300 mg QD, 325 mg QD, 350 mg QD, 360 mg QD, 375 mg QD, 480 mg QD, 15 mg BID, 25 mg BID, 30 mg BID, 50 mg BID, 60 mg BID, 75 mg BID, 100 mg BID, 120 mg BID, 150 mg BID, 175 mg BID, 200 mg BID, 225 mg BID, 240 mg BID, 250 mg BID, 275 mg BID, 300 mg BID, 325 mg BID, 350 mg BID, 360 mg BID, 375 mg BID, and 480 mg BID. In an embodiment, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD). In an embodiment, the myelofibrosis is selected from the group consisting of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF). In an embodiment, the primary myelofibrosis (PMF) is selected from the group consisting of prefibrotic/early stage PMF and overt fibrotic stage PMF. In an embodiment, the MPN is selected from the group consisting of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), hypereosinophilic syndromes (HES), and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). In an embodiment, the MDM2 inhibitor is the compound of Formula (I) or Formula (II). In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B, SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805,

Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride. In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof. In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof. In an embodiment, the anti-PD- L2 antibody is rHIgM12B7A. In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof. In an embodiment, the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof. In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof. In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof. In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof. In an embodiment, the interferon is selected from the group consisting of interferon-

alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0498] In an embodiment, the invention relates to a combination of a therapeutically effective amount of a MDM2 inhibitor and a therapeutic agent for use of treating a MPN in a human, wherein the MDM2 inhibitor and the therapeutic agent are administered in a dosage independently selected from the group consisting of 15 mg QD, 25 mg QD, 30 mg QD, 50 mg QD, 60 mg QD, 75 mg QD, 100 mg QD, 120 mg QD, 150 mg QD, 175 mg QD, 200 mg QD, 225 mg QD, 240 mg QD, 250 mg QD, 275 mg QD, 300 mg QD, 325 mg QD, 350 mg QD, 360 mg QD, 375 mg QD, 480 mg QD, 15 mg BID, 25 mg BID, 30 mg BID, 50 mg BID, 60 mg BID, 75 mg BID, 100 mg BID, 120 mg BID, 150 mg BID, 175 mg BID, 200 mg BID, 225 mg BID, 240 mg BID, 250 mg BID, 275 mg BID, 300 mg BID, 325 mg BID, 350 mg BID, 360 mg BID, 375 mg BID, and 480 mg BID. In an embodiment, the MPN is selected from the group consisting of polycythemia vera (PV), myelofibrosis, primary myelofibrosis, thrombocythemia, essential thrombocythemia (ET), idiopathic myelofibrosis, systemic mastocystosis (SM), chronic neutrophilic leukemia (CNL), myelodysplastic syndrome (MDS), and systemic mast cell disease (SMCD). In an embodiment, the myelofibrosis is selected from the group consisting of primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF). In an embodiment, the primary myelofibrosis (PMF) is selected from the group consisting of prefibrotic/early stage PMF and overt fibrotic stage PMF. In an embodiment, the MPN is selected from the group consisting of chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia (aCML), juvenile myelomonocytic leukemia (JMML), hypereosinophilic syndromes (HES), and myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). In an embodiment, the MDM2 inhibitor is the compound of Formula (I) or Formula (II). In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, Triptolide, HDM201, RG7112, CGM097A, CGM0970B, SJ-172550, SAR405838, MI-773, MX69, YH239-EE, RO8994, Nutlin-3, Nutlin-3a, Nutlin-3b, Serdemetan, NSC59984, CHEMBL2386350, MK-8242, DS-3032, DS-3032B, RO6839921, APG-115, MI-1601, and

pharmaceutically acceptable salts thereof. In an embodiment, the MDM2 inhibitor is selected from the group consisting of a compound of Formula (I), Formula (II), RG7388, HDM201, RG7112, CGM097A, CGM0970B, SAR405838, MK-8242, DS-3032B, RO6839921, APG-115, MI-1601, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof. In an embodiment, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride. In an embodiment, the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof. In an embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof. In an embodiment, the anti-PD- L2 antibody is rHIgM12B7A. In an embodiment, the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof. In an embodiment, the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof. In an embodiment, the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib,

Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof. In an embodiment, the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof. In an embodiment, the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof. In an embodiment, the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

[0499] The methods described above may be used as first-line cancer therapy, or after treatment with conventional chemotherapic active pharmaceutical ingredients, including cyclophosphamide, fludarabine (FC chemotherapy), and chlorambucil.

[0500] The combination of the MDM2 inhibitor and the therapeutic agent may also be used in combination with radiation therapy, hormone therapy, surgery and immunotherapy, which therapies are well known to those skilled in the art.

Examples

[0501] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1: Effects of the combination of the compound of Formula (I) with a therapeutic agent on Polycythemia Vera Cells

[0502] The procedure of testing the effects of the combination of the compound of Formula (I) with a therapeutic agent on polycythemia vera cells follows that described in Lu, Blood, 2012, 120(15); 3098-3105, the entirety of which is incorporated by reference. The following describes

the procedure briefly. The therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

Cell Preparation:

[0503] Peripheral blood will be obtained from polycythemia vera (PV) patients. Appropriate approval will be obtained from the Institutional Review Board. Informed consent will be obtained before the study. All patients will meet the World Health Organization diagnostic criteria for polycythemia vera (PV). The peripheral blood samples are layered onto Ficoll-Hypaque (1.077 g/mL; GE Healthcare) and low-density mononuclear cells are separated via centrifugation. The CD34+ cells will be isolated using a human CD34+ cell selection kit (StemCell Technologies) according to the manufacturer's instructions. The purity of the CD34+ cell population will be analyzed using a FACSCalibur flow cytometer (BD Biosciences); and is required for at least 85% for all experiments. Fresh normal human bone marrow CD34+ cells will be purchased from ALLCELLS as a control.

