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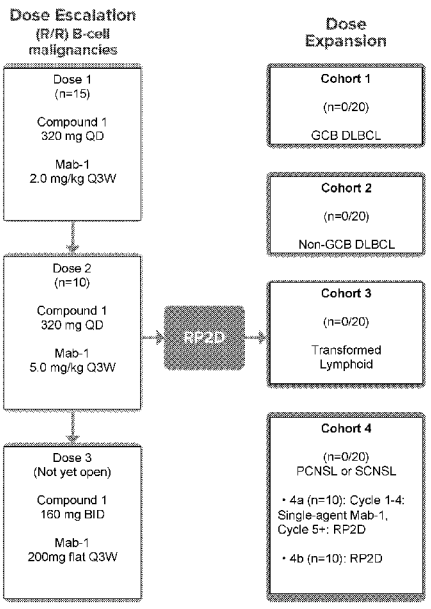
(54) Title: TREATMENT OF INDOLENT OR AGGRESSIVE B-CELL LYMPHOMAS USING A COMBINATION COMPRISING BTK INHIBITORS



BID, twice daily; GCB DLBCL, germinal center B-cell diffuse B-cell lymphoma; PCNSL, primary central nervous system lymphoma; Q3W, every 3 weeks; QD, once daily; RP2D, recommended Phase 2 dose; SCNSL, secondary central nervous system lymphoma.

FIG. 1

(57) Abstract: Disclosed herein is a method for the prevention, delay of progression or treatment of indolent or aggressive B-cell lymphomas in an individual in need thereof, comprising administering a Btk inhibitor (in particularly (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidine-3-carboxamide or a pharmaceutically acceptable salt thereof) in combination with an anti-PD-1 antibody. The potent and selective BTK inhibitor in combination with the anti-PD-1 antibody have a manageable toxicity profile in patients with indolent and aggressive lymphomas.

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[Continued on next page]

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TREATMENT OF INDOLENT OR AGGRESSIVE B-CELL LYMPHOMAS USING A COMBINATION COMPRISING BTK INHIBITORS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. U.S. 62/592,111 filed on November 29, 2017, the disclosure of which is hereby incorporated by reference for all purposes.

DESCRIPTION OF THE TEXT FILE SUBMITTED ELECTRONICALLY

[0002] The contents of the text file submitted electronically herewith are incorporated herein by reference in their entirety: A computer readable format copy of the Sequence Listing (filename: BEIG-030_01WOSeqList.TXT, date recorded November 29, 2018 file size 126 kilobytes).

FIELD OF THE INVENTION

[0003] Disclosed herein is a method for the prevention, delay of progression or treatment of indolent or aggressive B-cell lymphomas in an individual in need thereof, comprising administering a Btk inhibitor (in particular (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidine-3-carboxamide or a pharmaceutically acceptable salt thereof) in combination with an anti-PD-1 antibody. The potent and selective BTK inhibitor in combination with the anti-PD-1 antibody have a manageable toxicity profile in patients with indolent and aggressive lymphomas.

BACKGROUND OF THE INVENTION

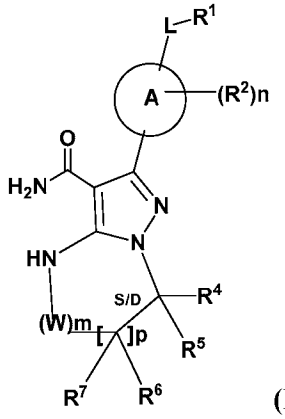
[0004] The lymphatic system is made up of lymph nodes, lymphatic organs, and lymphatic vessels and the lymphatic system carries lymph, a colorless fluid that contains lymphocytes. There are several types of lymphocytes, including: B-lymphocytes, or B cells and T-lymphocytes, or T cells.

[0005] Lymphomas are cancers of lymphoid tissue. They comprise a group of heterogeneous cancers, divided into non-Hodgkin's lymphomas (NHL) and Hodgkin's lymphomas (HL). There are two main types of lymphoma: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). About 90% of people in western countries with lymphoma have B-cell non-Hodgkin's lymphoma (https://www.cancer.net/cancer-types/lymphoma-non-hodgkin/subtypes).

[0006] Based on how quickly the cancer is growing, NHL can be categorized as aggressive or indolent. Indolent NHL types have a relatively good prognosis but they are not curable in advanced clinical stages. Most of the indolent types are nodular (or follicular) in morphology. Follicular lymphoma (FL) is by far the most common of the indolent NHLs and represents almost 25% of all new cases of NHL. The aggressive type of NHL (e.g. diffuse large B-cell lymphoma (DLBCL)) has a shorter life expectancy.

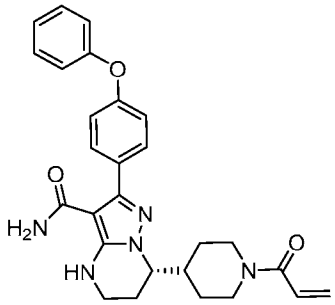
[0007] Bruton's tyrosine kinase (Btk) belongs to the Tec family of cytoplasmic tyrosine kinases, which is the second largest family of non-receptor kinases in humans [Vetrie et al., *Nature* **361**: 226-233, 1993; Bradshaw, *Cell Signal.* **22**: 1175-84, 2010]. It is expressed in all cell lineages of the hematopoietic system, except for T cells and is localized in bone marrow, spleen and lymph node tissue [Smith et al., *J. Immunol.* **152:** 557-565, 1994]. Inactivating mutations in the gene encoding Btk cause X-linked agammaglobulinemia (XLA) in humans and X-linked immunodeficiency (XID) in mice [Conley et al., *Annu. Rev. Immunol.* **27**: 199-227, 2009]. Both diseases are characterized by dramatic defects in B cell development and function, suggesting the essential role of Btk for B cell development and function. In addition, constitutive activation of Btk in B cells results in the accumulation of autoreactive plasma cells [Kersseboom et al., *Eur J Immunol.* **40**:2643-2654, 2010]. Btk is activated by upstream Src-family kinases in BCR signaling pathway. Once activated, Btk in turn phosphorylates phospholipase-Cγ (PLCγ), leading to Ca^{2+} mobilization and activation of NF-κB and MAP kinase pathways. These proximal signaling events promote expression of genes involved in proliferation and survival [Humphries et al., *J. Biol.Chem.* **279**: 37651, 2004]. In addition to its essential regulatory role as downstream of BCR, Btk activity also plays a critical role in FcR signaling. Signaling via FcRγ associated receptors also promotes Btk-dependent proinflammatory cytokine production by cells such as macrophages [Di Paolo et al., *Nat. Chem. Biol.* **7**: 41–50, 2011]. Btk has been an important target due to its proximal location in the BCR and FcR signaling pathways. Preclinical studies show that Btk deficient mice are resistant to developing collagen-induced arthritis. In addition, aberrant activating of Btk plays important role in pathogenesis of B-cell lymphomas indicating that inhibition of Btk is useful in the treatment of hematological malignancies [Davis et al., **Nature** *463*: 88-92, 2010].

[0008] **WO2014/173289A1** disclosed a series of fused heterocyclic compounds having the following general Formula **(I)** or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof as Btk inhibitors, which have demonstrated potent inhibitory activity against Bruton's tyrosine kinase.



(I)

[0009] **WO2018/033853A2** disclosed a crystalline form of the Btk inhibitor in **WO2014/173289A1**, particularly, (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetra-hydropyrazolo[1,5-a]pyrimidine-3-carboxamide (hereinafter **Compound 1**) for the treatment of cancers with aberrations in the B-cell receptor (BCR) and FcR signaling pathway in which Btk plays important roles. **Compound 1** has demonstrated to have potent and irreversible inhibitory activities against Btk. The contents of the publications WO2014/173289 and WO2018/033853 are hereby incorporated by reference in their entireties for all purposes.



Compound 1

SUMMARY OF THE INVENTION

[0010] The inventors of the present application have found that the combination of a Btk inhibitor (in particular, **Compound 1**) with an anti-PD-1 antibody can be used to treat indolent or aggressive B-cell lymphomas in an individual.

[0011] In a first aspect, disclosed herein is a method for the prevention, delay of progression or treatment of indolent or aggressive B-cell lymphomas in an individual in need thereof, comprising administering a therapeutically effective amount of a Btk inhibitor of Formula **(I)** or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in combination with a therapeutically effective amount of an anti-PD-1 antibody.

[0012] In a second aspect, disclosed herein is a Btk inhibitor of Formula **(I)** or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, for use in the prevention, delay of progression or treatment of indolent or aggressive B-cell lymphomas in combination with an anti-PD-1 antibody. In one embodiment of this aspect, disclosed herein is an anti-PD-1 antibody for use in the prevention, delay of progression or treatment of indolent or aggressive B-cell lymphomas in combination with a Btk inhibitor of Formula **(I)** or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[0013] The methods disclosed herein, as a combination therapies, provide methods of treatment that are significantly more efficacious than either single agent.

[0014] In an embodiment of each of the above aspects, the anti-PD-1 antibody is a monoclonal antibody.

[0015] In an embodiments of each of the above aspects, the indolent or aggressive B-cell lymphomas is indolent or aggressive Hodgkin's lymphoma. In other embodiment, the indolent or aggressive B-cell lymphomas is the indolent or aggressive non-Hodgkin's lymphoma. In a further embodiment, the indolent or aggressive B-cell lymphomas is indolent or aggressive chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM), Hairy cell leukemia (HCL), Burkitt's-like leukemia (BL), B cell prolymphocytic leukemia (B-PLL), diffuse large B cell lymphoma (DLBCL), germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL), non-germinal center B-cell diffuse large B-cell lymphoma (non-GCB DLBCL), DLBCL with undetermined subtype, primary central nervous system lymphoma (PCNSL), secondary central nervous system lymphoma (SCNSL) of breast or testicular origin, transformed lymphoma, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, or a combination thereof. In an embodiment of each of the above aspects, the indolent or aggressive B-cell lymphomas is indolent or aggressive diffuse large B-cell lymphoma (DLBCL). In an embodiment of each of the above aspects, DLBCL is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), GCB-DLBCL or Non-GCB DLBCL. In an embodiment of each of the above aspects, the indolent or aggressive B-cell lymphomas is indolent or aggressive chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma

(SLL), B cell prolymphocytic leukemia (B-PLL), non-CLL/SLL lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM), multiple myeloma or a combination thereof. In an embodiment of each of the above aspects, the indolent or aggressive B-cell lymphomas is indolent or aggressive relapsed or refractory (R/R) B-cell malignancy. In an embodiment of each of the above aspects, the relapsed or refractory B-cell malignancy is diffuse large B-cell lymphoma (DLBCL). In an embodiments of each of the above aspects, the relapsed or refractory DLBCL is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), GCB-DLBCL or Non-GCB DLBCL. In an embodiment of each of the above aspects, the relapsed or refractory (R/R) B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia (B-PLL), non-CLL / SLL lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, or a combination thereof. In an embodiment of each of the above aspects, the B-cell malignancy is a metastasized B-cell malignancy. In an embodiment of each of the above aspects, the metastasized B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia (B-PLL), non-CLL/SLL lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM), multiple myeloma or a combination thereof.

[0016] In an embodiment of each of the above aspects, the BTK inhibitor is (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetra-hydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound 1**), or a pharmaceutically acceptable salt thereof. In an embodiment of each of the above aspects, the anti-PD-1 antibody is **Mab 1** as disclosed herein. In an embodiment of each of the above aspects, the Btk inhibitor and the anti-PD-1 antibody are administered simultaneously, sequentially or intermittently.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] **FIG. 1** shows the trial design of the combination of Compound 1 and **Mab-1**.

[0018] **FIG. 2** shows the patient disposition at the current cutoff.

[0019] **FIG. 3A** and **FIG. 3B** show Maximum Improvement in SPD in patients with indolent and aggressive lymphoma, respectively.

[0020] **FIG. 4A** and **FIG. 4B** show duration of treatment in patients with indolent and aggressive lymphoma, respectively.

[0021] **FIG. 5A** and **FIG. 5B** show progression-free survival in patients with indolent and aggressive lymphoma, respectively.

[0022] **FIG. 6** shows an X-ray diffraction pattern of **Compound 1** in a crystalline form.

[0023] **FIG. 7** shows ^{1}H-NMR of the crystalline form of **Compound 1**.

[0024] **FIG. 8** shows ^{13}C-NMR of the crystalline form of **Compound 1**.

DETAILED DESCRIPTION OF THE INVENTION

[0025] **Abbreviations (1):**

ABC-DLBCL	Activated B-cell diffuse large B-cell lymphoma
A2AR	Adenosine A2A receptor
B-PLL	B cell prolymphocytic leukemia
Btk	Bruton's Tyrosine Kinase
BTLA	B and T Lymphocyte Attenuator, CD272
CDR	Complementarity Determining Region
CLL	chronic lymphocytic leukemia
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4, CD152
DLBCL	diffuse large B-cell lymphoma
DMEM	Dulbecco minimum essential medium
HVEM	Herpesvirus Entry Mediator
non-CLL/SLL	non-chronic lymphocytic leukemia / small lymphocytic lymphoma
IG	immunoglobulin G
i.p.	Intraperitoneal or Intraperitoneally
mAb	Monoclonal antibodies
PD-1	Programmed Death 1 protein, Pdcd-1, CD279
p.o.	"by mouth" or "per os"
QD	Once daily
BID	Twice daily
Q4D	Once every four days
QW	Once weekly
Q2W	Once every two weeks
Q3W	Once every three weeks
SLL	small lymphocytic lymphoma
Vh	Heavy chain variable region
Vl	Light chain variable region
VISTA	V-domain Ig suppressor of T-cell activation

[0026] Abbreviations (2):

ACN	acetonitrile
AcOH	Acetic acid
D-DBTA	(2S, 3S)-Dibenzoyl tartaric acid
DCM	Dichloromethane
DMF	*N,N*-dimethylformamide
DMF-DMA	*N,N*-dimethylformamide dimethyl acetal
EA	Ethyl Acetate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EtOAc	ethyl acetate
HOBt	Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
L-DBTA	(2R, 3R)-Dibenzoyl tartaric acid
MeCN	Acetonitrile
MeOH	Methanol
MeMgBr	Methyl Magnesium Bromide
MsOH	Methanesulfonic Acid
MTBE	Methyl tertiary butyl ether
NLT	not less than
NMR	Nuclear Magnetic Resonance
NMT	not more than
Pd	Palladium
pH	Hydrogen ion concentration
RT	Room Temperature
TEA	Triethylamine
XRPD	X-ray Powder Diffraction

Definitions

[0027] Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0028] As used herein, including the appended claims, the singular forms of words such as "**a**", "**an**", and "**the**", include their corresponding plural references unless the context clearly indicates otherwise.

[0029] The term "**or**" is used to mean, and is used interchangeably with, the term "and/or" unless the context clearly dictates otherwise.

[0030] Throughout this specification and the claims which follow, unless the context requires otherwise, the word "**comprise**", and variations such as "**comprises**" and "**comprising**", will be understood to imply the inclusion of an active agent (e.g., a mAb or a Btk inhibitor) or a stated amino acid sequence, but not the exclusion of any other active ingredient or amino acid sequence. When used herein the term "comprising" can be interchangeable with the term "**containing**" or "**including**".

[0031] The term "**alkyl**" refers to a hydrocarbon group selected from linear and branched saturated hydrocarbon groups of 1-18, or 1-12, or 1-6 carbon atoms. Examples of the alkyl group include methyl, ethyl, 1 -propyl or n-propyl ("n-Pr"), 2-propyl or isopropyl ("i-Pr"), 1-butyl or n-butyl ("n-Bu"), 2-methyl-l -propyl or isobutyl ("i-Bu"), 1-methylpropyl or s-butyl ("s-Bu"), and 1,1-dimethylethyl or t-butyl ("t-Bu"). Other examples of the alkyl group include 1-pentyl, 2-pentyl, 3-pentyl, 2-methyl-2-butyl, 3-methyl-2-butyl, 3-methyl-1-butyl, 2-methyl-l -butyl, 1-hexyl, 2-hexyl, 3-hexyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 3-methyl-3-pentyl, 2-methyl-3-pentyl, 2,3-dimethyl-2-butyl and 3,3-dimethyl-2-butyl groups. Lower alkyl means 1-8, preferably 1-6, more preferably 1-4 carbon atoms; lower alkenyl or alkynyl means 2-8, 2-6 or 2-4 carbon atoms.

[0032] The term "**alkenyl**" refers to a hydrocarbon group selected from linear and branched hydrocarbon groups comprising at least one C=C double bond and of 2-18, or 2-12, or 2-6 carbon atoms. Examples of the alkenyl group may be selected from ethenyl or vinyl, prop-1-enyl, prop-2-enyl, 2-methylprop-l-enyl, but-l-enyl, but-2-enyl, but-3-enyl, buta-l,3-dienyl, 2-methylbuta-l,3-diene, hex-l-enyl, hex-2-enyl, hex-3-enyl, hex-4-enyl, and hexa-l,3-dienyl groups.