HPC Assays

[0504] The effects of the compound of Formula (I) on polycythemia vera (PV) patients can be assessed by the HPC assays, described in Lu, Blood, 2012, 3098-3105, the entirety of which is incorporated by reference. In brief, CD34+ cells will be cultured in serum free medium (StemCell Technologies) containing 50 ng/mL stem cell factor (SCF), 50 ng/mL thrombopoietin (TPO), 50 ng/mL fms-like tyrosine kinase 3 (Flt-3) ligand, and 50 ng/mL IL-3, and will be treated with various dose of the compound of Formula (I) for 4 days. After 4 days of treatment, CD34+ cells will be assayed in semisolid media as described in Bruno, Blood, 2006, 3128-3134, the entirety of which is incorporated by reference. Briefly, 5×10^2 CD34+ cells will be plated per dish in duplicate cultures containing 1 mL IMDM with 1.1% methylcellulose and 20% FBS, to which SCF, TPO, Flt-3 ligand, IL-3, and GM-CSF at each 50 ng/mL, and 2 U/mL erythropoietin (EPO) will be added. Colonies will be enumerated after 14 days of incubation, and individual colonies will be plucked and genotyped for JAK2V617F.

Nested allele-specific PCR for JAK2V617F-positive colonies

[0505] Genomic DNA will be isolated from randomized plucked colonies using the Extract-N-Amp Blood PCR Kits (Sigma-Aldrich). JAK2V617F will be detected by using a nested allele-specific PCR as described in Bruno, Blood, 2006, 3128-3134, the entirety of which is incorporated by reference. The final PCR products will be analyzed on 2.0% agarose gels. A 279-bp product indicates allele-specific JAK2V617F-positive, whereas a 229-bp product indicates JAK2V617F-negative. Colonies will be classified as homozygous for JAK2V617F if they contained only the 279-bp band, whereas heterozygous colonies will be identified based on the presence of both the 279-bp and 229-bp bands.

Apoptosis assay

[0506] Treated cells will be collected and washed with PBS for staining with annexin-V (BD Biosciences); the staining procedures will be performed according to the protocols provided by the manufacturer. Data will be acquired on a FACSCalibur flow cytometer (BD Biosciences), and at least 10 000 live cells will be acquired for each analysis (BD FACS Diva software; BD Biosciences).

Western blot analysis

[0507] CD34+ cells will be purified from the peripheral blood of patients with polycythemia vera (PV) and cultured in serum-free medium contained with SCF, FL-3 ligand, IL-3, and TPO. The cells will be treated with various dose of the compound of Formula (I) for 4 hours. Cells will be harvested and the whole cells protein extracts will be prepared with RIPA lysis buffer (Boston BioProducts) for Western blotting.

[0508] To prepare the cytoplasmic and nuclear protein fractions of cells from patients with polycythemia vera (PV), CD34+ cells will be expanded in serum-free media containing SCF, FL-3 ligand, and IL-3 for 10 days. CD34+ cells will be then repurified and treated with various doses of the compound of Formula (I) for 48 hours in the presence of SCF, FL-3 ligand, IL-3, and TPO. The protein extracts will be prepared using the NE-PER nuclear and cytoplasmic extraction reagent (Thermo Scientific) according to the manufacturer's instructions.

[0509] Before Western blotting, all the samples will be denatured with Laemmli SDS-sample buffer (Boston BioProducts) by heating at 95°C for 5 minutes; each sample will be separated on SDS-PAGE gels and transferred to polyvinyldifluoridine membranes (Bio-Rad). Phospho-p53, p53, MDM2, p21, p-STAT1, PUMA, and Bak were visualized using the antibodies (Cell Signaling Technologies) and ECL Western blotting reagents (Denville Scientific).

Example 2. Modeling transformation of JAK2V617F mutated MPNs: role of interferon alpha and MDM2 inhibition in Prevention of disease progression

[0510] Philadelphia chromosome-negative myeloproliferative neoplasms are clonal hematological malignancies characterized by increased proliferation of myeloid lineages, leading to an abnormally high number of mature blood cells. They comprise polycythemia vera (PV), essential thrombocytemia (ET) and primary myelofibrosis (PMF). At the opposite of PMF, PV and ET are chronic diseases with a median survival over 15 years. However, the major risk is the progression to secondary acute myeloid leukemia (sAML) associated to a very poor outcome. The hematopoietic stem or progenitor cells in MPN accumulate genetic and epigenetic alterations that model the phenotype and promote the hematologic evolution. The genomic landscape of sAML is close to that observed in therapy-related acute myeloid leukemia (tAML) with mutations of TP53. Indeed, leukemic transformation of PV and ET harbour TP53 mutations (loss of function mutation mainly) in approximatively 35-50% of cases.

[0511] Treatments are restricted to bone marrow transplantation when sAML develop, and currently available therapies (cytarabine, anthracyclines, hypomethylating agents etc.) remain poorly successful in such cases. Medical treatments for PMF developed to date are more or less only palliative (JAK2 inhibitors, hypomethylating agents, hydroxyurea) and don't prevent disease progression.

[0512] Modelling the myeloproliferation and the acute transformation in mice models harbouring JAK2V617F mutation and inactivated or not for TP53 and test in these models the influence on disease development of treatments with interferon-alpha (IFNa), the compound of Formula (I) or (II), or combination of both drugs.