[0033] The term "**alkynyl**" refers to a hydrocarbon group selected from linear and branched hydrocarbon group, comprising at least one C≡C triple bond and of 2-18, or 2-12, or 2-6 carbon atoms. Examples of the alkynyl group include ethynyl, 1-propynyl, 2-propynyl (propargyl), 1-butynyl, 2-butynyl, and 3-butynyl groups.

[0034] The term "**cycloalkyl**" refers to a hydrocarbon group selected from saturated and partially unsaturated cyclic hydrocarbon groups, comprising monocyclic and polycyclic (e.g., bicyclic and tricyclic) groups. For example, the cycloalkyl group may be of 3-12, or 3-8, or 3-6 carbon atoms. Even further for example, the cycloalkyl group may be a monocyclic group of 3-

12, or 3-8, or 3-6 carbon atoms. Examples of the monocyclic cycloalkyl group include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-l-enyl, l-cyclopent-2-enyl, l-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-l-enyl, l-cyclohex-2-enyl, l-cyclohex-3-enyl, cyclohexadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, and cyclododecyl groups. Examples of the bicyclic cycloalkyl groups include those having 7-12 ring atoms arranged as a bicycle ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems, or as a bridged bicyclic ring selected from bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, and bicyclo[3.2.2]nonane. The ring may be saturated or have at least one double bond (i.e. partially unsaturated), but is not fully conjugated, and is not aromatic, as aromatic is defined herein.

[0035] The term "**aryl**" herein refers to a group selected from:5- and 6-membered carbocyclic aromatic rings, for example, phenyl; bicyclic ring systems such as 7-12 membered bicyclic ring systems wherein at least one ring is carbocyclic and aromatic, selected, for example, from naphthalene, and indane; and tricyclic ring systems such as 10-15 membered tricyclic ring systems wherein at least one ring is carbocyclic and aromatic, for example, fluorene. For example, the aryl group is selected from 5- and 6-membered carbocyclic aromatic rings fused to a 5- to 7-membered cycloalkyl or heterocyclic ring optionally comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the carbocyclic aromatic ring when the carbocyclic aromatic ring is fused with a heterocyclic ring, and the point of attachment can be at the carbocyclic aromatic ring or at the cycloalkyl group when the carbocyclic aromatic ring is fused with a cycloalkyl group. Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, e.g., a naphthyl group with two points of attachment is termed naphthylidene. Aryl, however, does not encompass or overlap with heteroaryl, separately defined below. Hence, if one or more carbocyclic aromatic rings are fused with a heterocyclic aromatic ring, the resulting ring system is heteroaryl, not aryl, as defined herein.

[0036] The term "**halogen**" or "**halo**" refers to F, CI, Br or I.

[0037] The term "**heteroalkyl**" refers to alkyl comprising at least one heteroatom.

[0038] The term "**heteroaryl**" refers to a group selected from: 5- to 7-membered aromatic, monocyclic rings comprising 1, 2, 3 or 4 heteroatoms selected from N, O, and S, with the remaining ring atoms being carbon; 8- to 12-membered bicyclic rings comprising 1, 2, 3 or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in the aromatic ring; and 11-

to 14-membered tricyclic rings comprising 1, 2, 3 or 4 heteroatoms, selected from N, O, and S, with the remaining ring atoms being carbon and wherein at least one ring is aromatic and at least one heteroatom is present in an aromatic ring. For example, the heteroaryl group includes a 5- to 7-membered heterocyclic aromatic ring fused to a 5- to 7-membered cycloalkyl ring. For such fused, bicyclic heteroaryl ring systems wherein only one of the rings comprises at least one heteroatom, the point of attachment may be at the heteroaromatic ring or at the cycloalkyl ring. When the total number of S and O atoms in the heteroaryl group exceeds 1, those heteroatoms are not adjacent to one another. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the aromatic heterocycle is not more than 1. Examples of the heteroaryl group include, but are not limited to, (as numbered from the linkage position assigned priority 1) pyridyl (such as 2-pyridyl, 3-pyridyl, or 4-pyridyl), cinnolinyl, pyrazinyl, 2,4-pyrimidinyl, 3,5-pyrimidinyl, 2,4-imidazolyl, imidazopyridinyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, tetrazolyl, thienyl, triazinyl, benzothienyl, furyl, benzofuryl, benzoimidazolyl, indolyl, isoindolyl, indolinyl, phthalazinyl, pyrazinyl, pyridazinyl, pyrrolyl, triazolyl, quinolinyl, isoquinolinyl, pyrazolyl, pyrrolopyridinyl (such as lH-pyrrolo[2,3-b]pyridin-5-yl), pyrazolopyridinyl (such as lH-pyrazolo[3,4-b]pyridin-5-yl), benzoxazolyl (such as benzo[d]oxazol-6-yl), pteridinyl, purinyl, 1-oxa-2,3-diazolyl, l-oxa-2,4-diazolyl, l-oxa-2,5-diazolyl, l-oxa-3,4-diazolyl, l-thia-2,3-diazolyl, l-thia-2,4-diazolyl, l-thia-2,5-diazolyl, l-thia-3,4-diazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, furopyridinyl, benzothiazolyl (such as benzo[d]thiazol-6-yl), indazolyl (such as lH-indazol-5-yl) and 5,6,7,8-tetrahydroisoquinoline.

[0039] The term "**heterocyclic**" or "**heterocycle**" or "**heterocyclyl**" refers to a ring selected from 4- to 12-membered monocyclic, bicyclic and tricyclic, saturated and partially unsaturated rings comprising at least one carbon atoms in addition to 1, 2, 3 or 4 heteroatoms, selected from oxygen, sulfur, and nitrogen. "Heterocycle" also refers to a 5- to 7-membered heterocyclic ring comprising at least one heteroatom selected from N, O, and S fused with 5-, 6-, and/or 7-membered cycloalkyl, carbocyclic aromatic or heteroaromatic ring, provided that the point of attachment is at the heterocyclic ring when the heterocyclic ring is fused with a carbocyclic aromatic or a heteroaromatic ring, and that the point of attachment can be at the cycloalkyl or heterocyclic ring when the heterocyclic ring is fused with cycloalkyl.

[0040] The "**heterocycle**" also refers to an aliphatic spirocyclic ring comprising at least one heteroatom selected from N, O, and S, provided that the point of attachment is at the heterocyclic ring. The rings may be saturated or have at least one double bond (i.e. partially unsaturated). The heterocycle may be substituted with oxo. The point of the attachment may be carbon or

heteroatom in the heterocyclic ring. A heterocycle is not a heteroaryl as defined herein. Examples of the heterocycle include, but not limited to, (as numbered from the linkage position assigned priority 1) 1-pyrrolidinyl, 2-pyrrolidinyl, 2,4-imidazolidinyl, 2,3-pyrazolidinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 2,5-piperazinyl, pyranyl, 2-morpholinyl, 3-morpholinyl, oxiranyl, aziridinyl, thiiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-difhietanyl, dihydropyridinyl, tetrahydropyridinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, azepanyl, oxepanyl, thiepanyl, 1,4-oxathianyl, 1,4-dioxepanyl, 1,4-oxafhiepanyl, 1,4-oxaazepanyl, 1,4-difhiepanyl, 1 ,4-fhiazepanyl and 1,4-diazepane 1,4-dithianyl, 1 ,4-azathianyl, oxazepinyl, diazepinyl, thiazepinyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, 1 ,4-dioxanyl, 1,3-dioxolanyl, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolanyl, pyrazolidinyl, imidazolinyl, pyrimidinonyl, 1,1-dioxo-thiomorpholinyl, 3-azabicyco[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl and azabicyclo[2.2.2]hexanyl. Substituted heterocycle also includes ring systems substituted with one or more oxo moieties, such as piperidinyl N-oxide, morpholinyl-N-oxide, 1-oxo-1 -thiomorpholinyl and 1, 1-dioxo-l-thiomorpholinyl.