[0513] In order to study disease progression in vivo, the cooperation of 2 mutations JAK2 with P53 deletion through mice models are studied. The inducible KI JAK2V617F mice will be used, which develop polycythemia, granulocytosis and thrombocytosis along with myelofibrosis. The JAK2V617F mutation is expressed in these CD45.2 mice after crossing with CD45.2 Tg(Vav-cre) A2Kio mice. The CD45.2 vav-cre mice crossed with the JAK2V617F induce a MPN in less than 6 weeks leading to development of myelofibrosis without leukemia in 6 months. These JAK2V617F KI mice and vav-cre will be crossed to P53 KO mice and then backcrossed in TP53KO background in order to obtain on one hand vav-cre/TP53 KO mice and JAK2V617F flox +/-/ TP53 KO mice on the other hand. The two types of mice will be crossed to obtain CD45.2 vav-cre/JAK2V617F/TP53 KO mice.

[0514] The combination of JAK2V617F and P53KO has already been studied though retroviral mouse models, the mice develop AML with a massive expansion of erythromegakaryocytic progenitors. However, these studies used retroviral mouse models then the expression level of the transgene vary from one clone to another, and the JAK2V617F KI mice used here will be closer to what occurs in patients with expression of JAK2V617F at the same level in all stem cells.

[0515] Bone marrow transplanted cells will be used in order to mix normal and mutant cells in a mouse recipient. Then, bone marrow cells of the JAK2V617F mice marrow (CD45.2 phenotype), of the JAK2V617F / TP53 KO mice (CD45.2), or of CD451+2 normal mice will be sorted. A healthy mouse (WT) of CD45.1 phenotype, will serve as a host after irradiation. Either the JAK2V617F CD45.1 and the normal CD451+2 cells in CD45.2 background or the CD45.1 JAK2V617F / TP53 KO cells with CD451+2 normal cells in CD45.2 irradiated mice will be transplanted. The ratio of pathological cells versus normal cells will be 20/80, a ratio previously demonstrated as able to induce MPN in recipients in less than 2 months. Ten mice will be transplanted from one donor, leading to 10 grafted mice/pathological mouse. Groups of 20 mice will be studied.

[0516] To measure the impact of IFN alpha, the compound of Formula (I) or (II), or combination therapy on the potential effect on malignant clones, the grafted mice will be divided into four groups that will be treated at day 15 after BMT (normalization of blood cell count after

transplant): one by IFN alpha, one by the compound of Formula (I) or (II), one by a combination of both drugs and one with PBS as control. Chimerism and phenotype (weight, hematologic parameters, etc.) will be analyzed every week (on blood), and on bone marrow chimerism in each stem cell and progenitor compartment (SLAM, Short term, progenitors) at months 1, 3 and 6. Secondary transplantations will be performed if chimerism demonstrates statistically significant modification in the blood. The monitoring of their hematological parameters will help detect the chronic disease, namely a PV/MF phase (increase in the number of red blood cells, platelets, etc.) or AML (increase in the number of circulating immature cells). If treatments modify the chimerism and allow for the selection of normal cells, in the group of treated mice, an increase in the percentage of CD451+2 cells leading to a lower rate or absence of transformation to AML will be observed. Such an outcome indicates that the treatments are able to reduce or cure the JAK2V617F clones and / or the P53 mutated/inactivated JAK2V617F sub-clones respectively.

Example 3: Effect of the Combination of the Compound of Formula (I) and Decitabine on MPN-BP Stem Cells

MPN-BP cell preparation

[0517] Currently, $CD3^+$ cell-depleted mononuclear cells (MNC) from 1 patient with MPN-BP who had WT *TP53* gene have been shown to be capable of serially engrafting and causing leukemia in NSG mice. In order to harvest sufficient cells to assess the effects of the combination of the compound of Formula (I) and decitabine on MPN-BP stem cells, MPN-BP cells collected from the bone morrow (BM) or spleens of NSG mice will be passaged in NSG mice by serial transplantation. The mutational patterns and karyotypic abnormalities present in the cells following serial transplantation will be determined by capture based next generation sequencing (NGS) and fluorescence in situ hybridization (FISH).

Effects of the Combination of the Compound of Formula (I) and Decitabine

[0518] In order to examine the effects of the combination of the compound of Formula (I) and decitabine on MPN-BP stem cells, $0.5\text{-}2\times10^6$ cells/mouse harvested from NSG mice receiving MPN-BP cells will be transplanted into sublethally irradiated (220 cGy) 8-9-week-old NSG mice. The mice will then be monitored daily for their general condition and their body weight

measured weekly. Twenty-eight days after transplantation, peripheral blood from the recipient mice will be collected and analyzed with the performance of complete blood counts (CBC) and flow cytometric analysis to determine if human MPN-BP has developed in these mice. These mice will be used in the following studies.

High Dose Study of the Compound of Formula (I) or decetabine

[0519] The mice that have developed MPN-BP and have a similar leukemic burden in peripheral blood will be randomly divided into 4 groups of 3-4 mice. Two groups of mice will be treated with vehicle or the compound of Formula (I) (high dose, either 100 or 150 mg/kg) by oral gavage once per day for 7 days. The other two groups of mice will be treated with vehicle or decitabine at 5 mg/kg by IP injection 3 times/week for 7 days. After the treatment, peripheral blood blast count will be monitored using flow cytometric analysis weekly. Tolerability to the treatment will be assessed by daily body weight (BW) measurements. These analyses will allow to establish dynamics of MPN-BP return following each drug treatment which will be used to determine the treatment-free interval for the following survival and combination treatment studies.

Combination treatment with Low Doses of the Compound of Formula (I) and Decitabine

[0520] NSG mice engrafted with MPN-BP cells will be randomly assigned to 4 groups of 4-5 mice. These mice will be treated with the compound of Formula (I), decitabine alone or in combination as following. Group 1: the compound of Formula (I)+PBS; Group; 2: Vehicle + decitabine; Group 3: the compound of Formula (I)+ decitabine; Group 4: Vehicle + PBS. The compound of Formula (I) at 30-50 mg/kg or vehicle will be dosed once daily by oral gavage on days 1-7 for 7 days. Decitabine (2.5 mg/kg) or PBS will be dosed by IP injection 3 times/week for 7 days. Treatments will be repeated for up to 3 cycles. After the treatment, survival and disease progression will be monitored and mice will be sacrificed and analyzed. After the mice are sacrificed, cells will be recovered from the BM, spleen, and the peripheral blood. The presence of human $CD45^+$, $CD34^+$, $CD33^+$, $CD14^+$, Gly A^+, $CD41a^+$, $CD19^+$, and $CD3^+$ cells in these organs will be determined by mAb staining and flow cytometric analysis.

Example 4: An Open-Label, Multicenter, Phase 1b/2 Study of the Safety and Efficacy of the compound of formula I Combined with Low-Dose Cytarabine (LDAC) or Decitabine in Patients with Acute Myeloid Leukemia (AML)

[0521] All subjects will receive the compound of formula I combined with low-dose cytarabine (LDAC) or decitabine. Dosing Formulation for the compound of formula I: this compound is formulated as an immediate-release, oral, solid dosage form, in tablet strengths of 15 mg and 60 mg. For administration: the compound of formula I should be taken on an empty stomach in the morning (no food or liquids except water 2 hours prior to drug) and refrain from food and liquid intake (except water) for 2 hours post dose. Tablets should not be crushed, chewed, or dissolved in water. The compound of formula I will be administered on Days 1 through 7 of every treatment cycle, which is 28 days.

[0522] For cytarabine, LDAC will be administered at 20 mg/m2/day by subcutaneous (SC) injection once daily on Days 1 through 10 of each 28-day cycle. For decitabine, it will be administered at 20 mg/m2/day intravenously (IV) once daily on Days 1 through 5 of each 28-day cycle.

Study Polulation

Part A (Phase 1b): The subject population will consist of male or female individuals age 18 years or older with relapsed or refractory AML.

Part B (Phase 2): The subject population will consist of male or female individuals age 18 years or older with newly diagnosed or relapsed or refractory AML secondary to myeloproliferative neoplasms (MPN).

Study Treatments

[0523] All subjects will receive the compound of formula I combined with low-dose cytarabine (LDAC) or decitabine.

Study Design

[0524] Part A (Phase 1b): The phase 1b portion of the study follows a 3+3 dose-escalation design to determine the recommended phase 2 dose (RP2D) of the compound of formula I for the

phase 2 portion of the study. The investigator may assign subjects to either Cohort 1 (LDAC) or Cohort 2 (decitabine) if there are open spots for enrollment in that cohort, and if the subject meets eligibility criteria for that cohort.

[0525] Compound of formula I Dose Level 1 (Starting Dose): 240 mg orally once daily administered on Days 1 through 7 of each 28-day cycle in combination with LDAC at 20 mg/m^2/day SC once daily on Days 1 through 10 of each 28-day cycle (Cohort 1A, n=3 to 6 subjects), or Decitabine 20 mg/m^2/day IV once daily on Days 1 through 5 of each 28-day cycle (Cohort 2A, n=3 to 6 subjects).

[0526] If there are no dose-limiting toxicities (DLTs) in the first 3 subjects enrolled in Dose Level 1 (Cohort 1A or Cohort 2A), Dose Level 2 will open for that cohort. If there is at least 1 DLT among the first 3 subjects enrolled in Cohort 1A or Cohort 2A, then 3 additional subjects will be added to the cohort in which the DLT occurred, for a total of 6 subjects in the cohort. If there is ≤1 DLT among the 6 subjects in a cohort, then Dose Level 2 will open for that cohort. If there are 2 or more DLTs in Cohort 1A or Cohort 2A, then the Dose Level 1 Step-Down cohorts will open.

[0527] Dose Level 1 Step-Down Cohorts: 180 mg of the compound of formula I orally once daily administered on Days 1 through 7 of each 28-day cycle in combination with LDAC at 20 mg/m^2/day SC once daily on Days 1 through 10 of each 28-day cycle (Cohort 1A-1, n=3 to 6 subjects), or Decitabine 20 mg/m2/day IV once daily on Days 1 through 5 of each 28-day cycle (Cohort 2A-1, n=3 to 6 subjects). If there are no DLTs among the first 3 subjects enrolled in the Dose Level 1 Step-Down (Cohort 1A-1 or Cohort 2A-1), then the Dose Level 1 Step-Down will be declared the RP2D for that cohort. If there is at least 1 DLT among the first 3 subjects enrolled in Cohort 1A-1 or Cohort 2A-1, 3 additional subjects will be added to the cohort in which the DLT occurred, for a total of 6 subjects in the cohort. If there is ≤1 DLT among the 6 subjects in a cohort, then the Dose Level 1 Step-Down will be declared the recommended RP2D for the cohort. If there are 2 or more DLTs at the Dose Level 1 Step-Down (Cohort 1A-1 or Cohort 2A-1), then that cohort will be closed.