[0041] Substituents are selected from: halogen, $-R^a$, $-OR^a$, $=O$, $=NR^a$, $=N-OR^a$, $-NR^aR^b$, $-SR^a$, $-SiR^aR^aR^b$, $-OC(O)R^a$, $-C(O)R^a$, $-CO_2R^a$, $-CONR^aR^b$, $-OC(O)NR^aR^b$, $-NR^bC(O)R^a$, $-NR^a-C(O)NR^bR^b$, $-NR^a-SO_2NR^b$, $-NR^bCO_2R^a$, $-NH-C(NH_2)=NH$, $-NR^aC(NH_2)=NH$, $-NH-C(NH_2)=NR^a$, $-S(O)R^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^bSO_2R$, $-CN$ and $-NO_2$, $-N_3$, $-CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to three, with those groups having zero, one or two substituents being particularly preferred. R^a, R^b and R^c each independently refer to hydrogen, unsubstituted (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with one to three halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C_1-C_4)alkyl groups. When R^a and R^b are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6- or 7-membered ring. Hence, $-NR^aR^b$ includes 1-pyrrolidinyl and 4-morpholinyl, "alkyl" includes groups such as trihaloalkyl (e.g., $-CF_3$ and $-CH_2CF_3$), and when the aryl group is 1,2,3,4-tetrahydronaphthalene, it may be substituted with a substituted or unsubstituted (C_3-C_7)spirocycloalkyl group. The (C_3-C_7)spirocycloalkyl group may be substituted in the same manner as defined herein for "cycloalkyl". Preferred substituents are selected from: halogen, $-R^a$, $-OR^a$, $=O$, $-NR^aR^b$, $-SR^a$, $-SiR^aR^aR^b$, $-OC(O)R^a$, $-C(O)R^a$, $-CO_2R^a$, $-CONR^aR^b$, $-OC(O)NR^aR^b$, $-NR^bC(O)R^a$, $-NR^bCO_2R^a$, $-NR^a-SO_2NR^bR^b$, $-S(O)R^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^bSO_2R$, $-CN$ and $-NO_2$, perfluoro(C_1-C_4)alkoxy and perfluoro(C_1-C_4)alkyl, where R^a and R^b are as defined above.

[0042] The term "**fused ring**" herein refers to a polycyclic ring system, e.g., a bicyclic or tricyclic ring system, in which two rings share only two ring atoms and one bond in common. Examples of fused rings may comprise a fused bicyclic cycloalkyl ring such as those having from 7 to 12 ring atoms arranged as a bicyclic ring selected from [4,4], [4,5], [5,5], [5,6] and [6,6] ring systems as mentioned above; a fused bicyclic aryl ring such as 7 to 12 membered bicyclic aryl ring systems as mentioned above, a fused tricyclic aryl ring such as 10 to 15 membered tricyclic aryl ring systems mentioned above; a fused bicyclic heteroaryl ring such as 8- to 12-membered bicyclic heteroaryl rings as mentioned above, a fused tricyclic heteroaryl ring such as 11- to 14-membered tricyclic heteroaryl rings as mentioned above; and a fused bicyclic or tricyclic heterocyclyl ring as mentioned above.

[0043] When compounds contain olefin double bonds, unless specified otherwise, such double bonds are meant to include both E and Z geometric isomers.

[0044] Some of the compounds may exist with different points of attachment of hydrogen, referred to as tautomers. For example, compounds including carbonyl -$CH_2C(O)$- groups (keto forms) may undergo tautomerism to form hydroxyl -CH=C(OH)- groups (enol forms). Both keto and enol forms, individually as well as mixtures thereof, are also intended to be included where applicable.

[0045] The term "**pharmaceutically acceptable salts**" include, but are not limited to salts with inorganic acids, selected, for example, from hydrochlorates, phosphates, diphosphates, hydrobromates, sulfates, sulfinates, and nitrates; as well as salts with organic acids, selected, for example, from malates, maleates, fumarates, tartrates, succinates, citrates, lactates, methanesulfonates, p-toluenesulfonates, 2-hydroxyethylsulfonates, benzoates, salicylates, stearates, alkanoates such as acetate, and salts with $HOOC-(CH_2)_n-COOH$, wherein n is selected from 0 to 4. Similarly, examples of pharmaceutically acceptable cations include, but are not limited to, sodium, potassium, calcium, aluminum, lithium, and ammonium.

[0046] In addition, if a compound is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, such as a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used without undue experimentation to prepare non-toxic pharmaceutically acceptable addition salts.

[0047] The terms "**administration**", "**administering**", "**treating**" and "**treatment**" herein, when applied to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, mean contact of an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition to

the animal, human, subject, cell, tissue, organ, or biological fluid. Treatment of a cell encompasses contact of a reagent to the cell, as well as contact of a reagent to a fluid, where the fluid is in contact with the cell. The term "**administration**" and "**treatment**" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. The term "subject" herein includes any organism, preferably an animal, more preferably a mammal (e.g., rat, mouse, dog, cat, rabbit) and most preferably a human.

[0048] An "**effective amount**" refers to an amount of at least one compound and/or at least one stereoisomer thereof, and/or at least one pharmaceutically acceptable salt thereof effective to "treat" a disease or disorder in a subject, and that will elicit, to some significant extent, the biological or medical response of a tissue, system, animal or human that is being sought, such as when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the condition or disorder being treated. The therapeutically effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

[0049] The term "**at least one substituent**" includes, for example, from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents. For example, "at least one substituent R^{16}" herein includes from 1 to 4, such as from 1 to 3, further as 1 or 2, substituents selected from the list of R<16>as described herein.

[0050] The term "**antibody**" herein is used in the broadest sense and specifically covers antibodies (including full length monoclonal antibodies) and antibody fragments so long as they recognize antigen, such as, an immune checkpoint (e.g., PD-1). An antibody molecule is usually monospecific, but may also be described as idiospecific, heterospecific, or polyspecific. Antibody molecules bind by means of specific binding sites to specific antigenic determinants or epitopes on antigens..

[0051] The term "**monoclonal antibody**" or "**mAb**" or "**Mab**" herein means a population of substantially homogeneous antibodies, i.e., the antibody molecules comprised in the population are identical in amino acid sequence except for possible naturally occurring mutations that may be present in minor amounts. In contrast, conventional (polyclonal) antibody preparations typically include a multitude of different antibodies having different amino acid sequences in their variable domains, particularly their CDRs, which are often specific for different epitopes. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. Monoclonal antibodies (mAbs) may be obtained by methods known to those skilled in the art. See, for example, *U.S. Pat. No. 4,376,110*. The mAbs disclosed herein may be of any immunoglobulin class including IgG, IgM, IgD, IgE,

IgA, and any subclass thereof. A hybridoma producing a mAb may be cultivated *in vitro* or *in vivo*. High titers of mAbs can be obtained in *in vivo* production where cells from the individual hybridomas are injected intraperitoneally into mice, such as pristine-primed Balb/c mice to produce ascites fluid containing high concentrations of the desired mAbs. MAbs of isotype IgM or IgG may be purified from such ascites fluids, or from culture supernatants, using column chromatography methods well known to those of skill in the art.

[0052] In general, the basic antibody structural unit comprises a tetramer. Each tetramer includes two identical pairs of polypeptide chains, each pair having one "**light chain**" (about 25 kDa) and one "**heavy chain**" (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of the heavy chain may define a constant region primarily responsible for effector function. Typically, human light chains are classified as kappa and lambda light chains. Furthermore, human heavy chains are typically classified as α, δ, ε, γ, or μ, and define the antibody's isotypes as IgA, IgD, IgE, IgG, and IgM, respectively. Within light and heavy chains, the variable and constant regions are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids.

[0053] The variable regions of each light/heavy chain (Vl/Vh) pair form the antibody binding site. Thus, in general, an intact antibody has two binding sites. Except in bifunctional or bispecific antibodies, the two binding sites are, in general, the same.

[0054] Typically, the variable domains of both the heavy and light chains comprise three hypervariable regions, also called "**complementarity determining regions (CDRs)**", which are located between relatively conserved framework regions (FR). The CDRs are usually aligned by the framework regions, enabling binding to a specific epitope. In general, from N-terminal to C-terminal, both light and heavy chain variable domains comprise FR-1 (or FR1), CDR-1 (or CDR1), FR-2 (FR2), CDR-2 (CDR2), FR-3 (or FR3), CDR-3 (CDR3),, and FR-4 (or FR4). The assignment of amino acids to each domain is, generally, in accordance with the definitions of Sequences of Proteins of Immunological Interest, *Kabat, et al., National Institutes of Health, Bethesda, Md. ; 5<m> ed.; NIH Publ. No. 91-3242 (1991); Kabat (1978) Adv. Prot. Chem. 32: 1-75; Kabat, et al., (1977) J. Biol. Chem. 252:6609-6616; Chothia, et al, (1987) J Mol. Biol. 196:901-917 or Chothia, et al, (1989) Nature 342:878-883.*

[0055] The term "**hypervariable region**" means the amino acid residues of an antibody that are responsible for antigen-binding. The hypervariable region comprises amino acid residues from a "complementarity determining region" or "CDR" (i.e., CDR-L1, CDR-L2 and CDR-L3 in the light chain variable domain and CDR-H1, CDR-H2 and CDR-H3 in the heavy chain variable

domain). See, *Kabat et al. (1991) Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md.* (defining the CDR regions of an antibody by sequence); see also *Chothia and Lesk (1987) J. Mol. Biol. 196: 901-917* (defining the CDR regions of an antibody by structure). The term "framework" or "FR" means those variable domain residues other than the hypervariable region residues defined herein as CDR residues.

[0056] Unless otherwise indicated, "**antibody fragment**" or "**antigen-binding fragment**" means antigen binding fragments of antibodies, i.e. antibody fragments that retain the ability to bind specifically to the antigen bound by the full-length antibody, e.g. fragments that retain one or more CDR regions. Examples of antigen binding fragments include, but not limited to, Fab, Fab', F(ab')2, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules, e.g., single chain Fv (ScFv); nanobodies and multispecific antibodies formed from antibody fragments.

[0057] An antibody that "**specifically binds to**" a specified target protein is an antibody that exhibits preferential binding to that target as compared to other proteins, but this specificity does not require absolute binding specificity. An antibody is considered "specific" for its intended target if its binding is determinative of the presence of the target protein in a sample, e.g. without producing undesired results such as false positives. Antibodies or binding fragments thereof, useful in the present invention will bind to the target protein with an affinity that is at least two fold greater, preferably at least ten times greater, more preferably at least 20-times greater, and most preferably at least 100-times greater than the affinity with non-target proteins. An antibody herein is said to bind specifically to a polypeptide comprising a given amino acid sequence, e.g. the amino acid sequence of a mature human PD-1 molecule, if it binds to polypeptides comprising that sequence but does not bind to proteins lacking that sequence.

[0058] The term "**human antibody**" herein means an antibody that comprises human immunoglobulin protein sequences only. A human antibody may contain murine carbohydrate chains if produced in a mouse, in a mouse cell, or in a hybridoma derived from a mouse cell. Similarly, "**mouse antibody**" or "rat antibody" mean an antibody that comprises only mouse or rat immunoglobulin protein sequences, respectively.

[0059] The term "**humanized antibody**" means forms of antibodies that contain sequences from non-human (e.g., murine) antibodies as well as human antibodies. Such antibodies contain minimal sequence derived from non-human immunoglobulin. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human

immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. The prefix "**hum**", "**hu**", "**Hu**" or "**h**" is added to antibody clone designations when necessary to distinguish humanized antibodies from parental rodent antibodies. The humanized forms of rodent antibodies will generally comprise the same CDR sequences of the parental rodent antibodies, although certain amino acid substitutions may be included to increase affinity, increase stability of the humanized antibody, or for other reasons.

[0060] The terms "**disease**" refers to any disease, discomfort, illness, symptoms or indications, and can be substituted with the term "**disorder**" or "**condition**".

[0061] In some embodiments, the B-cell malignancy is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenström's macroglobulinemia (WM), Hairy cell leukemia (HCL), Burkitt's-like leukemia (BL), B cell prolymphocytic leukemia (B-PLL), diffuse large B cell lymphoma (DLBCL), germinal center B-cell diffuse large B-cell lymphoma (GCB-DLBCL), non-germinal center B-cell diffuse large B-cell lymphoma (non-GCB DLBCL), DLBCL with undetermined subtype, primary central nervous system lymphoma (PCNSL), secondary central nervous system lymphoma (SCNSL) of breast or testicular origin, transformed lymphoma, multiple myeloma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, Burkitt's lymphoma, non-Burkitt high grade B cell lymphoma, primary mediastinal B-cell lymphoma (PMBL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, B cell prolymphocytic leukemia, lymphoplasmacytic lymphoma, splenic marginal zone lymphoma, plasma cell myeloma, plasmacytoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, lymphomatoid granulomatosis, or a combination thereof. In some embodiments, the B-cell malignancy is diffuse large B-cell lymphoma (DLBCL). In some embodiments, DLBCL is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), GCB-DLBCL or Non-GCB DLBCL. In some embodiments, the B-cell malignancy is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia (B-PLL), non-CLL / SLL lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, or a combination thereof. In some embodiments, the B-cell malignancy is a relapsed or refractory (R/R) B-cell malignancy. In some embodiments, the relapsed or refractory (R/R) B-cell malignancy is diffuse large B-cell lymphoma (DLBCL). In some embodiments, the relapsed or refractory DLBCL is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), GCB-DLBCL or Non-GCB DLBCL. In some embodiments, the relapsed or refractory (R/R) B-cell malignancy is chronic lymphocytic

leukemia (CLL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia (B-PLL), non-CLL / SLL lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, or a combination thereof. In some embodiments, the B-cell malignancy is a metastasized B-cell malignancy. In some embodiments, the metastasized B-cell malignancy is diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), B cell prolymphocytic leukemia (B-PLL), non-CLL / SLL lymphoma, follicular lymphoma (FL), mantle cell lymphoma (MCL), marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM), multiple myeloma, or a combination thereof.

[0062] The term "CDRs" means complementarity determining region(s) in an immunoglobulin variable region, defined using the Kabat numbering system, unless otherwise indicated.

Anti-PD-1 antibody

[0063] PD-1 is an immune checkpoint protein, that limits the activity of T cells in peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity PD-1 blockade *in vitro* enhances T-cell proliferation and cytokine production in response to a challenge by specific antigen targets or by allogeneic cells in mixed lymphocyte reactions. A strong correlation between PD-1 expression and response was shown with blockade of PD-1 (*Pardoll, Nature Reviews Cancer, 12: 252-264, 2012*). PD-1 blockade can be accomplished by a variety of mechanisms including antibodies that bind PD-1 or its ligands. Examples of PD-1 and PD-L1 blockers, also named PD-1 and PD-L1 inhibitors, are described in US7488802; US7943743; US8008449; US8,168,757; US8217149, and WO03042402, WO2008156712, WO2010089411, WO2010036959, WO2011066342, WO2011159877, WO2011082400, WO2011161699, and WO2015035606, the entire contents of each of which are incorporated herein by reference. In some embodiments the PD-1 inhibitors include an antibody or a fragment antigen binding thereof, which specifically binds to PD-1. In certain other embodiments the PD-1 blockers include anti-PD-1 antibodies and similar binding proteins such as nivolumab (MDX 1106, BMS 936558, ONO-4538, Opdivo®) described in US8008449B2, a fully human IgG4 antibody that binds to and blocks the activation of PD-1 by its ligands PD-L1 and PD-L2; pembrolizumab (lambrolizumab, MK-3475 or SCH 900475, Keytruda®) disclosed in US8168757B2, a humanized monoclonal IgG4 antibody against PD-1; pidilizumab (CT-011), a humanized antibody that binds PD-1; AMP-224, a fusion protein of B7-DC; an antibody Fc portion; BMS-936559 (MDX-1105-01) for PD-L1 (B7-H1) blockade for PD-1 blockade.

[0064] In some embodiments, the anti-PD-1 antibody is a monoclonal antibody. In some embodiments, the anti-PD-1 antibody is nivolumab or pidilizumab.

[0065] In some embodiments, the anti-PD-1 antibody is a monoclonal antibody or a fragment thereof, disclosed in **WO2015/035606 A1** or **US2015-0315274**, the entire disclosures of which are expressly incorporated herein by reference.

[0066] Preferably, the anti-PD-1 monoclonal antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) that contain complement determinant regions (CDRs) listed as follows:

a) mu317	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 12, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);
b) mu326	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 18, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);
c) 317-4B6	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 31, 32, 33, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 34, 35, 36, respectively);
d) 326-4A3	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 37, 38, 39, respectively); and CDR-L1, CDR--L2 and CDR-L3 (SEQ ID NOs: 40, 41, 42, respectively);
e) 317-1H	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 59, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 14, 15, 16, respectively);
f) 317-4B2	CDR-HL CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61 , 15, 16, respectively);
g) 317-4B5	CDR-Hl, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 60, 13, respectively); and CDR-L1 , CDR-L2 and CDR-L3 (SEQ ID NOs: 61 , 15, 16, respectively);
h) 317-4B6	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 11, 32, 13, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 61, 15, 16, respectively);

i) 326-1	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);
j) 326-3B1	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-L2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively);
or k) 326-3G1	CDR-H1, CDR-H2 and CDR-H3 (SEQ ID NOs: 17, 62, 19, respectively); and CDR-L1, CDR-I 2 and CDR-L3 (SEQ ID NOs: 20, 21, 22, respectively).