[0528] Dose Level 2: 360 mg of the compound of formula I orally once daily administered on Days 1 through 7 of each 28-day cycle in combination with LDAC at 20 mg/m^2/day SC once daily on Days 1 through 10 of each 28-day cycle (Cohort 1B, n=3 to 6 subjects), or decitabine 20 mg/m^2/day IV once daily on Days 1 through 5 of each 28-day cycle (Cohort 2B, n=3 to 6 subjects). If there are no DLTs among the first 3 subjects enrolled in Dose Level 2 (Cohort 1B or Cohort 2B), then the compound of formula I Dose Level 3 will open for that cohort. If there is at least 1 DLT among the 3 subjects enrolled in Dose Level 2 (Cohort 1B or Cohort 2B), then 3 additional subjects will be added to the cohort in which the DLT occurred, for a total of 6 subjects in the cohort. If there is ≤1 DLT among the 6 subjects in a cohort, then Dose Level 3 will open for that Cohort. If there are 2 or more DLTs in Cohort 1B or Cohort 2B, then the Dose Level 2 Step-Down cohorts will open.

[0529] Dose Level 2 Step-Down Cohorts*:* 300 mg of the compound of formula I orally once daily administered on Days 1 through 7 of each 28-day cycle in combination with LDAC at 20 mg/m^2/day SC once daily on Days 1 through 10 of each 28-day cycle (Cohort 1B-1, n=3 to 6 subjects), or decitabine 20 mg/m^2/day IV once daily on Days 1 through 5 of each 28-day cycle (Cohort 2B-1, n=3 to 6 subjects). If there are no DLTs among the first 3 subjects enrolled in the Dose Level 2 Step-Down (Cohort 1B-1 or Cohort 2B- 1), then the Dose Level 2 Step-Down will be declared the RP2D for that cohort. If there is at least 1 DLT among the first 3 subjects enrolled in Cohort 1B-1 or Cohort 2B-1, 3 additional subjects will be added to the cohort in which the DLT occurred, for a total of 6 subjects in the cohort. If there is ≤1 DLT among the 6 subjects in a cohort, then the Dose Level 2 Step-Down will be declared the recommended RP2D for the cohort. If there are 2 or more DLTs at the Dose Level 2 Step-Down (Cohort 1B-1 or Cohort 2B-1), then Dose Level 1 for that cohort will be declared the RP2D.

[0530] Dose Level 3: Cycle 1 only: 480 mg of the compound of formula I orally once daily administered on Days 1 through 7 of the first 28-day cycle in combination with LDAC or decitabine. Cycle 2 and beyond: 360 mg of the compound of formula I orally once daily administered on Days 1 through 7 of each 28-day cycle in combination with LDAC or decitabine. LDAC at 20 mg/m^2/day SC once daily on Days 1 through 10 of each 28-day cycle (Cohort 1C, n=3 to 6 subjects), or decitabine 20 mg/m^2/day IV once daily on Days 1 through 5 of each 28-day cycle (Cohort 2C, n=3 to 6 subjects). If there are no DLTs among the first 3 subjects

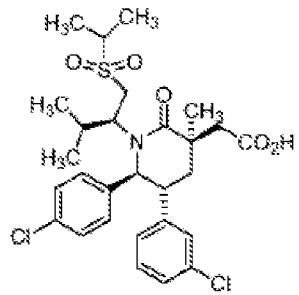
enrolled in Cohort 1C or Cohort 2C, then Dose Level 3 will be considered the RP2D for the cohort. If there is at least 1 DLT among the first 3 subjects enrolled in Cohort 1C or Cohort 2C, then 3 additional subjects will be added to the cohort in which the DLT occurred, for a total of 6 subjects in the cohort. If there is ≤1 DLT among the 6 subjects in a cohort, that dose of will be declared the RP2D for the cohort. If there are 2 or more DLTs in Cohort 1C or Cohort 2C, then the Dose Level 3 Step-Down cohorts will open.

[0531] Dose Level 3 Step-Down Cohorts*:* Cycle 1 only will be 420 mg of the compound of formula I orally once daily administered on Days 1 through 7 of the first 28-day cycle in combination with LDAC or decitabine. Cycle 2 and beyond: 360 mg of the compound of formula I orally once daily administered on Days 1 through 7 of each 28-day cycle in combination with LDAC or decitabine. LDAC at 20 mg/m^2/day SC once daily on Days 1 through 10 of each 28-day cycle (Cohort 1C-1, n=3 to 6 subjects), or decitabine 20 mg/m2/day IV once daily on Days 1 through 5 of each 28-day cycle (Cohort 2C-1, n=3 to 6 subjects). If there are no DLTs among the first 3 subjects enrolled in the Dose Level 3 Step-Down (Cohort 1C-1 or Cohort 2C-1), then the Dose Level 3 Step-Down will be declared the RP2D for that cohort. If there is at least 1 DLT among the first 3 subjects enrolled in Cohort 1C-1 or Cohort 2C-1, 3 additional subjects will be added to the cohort in which the DLT occurred, for a total of 6 subjects in the cohort. If there is ≤1 DLT among the 6 subjects in a cohort, then the Dose Level 3 Step-Down will be declared the recommended RP2D for the cohort. If there are 2 or more DLTs at the Dose Level 3 Step-Down (Cohort 1C-1 or Cohort 2C-1), then Dose Level 2 for that cohort will be declared the RP2D.

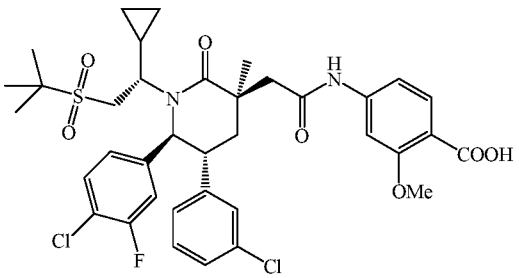
[0532] The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

CLAIMS

1. A method of treating a myeloproliferative neoplasm (MPN) comprising administering to a human in need thereof, therapeutically effective amounts of a MDM2 inhibitor in combination with a therapeutic agent, wherein the MDM2 inhibitor is a compound of Formula (I) or a compound of Formula (II):



(I)



(II)

or a pharmaceutically acceptable salt thereof, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

2. The method of claim 1, wherein the MPN is polycythemia vera (PV).

3. The method of claim 1, wherein the MPN is thrombocythemia.

4. The method of claim 3, wherein thrombocythemia is essential thrombocythemia (ET).

5. The method of claim 1, wherein the MPN is myelofibrosis.

6. The method of claim 5, wherein myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

7. The method of claim 1, wherein the MPN is chronic myelogenous leukemia.

8. The method of claim 1, wherein the MPN is systemic mastocystosis (SM).

9. The method of claim 1, wherein the MPN is chronic neutrophilic leukemia (CNL).

10. The method of claim 1, wherein the MPN is myelodysplastic syndrome (MDS).

11. The method of claim 1, wherein the MPN is mast cell disease (SMCD).

12. The method of claim 1, wherein the MPN is chronic eosinophilic leukemia.

13. The method of claim 1, wherein the MPN is chronic myelomonocytic leukemia (CMML).

14. The method of claim 1, wherein the MPN is atypical chronic myeloid leukemia (aCML).

15. The method of claim 1, wherein the MPN is juvenile myelomonocytic leukemia (JMML).

16. The method of claim 1, wherein the MPN is hypereosinophilic syndromes (HES).

17. The method of any one of claims 1 to 16, wherein the compound of Formula (I) or Formula (II) is in a crystalline form.

18. The method of claim 17, wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6 ± 0.1.

19. The method of any one of claims 1 to 16, wherein the compound of Formula (I) or Formula (II) is in a free form.

20. The method of any one of claims 1 to 16, wherein the compound of Formula (I) or Formula (II) is in an amorphous form.

21. The method of any one of claims 1 to 20, wherein the MDM2 inhibitor is a pharmaceutically acceptable salt of a compound of Formula (I) or Formula (II).

22. The method of any one of claims 1 to 21, wherein the compound of Formula (I) or Formula (II) is administered once daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

23. The method of any one of claims 1 to 21, wherein the compound of Formula (I) or Formula (II) is administered twice daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

24. The method of any one of claims 1 to 23, wherein the human is treated with the MDM2 inhibitor for a period selected from the group consisting of about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, and about 56 days.

25. The method of any one of claims 1 to 24, wherein the compound of Formula (I) or Formula (II) is orally administered.

26. The method of any one of claims 1 to 25, wherein the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof.

27. The method of any one of claims 1 to 25, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride.

28. The method of any one of claims 26 to 27, wherein the JAK inhibitor is administered orally.

29. The method of claim 1, wherein the MDM2 inhibitor is administered before administration of the therapeutic agent.

30. The method of claim 1, wherein the MDM2 inhibitor is administered after administration of the therapeutic agent.

31. The method of claim 1, wherein the MDM2 inhibitor is administered concurrently with administration of the therapeutic agent.

32. The method of any one of claims 1 to 31, wherein the therapeutically effective amount of the MDM2 inhibitor is 100 mg.

33. The method of claim 1, wherein the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof.

34. The method of claim 1, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof.

35. The method of claim 1, wherein the anti-PD-L2 inhibitor is rHIgM12B7A.

36. The method of claim 1, wherein the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof.

37. The method of claim 1, wherein the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof.

38. The method of claim 1, wherein the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof.

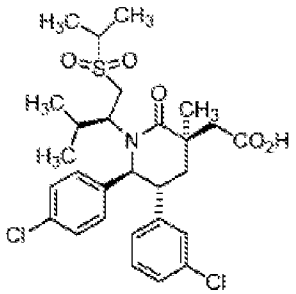
39. The method of claim 1, wherein the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof.

40. The method of claim 1, wherein the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof.

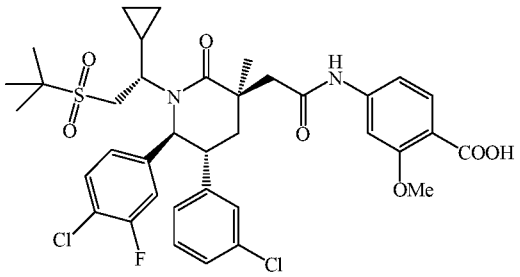
41. The method of claim 1, wherein the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

42. The method of any one of claims 1-41, wherein the MPN in the human subject has a JAK2V617F mutation.

43. A combination of therapeutically effective amounts of a MDM2 inhibitor and a therapeutic agent for use to treat a myeloproliferative neoplasm (MPN), wherein the MDM inhibitor is a compound of Formula (I) or a compound of Formula (II):



(I)



(II)

or a pharmaceutically acceptable salt thereof, wherein the therapeutic agent is selected from the group consisting of a JAK inhibitor, an IDH inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a PD-L2 inhibitor, an interferon, a PI3K inhibitor, an AKT inhibitor, an mTOR inhibitor, a nucleoside analog, and combinations thereof.

44. The use of claim 43, wherein the MPN is polycythemia vera (PV).

45. The use of claim 43, wherein the MPN is thrombocythemia.

46. The use of claim 45, wherein thrombocythemia is essential thrombocythemia (ET).

47. The use of claim 43, wherein the MPN is myelofibrosis.

48. The use of claim 47, wherein myelofibrosis is selected from primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF), and post-essential thrombocythemia myelofibrosis (post-ET MF).