[0067] Preferably, the anti-PD-1 monoclonal antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) that contain any combinations of CDRs listed as follows:

(a)	CDR-H1 (SEQ ID NO 31), CDR-H2 (SEQ ID NO 12, 32, 59 or 60) and CDR-H3 (SEQ ID NO 33), CDR-L1 (SEQ ID NO 14, 34 or 61), CDR-L2 (SEQ ID NO 35) and CDR-L3 (SEQ ID NO 36); or
(b)	CDR-H1 (SEQ ID NO 37), CDR-H2 (SEQ ID NO 18, 38 or 62) and CDR-H3 (SEQ ID NO 39), CDR-L1 (SEQ ID NO 40), CDR-L2 (SEQ ID NO 41) and CDR-L3 (SEQ ID NO 42).

[0068] Preferably, the anti-PD-1 monoclonal antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) comprising:

a) mu317 (SEQ ID NOs: 4 and 6, respectively); b) mu326 (SEQ ID NOs: 8 and 10, respectively); c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively); d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively);	p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively); q) 317-311 (SEQ ID NOs: 70 and 26, respectively); r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively); s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively);

e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively); f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively); g) 317-1 (SEQ ID NOs: 48 and 50, respectively); h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively); i) 326-3GI (SEQ ID NOs: 53 and 54, respectively); j) 326-1 (SEQ ID NOs: 56 and 58, respectively); k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively); l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively); m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively); n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively); o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);	t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively); u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively); v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively); w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively); x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively); y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively); z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively); aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively); ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

[0069] In some embodiments, the antibody comprises an IgG4 Fc region having a serine to proline mutation at position 228 (EU numbering system). In some embodiments, this mutation is referred to as the S228P mutation. In some embodiments, the antibody comprises an IgG4 Fc region having a mutation at one or more of positions 233, 234, 235, 265, 309, and 409 (EU numbering system). For example, in some embodiments, the antibody comprises an IgG4 region having a mutation at 228 and at least one other position, wherein the at least one other mutation results in reduced binding to one or more FcγR. In further embodiments, the antibody comprises an IgG4 region having a mutation at position 228 and at least two, at least 3, at least 4, at least 5, or at least 6 additional positions, wherein one or more of the additional mutations results in reduced binding to one or more FcγR. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234 and 235. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 235, and 235. In some

embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, and 265. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, and 265. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, 265, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, 265, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 234, 235, 265, 309, and 409. In some embodiments, the antibody comprises an IgG4 region having mutations at positions 233, 234, 235, 265, 309, and 409. The mutation at position 234 may be a phenylalanine to valine substitution or a phenylalanine to alanine substitution. The mutation at position 235 may be a leucine to alanine substitution. The mutation at position 233 may be a glutamic acid to proline substitution. The mutation at position 265 may be a aspartic acid to valine substitution or an aspartic acid to threonine substitution. The mutation at position 309 may be a leucine to valine substitution. The mutation at position 409 may be an arginine to a lysine, threonine, or methionine substitution.

[0070] Preferably, the anti-PD-1 monoclonal antibody is an antibody which comprises a IgG4 heavy chain effector or constant domain comprising any of SEQ ID NOs: 83-88 or 91-106.

[0071] Preferably, the anti-PD-1 monoclonal antibody is an antibody which contains a F(ab) or F(ab)2 comprising a domain said above, including a heavy chain variable region (Vh), a light chain variable region (Vl) and a IgG4 heavy chain effector or constant domain .

[0072] Preferably, the anti-PD-1 monoclonal antibody is an antibody which comprise a heavy chain variable region (Vh) and a light chain variable region (Vl), and a IgG4 heavy chain effector or constant domain comprising SEQ ID NOs: 87 or 88, wherein the heavy chain variable region (Vh) and the light chain variable region (Vl) comprise:

a) mu317 (SEQ ID NOs: 4 and 6, respectively); b) mu326 (SEQ ID NOs: 8 and 10, respectively); c) 317-4B6 (SEQ ID NOs: 24 and 26, respectively); d) 326-4A3 (SEQ ID NOs: 28 and 30, respectively); e) 317-4B2 (SEQ ID NOs: 43 and 44, respectively); f) 317-4B5 (SEQ ID NOs: 45 and 46, respectively);	p) 317-3H1 (SEQ ID NOs: 69 and 26, respectively); q) 317-311 (SEQ ID NOs: 70 and 26, respectively); r) 317-4B 1 (SEQ ID NOs: 71 and 26, respectively); s) 317-4B3 (SEQ ID NOs: 72 and 26, respectively); t) 317-4B4 (SEQ ID NOs: 73 and 26, respectively);

g) 317-1 (SEQ ID NOs: 48 and 50, respectively); h) 326-3B1 (SEQ ID NOs: 51 and 52, respectively); i) 326-3GI (SEQ ID NOs: 53 and 54, respectively); j) 326-1 (SEQ ID NOs: 56 and 58, respectively); k) 317-3A1 (SEQ ID NOs: 64 and 26, respectively); l) 317-3C1 (SEQ ID NOs: 65 and 26, respectively); m) 317-3E1 (SEQ ID NOs: 66 and 26, respectively); n) 317-3F1 (SEQ ID NOs: 67 and 26, respectively); o) 317-3G1 (SEQ ID NOs: 68 and 26, respectively);	u) 317-4A2 (SEQ ID NOs: 74 and 26, respectively); v) 326-3 A 1 (SEQ ID NOs: 75 and 30, respectively); w) 326-3C1 (SEQ ID NOs: 76 and 30, respectively); x) 326-3D1 (SEQ ID NOs: 77 and 30, respectively); y) 326-3E1 (SEQ ID NOs: 78 and 30, respectively); z) 326-3F1 (SEQ ID NOs: 79 and 30, respectively); aa) 326-3B N55D (SEQ ID NOs: 80 and 30, respectively); ab) 326-4A1 (SEQ ID NOs: 28 and 81, respectively); or ac) 326-4A2 (SEQ ID NOs: 28 and 82, respectively).

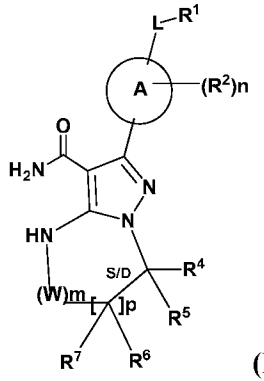
[0073] In some embodiments, the anti-PD-1 antibody is an antibody which comprises a heavy chain CDR-H1, CDR-H2, and CDR-H3 according to SEQ ID NOs: 11, 32, and 13, respectively; and a light chain CDR-L1, CDR-L2, and CDR-L3 according to SEQ ID NOs: 61, 15, and 16, respectively. Preferably, the anti-PD-1 monoclonal antibody is an antibody which comprises a heavy chain variable region (Vh) and a light chain variable region (Vl) (comprising SEQ ID No 24 and SEQ ID No 26, respectively) and a IgG4 heavy chain effector or constant domain (comprising SEQ ID NO 88), hereinafter **Mab 1,** which specifically binds to PD-1, especially PD-1 residues including K45 and I93; or, I93, L95 and P97, and inhibits PD-1-medidated cellular signaling and activities in immune cells, antibodies binding to a set of amino acid residues required for its ligand binding..

[0074] The anti-PD1 monoclonal antibodies and antibody fragments thereof may be prepared in accordance with the disclosure of **WO2015/035606A1** or US 2015-0315274, the entire disclosures of which are expressly incorporated herein by reference. In a preferred embodiment, the anti-PD1 monoclonal antibodies is **Mab 1**, which is administered at a dosage of about 2 mg/kg Q3W to about 200 mg/kg Q3W, more preferably, is administered at a dosage of about 2 mg/kg Q3W, 5mg/kg Q3W or 200 mg flat Q3W.

Btk inhibitors

[0075] "Btk inhibitor" means a compound of Formula (**I**), or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.

[0076] The Btk inhibitor, as disclosed herein, is a compound of Formula (**I**),



(I)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

wherein:

A is a 5- or 6-membered aromatic ring comprising 0-3 heteroatoms of N, S or O;

each W is independently $-(CH_2)-$ or -C(O)-;

L is a bond, CH_2, NR^{12}, O, or S;

S/D is a single or double bond, and when a double bond, R^5 and R^7 are absent;

m is 0, or an integer of 1-4;

n is 0, or an integer of 1-4, wherein when n is more than 1, each R^2 may be different;

p is 0, or an integer of 1-2, wherein when p is 0, m is non-zero, and when p is more than 1, each R^6 and each R^7 may be different;

R^1, R^4, R^5, R^6, and R^7 are each independently H, halogen, heteroalkyl, alkyl,alkenyl, cycloalkyl, aryl, saturated or unsaturated heterocyclyl, heteroaryl, alkynyl, -CN, $-NR^{13}R^{14}$, $-OR^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-C(=NR^{13})NR^{14}R^{15}$, $-NR^{13}COR^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}CO_2R^{14}$, $-SO_2R^{13}$, $-NR^{13}SO_2NR^{14}R^{15}$, or $-NR^{13}SO_2R^{14}$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, aryl, and saturated or unsaturated heterocyclyl are optionally substituted with at least one substituent R^{16},wherein (R^4 and R^5), or (R^4 and R^6), or (R^6 and R^7), or (R^6 and R^6 when p is 2), together with the atoms to which they are attached, can form a ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings optionally substituted with at least one substituent R^{16};

R^2 is halogen, alkyl, -S-alkyl, -CN, $-NR^{13}R^{14}$, $-OR^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-C(=NR^{13})NR^{14}R^{15}$, $-NR^{13}COR^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}CO_2R^{14}$, $-SO_2R^{13}$, $-NR^{13}SO_2NR^{14}R^{15}$, or $-NR^{13}SO_2R^{14}$;

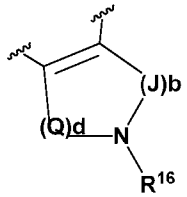
R^{12} is H or lower alkyl;

R^{13}, R^{14} and R^{15} are each independently H, heteroalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, saturated or unsaturated heterocyclyl, aryl, or heteroaryl; wherein (R^{13} and R^{14}), and/or (R^{14} and R^{15}) together with the atom(s) to which they are attached, each can form a ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings optionally substituted with at least one substituent R^{16};

R^{16} is halogen, subsituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, subsituted or unsubstituted alkynyl, subsituted or unsubstituted cycloalkyl, subsituted or unsubstituted aryl, subsituted or unsubstituted heteroaryl, subsituted or unsubstituted heterocyclyl, oxo, -CN, $-OR^a$, $-NR^aR^b$, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$, $-C(=NR^a)NR^bR^c$, $-NR^aCOR^b$, $-NR^aCONR^aR^b$, $-NR^aCO_2R^b$, $-SO_2R^a$, $-SO_2$aryl, $-NR^aSO_2NR^bR^c$, or $-NR^aSO_2R^b$, wherein R^a, R^b, and R^c are independently hydrogen, halogen, subsituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, subsituted or unsubstituted alkynyl, subsituted or unsubstituted cycloalkyl, subsituted or unsubstituted aryl, subsituted or unsubstituted heteroaryl, subsituted or unsubstituted heterocyclyl, wherein (R^a and R^b), and/or (R^b and R^c) together with the atoms to which they are attached, can form a ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings.

[0077] In some embodiments, the compound of Formula **(I)** is optically pure.

[0078] In some embodiments, S/D is a double bond and R^5 and R^7 are absent; p is 1 and m is 0, 1 or 2; A is phenyl; and $R^4$and R^6, together with the atoms to which they are attached, form a ring of formula



wherein Q is $-CH_2-$; J is $-CH_2-$; and d and b are each independently 0, or an integer of 1-4

S/D is a single bond; p is 1 and m is 0, 1 or 2; A is phenyl; or

S/D is a single bond; p is 0 and R^6 and R^7 are absent; A is phenyl.

[0079] In some embodiments, A is phenyl.

[0080] In some embodiments, W is $-(CH_2)-$.

[0081] In some embodiments, L is O.

[0082] In some embodiments, S/D is a single bond.

[0083] In some embodiments, m is 1.

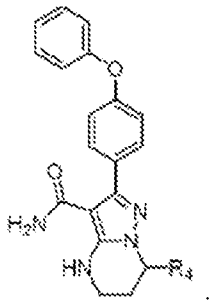
[0084] In some embodiments, n is 0. In some embodiments, R^2 is absent.

[0085] In some embodiments, p is 1.

[0086] In some embodiments, R^1 is phenyl.

[0087] In some embodiments, R^5 is H. In some embodiments, R^6 and R^7 are H.

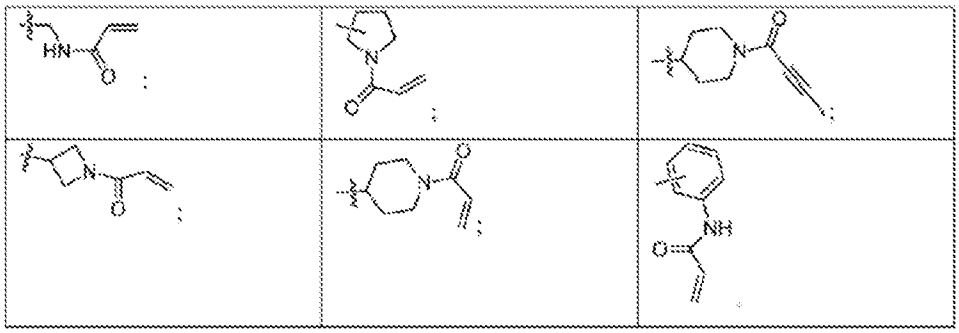
[0088] In some embodiments, A is phenyl; W is -(CH_2)-; L is O; S/D is a single bond; m is 1; n is 0; p is 1 ; R^1 is phenyl; R^2 is absent; R^5 is H; and R^6 and R^7 are H; yielding the combination structure:

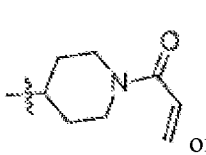
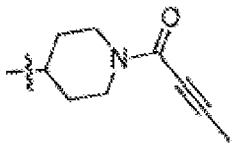


[0089] In some embodiments, R^4 is N-containing C_1-C_8 alkyl, N-containing C_3-C_8 cycloalkyl and phenyl, each optionally substituted.

[0090] In some embodiments, R^4 is methylamino, aniline group, azetidinyl, pyrrolidinyl, piperidinyl, azacycloheptenyl, each N-substituted with a moiety selected from benzyl, acyl, acryloyl, substituted-acryloyl, propiolyl, and substituted-propiolyl.

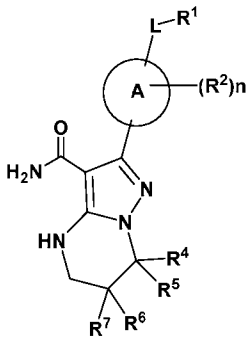
[0091] In some embodiments, R^4 is selected from structures,



[0092] In some embodiments, R^4 is  or  .

[0093] In some embodiments, R^4 is l-acryloylpiperidin-4-yl (i.e., Compound 27 in WO 2014/173289 A1).

[0094] In some embodiments, the Btk inhibitor of Formula **(I)** has the structure of Formula **(I-A)**,



(I-A)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

wherein:

A is phenyl;

L is a bond, CH_2, NR^{12}, O, or S;

n is 0, 1, or 2, wherein when n is more than 1, each R^2 may be different;

R^1 is phenyl, optionally substituted with at least one substituent R^{16};

R^4 is N-containing C_1-C_8 alkyl, N-containing C_3-C_8 cycloalkyl and phenyl, each optionally substituted with at least one substituent R^{16a};

R^5, R^6, and R^7 are each independently H, halogen, heteroalkyl, alkyl, alkenyl, alkynyl, -CN, -$NR^{13}R^{14}$, or -OR^{13}, wherein the alkyl (including alkyl portion of heteroalkyl), alkenyl, and alkynyl, are optionally substituted with at least one substituent R^{16};

R^2 is halogen, alkyl, -S-alkyl, -CN, -$NR^{13}R^{14}$, or -OR^{13};

R^{12} is H or C_1-C_3 alkyl;

R^{13} and R^{14} are each independently H, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl;

R^{16a} is halogen, alkyl, alkenyl, alkynyl, -CN, -OR^a, -NR^aR^b, -COR^a, -CO_2R^a, -$CONR^aR^b$, -NR^aCOR^b, -$NR^aCONR^aR^b$, -$NR^aCO_2R^b$, wherein R^a and R^b are independently hydrogen, halogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl; and

R^{16} is halogen, alkyl, alkenyl, alkynyl, -CN, -OR^a, or -NR^aR^b, wherein R^a and R^b are independently hydrogen, halogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl.