49. The use of claim 43, wherein the MPN is chronic myelogenous leukemia.

50. The use of claim 43, wherein the MPN is systemic mastocystosis (SM).

51. The use of claim 43, wherein the MPN is chronic neutrophilic leukemia (CNL).

52. The use of claim 43, wherein the MPN is myelodysplastic syndrome (MDS).

53. The use of claim 43, wherein the MPN is mast cell disease (SMCD).

54. The use of claim 43, wherein the MPN is chronic eosinophilic leukemia.

55. The use of claim 43, wherein the MPN is chronic myelomonocytic leukemia (CMML).

56. The use of claim 43, wherein the MPN is atypical chronic myeloid leukemia (aCML).

57. The use of claim 43, wherein the MPN is juvenile myelomonocytic leukemia (JMML).

58. The use of claim 43, wherein the MPN is hypereosinophilic syndromes (HES).

59. The use of any one of claims 43 to 58, wherein the compound of Formula (I) or Formula (II) is in a crystalline form.

60. The use of claim 59, wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising at least three peaks at diffraction angle 2 theta degrees selected from a group consisting of peaks at approximately 11.6, 12.4, 18.6, 19.0, 21.6 and 23.6 ± 0.1.

61. The use of any one of claims 43 to 58, wherein the compound of Formula (I) or Formula (II) is in a free form.

62. The use of any one of claims 43 to 58, wherein the compound of Formula (I) or Formula (II) is in an amorphous form.

63. The use of any one of claims 43 to 62, wherein the MDM2 inhibitor is a pharmaceutically acceptable salt of a compound of Formula (I) or Formula (II).

64. The use of any one of claims 43 to 63, wherein the compound of Formula (I) or Formula (II) is administered once daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

65. The use of any one of claims 43 to 63, wherein the compound of Formula (I) or Formula (II) is administered twice daily at a dose selected from the group consisting of 15 mg, 25 mg, 30 mg, 50 mg, 60 mg, 75 mg, 100 mg, 120 mg, 150 mg, 175 mg, 200 mg, 225 mg, 240 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 360 mg, 375 mg, and 480 mg.

66. The use of any one of claims 43 to 65, wherein the human is treated with the MDM2 inhibitor for a period selected from the group consisting of about 14 days, about 21 days, about 28 days, about 35 days, about 42 days, about 49 days, and about 56 days.

67. The use of any one of claims 43 to 66, wherein the compound of Formula (I) or Formula (II) is orally administered.

68. The use of claim 43, wherein the JAK inhibitor is selected from the group consisting of AC-410, AT9283, AZ960, AZD-1480, Baricitinib, BMS-911543, CEP-33779, Cerdulatinib, CHZ868, CYT387, Decernotinib, ENMD-2076, Filgotinib, Ganetespib, INCB039110, INCB-047986, Itacitinib, JAK3-IN-1, JANEX-1, LFM-A13, LY2784544, NS-018, NSC42834, NVP-BSK805, Oclacitinib, Pacritinib, Peficitinib, Pyridone 6, R348, RGB-286638, Ruxolitinib, Ruxolitinib-S, SAR-20347, SB1317, Solcitinib, TG101209, TG101348, Tofacitinib(3R,4S), Tofacitinib(3S,4R), Tofacitinib(3S,4S), Tofacitinib, TYK2-IN-2, Upadacitinib, WHI-P154, WHI-P97, WP1066, XL019, ZM39923, and pharmaceutically acceptable salts thereof.

69. The use of claim 43, the JAK inhibitor is selected from the group consisting of Baricitinib phosphate, CYT387 Mesylate, CYT387 sulfate salt, NS-018 hydrochloride, NS-018 maleate, NVP-BSK805 dihydrochloride, Oclacitinib maleate, Ruxolitinib phosphate, Ruxolitinib sulfate, Tofacitinib citrate, and ZM39923 hydrochloride.

70. The use of any one of claims 68 to 69, wherein the JAK inhibitor is administered orally.

71. The use of any one of claims 43 to 67, wherein the MDM2 inhibitor is administered before administration of the therapeutic agent.

72. The use of any one of claims 43 to 67, wherein the MDM2 inhibitor is administered after administration of the therapeutic agent.

73. The use of any one of claims 43 to 67, wherein the MDM2 inhibitor is administered concurrently with administration of the therapeutic agent.

74. The use of any one of claims 43 to 73, wherein the therapeutically effective amount of the MDM2 inhibitor is 100 mg.

75. The use of claim 43, wherein the PD-1 inhibitor is selected from group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-224, AMP-514, PDR001, and fragments, conjugates, or variants thereof.

76. The use of claim 43, wherein the PD-L1 inhibitor is an anti-PD-L1 antibody. In an embodiment, the PD-L1 inhibitor is selected from the group consisting of Atezolizumab, Avelumab, Durvalumab, BMS-936559, and fragments, conjugates, or variants thereof.

77. The use of claim 43, wherein the anti-PD- L2 inhibitor is rHIgM12B7A.

78. The use of claim 43, wherein the AKT inhibitor is selected from the group consisting of SB0203580, MK-2206, AZD5363, Miltefosine, Perifosine, PF-04691502, CCT128930, A-674563, RX-0201, PBI-05204, AKT inhibitor VIII, AT7867, AT13148, GDC-0068, TIC10, SC79, GSK690693, GSK2110183, GSK2141795, and pharmaceutically acceptable salts thereof.

79. The use of claim 43, wherein the mTOR inhibitor is selected from the group consisting of Sirolimus, Everolimus, Temsirolimus, Zotarolimus, Deforolimus, Wortmannin, Ascomycin, Tacrolimus, KU-0063794, Sapanisertib, AZD8055, Vistusertib, CC-223, OSI-027, Voxtalisib, Palomid 529, PP 242, Dactolisib, BGT226, Apitolisib, Omipalisib, PF-04691502, Gedatolisib, and pharmaceutically acceptable salts thereof.

80. The use of claim 43, wherein the PI3K inhibitor is selected from the group consisting of Buparlisib, Alpelisib, Pictilisib, Pilaralisib, Sonolisib, Copanlisib, CH5132799, Serabelisib, AZD8186, SAR260301, GSK2636771, Idelalisib, Acalisib, Duvelisib, Taselisib, AMG319, GDC-0084, and pharmaceutically acceptable salts thereof.

81. The use of claim 43, wherein the IDH inhibitor is selected from the group consisting of Enasidenib, Ivosidenib, AGI-5198, AGI-6780, CHEMBL3682093, Vorasidenib, IDH-305, BAY-1436032, GSK864, (R,S)-Ivosidenib, IDH1-IN-2, IDH1-IN-1, Enasidenib mesylate, and pharmaceutically acceptable salts thereof.

82. The use of claim 43, wherein the interferon is selected from the group consisting of interferon alpha (IFN-α), interferon beta (IFN-β), interferon lambda (IFN-λ), interferon gamma (IFN-γ), and combinations thereof.

83. The use of claim 43, wherein the interferon is selected from the group consisting of interferon-alpha-2a, interferon-alpha-2b, interferon-alpha-2c, interferon-alpha-n1, interferon-alpha-n3, PEGylated interferon-alpha-2a, PEGylated interferon-alpha-2b, PEGylated interferon-alpha-2c, PEGylated interferon-alpha-n1, PEGylated interferon-alpha-n3, and combinations thereof.

84. The use of any one of claims 43-83, wherein the MPN in the human subject has a JAK2V617F mutation.

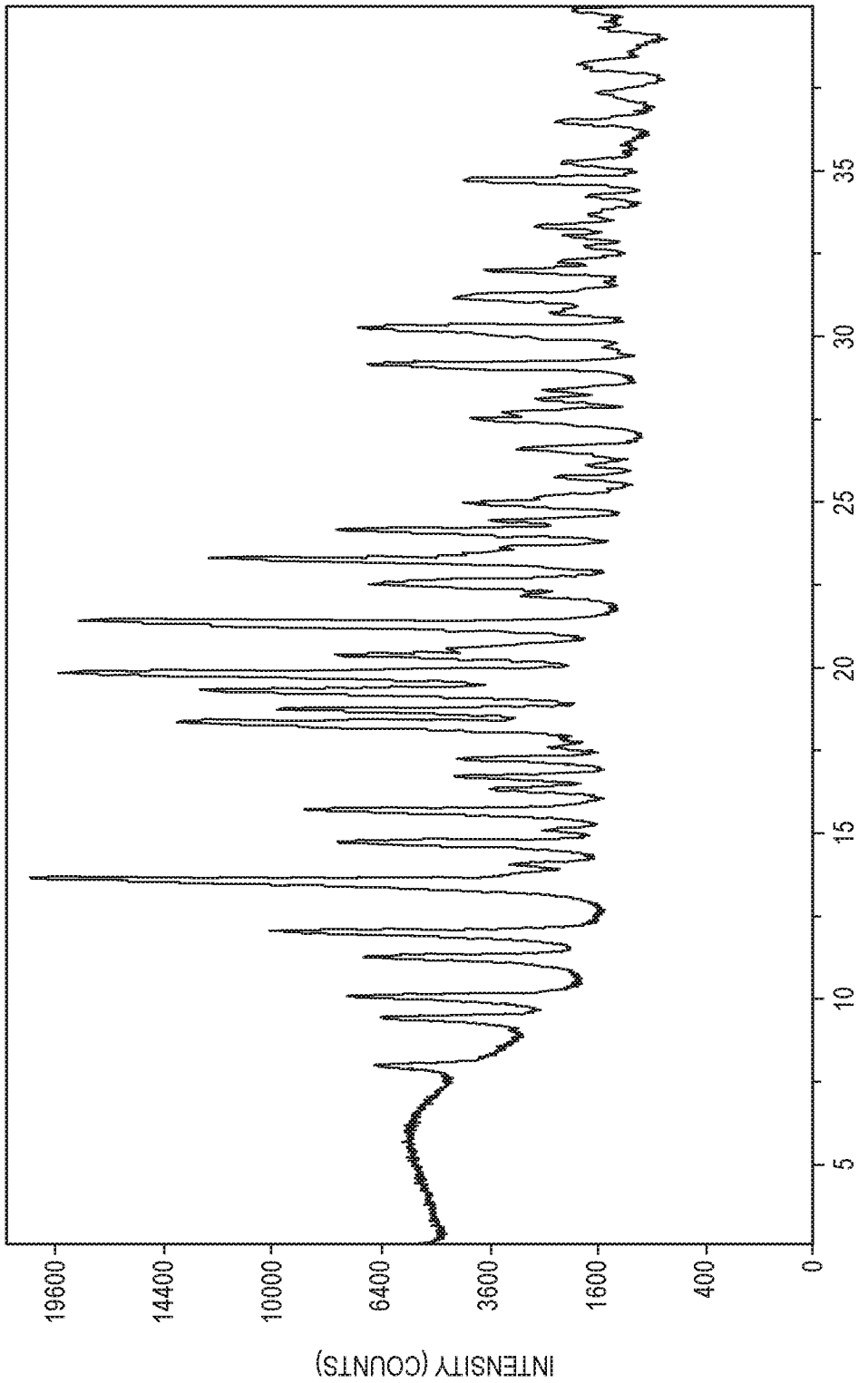

INTENSITY (COUNTS)
19600
14400
10000
6400
3600
1600
400
0
5
10
15
20
25
30
35
2THETA (*)

FIG. 1