[0095] In some embodiments of the Btk inhibitor of Formula (I-A) or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,

A is phenyl;

L is O;

n is 0, 1, or 2, wherein when n is more than 1, each R^2 may be different;

R^1 is phenyl, optionally substituted with at least one substituent R^{16};

R^4 is C_3-C_8 saturated heterocycle containing one N atom as a ring member, optionally substituted with at least one substituent R^{16a};

R^5, R^6, and R^7 are each independently H, halogen, heteroalkyl, alkyl, alkenyl, alkynyl, -CN, -$NR^{13}R^{14}$, or -OR^{13}, wherein the alkyl (including alkyl portion of heteroalkyl), alkenyl, and alkynyl, are optionally substituted with at least one substituent R^{16};

R^2 is halogen, alkyl, -S-alkyl, -CN, -$NR^{13}R^{14}$, or -OR^{13};

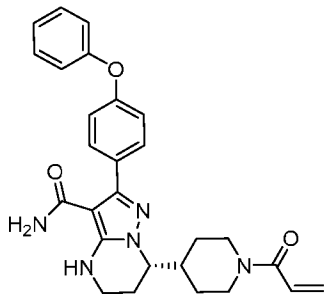
R^{12} is H or C_1-C_3 alkyl;

R^{13} and R^{14} are each independently H, C_1-C_3 alkyl, C_2-C_3 alkenyl, or C_2-C_3 alkynyl;

R^{16a} is $-C(O)CH=CH_2$, $-C(O)C\equiv CCH_3$, $-NHC(O)CH=CH_2$, or $-NHC(O)C\equiv CCH_3$; and

R^{16} is halogen, alkyl, alkenyl, alkynyl, -CN, -OR^a, or -NR^aR^b, wherein R^a and R^b are independently hydrogen, halogen, C_1-C_3 alkyl, C_2-C_3 alkenyl, C_2-C_3 alkynyl.

[0096] As disclosed in each of the above embodiments, the Btk inhibitor is a compound of Formula **(II)**--i.e., **Compound 1**,



(II)

or a pharmaceutically acceptable salt thereof.

[0097] The Btk inhibitor disclosed herein, such as the compound of Formula **(II)**, may be synthesized by synthetic routes disclosed in WO 2014/173289 A1 and unpublished PCT application WO 2018/033853, the entire disclosure of which is expressly incorporated herein by reference. The Btk inhibitor, i.e., **Compound 1**, disclosed herein, may be prepared in accordance with the procedures in WO 2018/033853, the entire disclosure of which is expressly incorporated herein by reference.

Combination therapy

[0098] The combination therapy may be administered as a simultaneous, or separate or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes co-administration, using separate formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities.

[0099] In some embodiments, the combination therapies provided herein provide a synergistic and/or statistically improved effect relative to either therapy when used as a single agent. For example, the combination therapies disclosed herein result in significant improvement in

patient outcome even in indolent and aggressive B-cell malignancies. For example, the combination therapies, in some embodiments, prolong patient survival and progression-free survival while having a manageable toxicity profile in patients suffering from B-cell malignancies, including indolent and aggressive lymphomas.

[0100] Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the Btk inhibitor and the targeted therapy agent or the immune checkpoint inhibitor, such as to increase the therapeutic index or mitigate toxicity or other side-effects or consequences.

[0101] In a particular embodiment of anti-cancer therapy, the Btk inhibitor and the anti-PD-1 antibody may be further combined with surgical therapy and radiotherapy.

[0102] In an embodiment of each of the above aspects, the amounts of the Btk inhibitor the anti-PD-1 antibody disclosed herein and the relative timings of administration be determined by the individual needs of the patient to be treated, administration route, severity of disease or illness, dosing schedule, as well as evaluation and judgment of the designated doctor.

[0103] The Btk inhibitor and the anti-PD-1 antibody disclosed herein may be administered in various known manners, such as orally, topically, rectally, parenterally, by inhalation spray, or via an implanted reservoir, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The term "**parenteral**" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[0104] In one embodiment of each of the above aspects, the Btk inhibitor the anti-PD-1 antibody disclosed herein may be administered in different route. In a preferred embodiment, the Btk inhibitor is administered orally, and the anti-PD-1 antibody is administered parenterally such as subcutaneously, intracutaneously, intravenously or intraperitoneally. In a preferred embodiment, the BTK inhibitor is administered once a day (once daily, QD), two times per day (twice daily, BID), three times per day (Q3D), four times per day (Q4D), or five times per day (Q5D), and is administered at a dosage of about 80 mg/day to about 640 mg/day. In a preferred embodiment, the BTK inhibitor is administered at a dose of 320 mg QD or 160 mg BID. In a preferred embodiment, the anti-PD1 monoclonal antibodies is **Mab 1**, which is administered at a dosage of about 2 mg/kg Q3W to about 200 mg/kg once every three weeks (Q3W), more preferably, is administered at a dosage of about 2mg/kg Q3W, 5mg/kg Q3W or 200 mg flat Q3W. In a more preferred embodiment, the anti-PD-1 antibody is administered at a dose of 200 mg flat dose every 21 days. In one embodiment, the anti-PD-1 antibody is administered intravenously. In one embodiment, the BTK inhibitor is administered at least 30

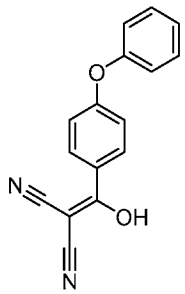
minutes before the anti-PD-1 antibody if administered on the same day. Specifically, the BTK inhibitor is administered per day and the anti-PD-1 antibody every three weeks, and the BTK inhibitor is administered at least 30 minutes (sometimes 1 hour or 2 hours) before the anti-PD-1 antibody if administered on the same day.

EXAMPLE

[0105] The present invention is further exemplified, but not limited to, by the following examples that illustrate the invention.

Example 1 Preparation of (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl) -4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide (Compound 1) and Crystalline Form A Thereof

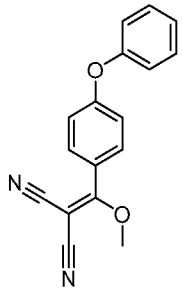
Step 1: Synthesis of BG-2



BG-2

[0106] Under nitrogen atmosphere, to a solution of EA (5 v), HOBT (1.2 eq.), EDCI (1.2 eq.), 4-phenoxybenzoic acid (BG-1, 80 Kg, 1.0 eq.) and malononitrile (1.2 eq.) was added TEA (2.4 eq.) at 10°C. The mixture was then stirred at RT until the reaction was completed. The mixture was then centrifuged and the cake was washed with EA. The filtrate was washed with aqueous $NaHCO_3$ twice and NH_4Cl. The organic phase was washed with 1.5 N H_2SO_4 twice and stirred. Concentrated, precipitated from methanol and purified water. The solid was collected by centrifugation and dried under vacuum. This gave 79.9 Kg of BG-2. ^1H NMR (DMSO-d_6) δ 7.62 (d, J = 8.6 Hz, 2H), 7.46-7.38 (m, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.6 Hz, 2H).

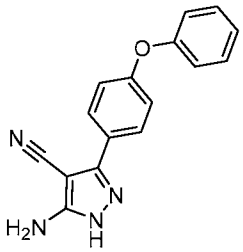
Step 2: Synthesis of BG-3



BG-3

[0107] Under nitrogen atmosphere, a solution of BG-2 (79.9 kg, 1.0 eq.) in MeCN (5.0 v) was added into trimethoxymethane (12.0 v) at 85°C. The resultant mixture was stirred until the reaction was completed. Sampled for HPLC analysis. Concentrated under vacuum. The residue was precipitated from *i*-PrOH and hexane. The mixture was centrifuged, and the cake was washed with hexane and dried under vacuum. This gave 71.7 Kg of product. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.70 (d, *J* = 8.4 Hz, 2H), 7.52-7.45 (m, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.22-7.06 (m, 4H), 3.93 (s, 3H).

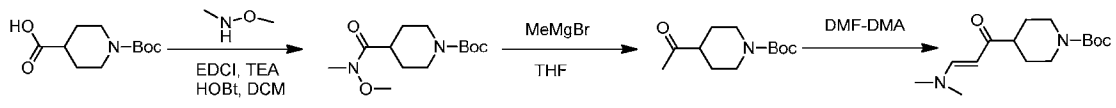
Step 3: Synthesis of BG-4



BG-4

[0108] Under nitrogen atmosphere, to a solution of BG-3 (71.6 kg, 1.0 eq.) in ethanol (2.5 v) hydrazinium hydroxide (1.0 eq) in ethanol (0.6 v) was charged dropwise to the reactor below 15°C. The solution was heated to RT and stirred until the reaction was completed. Water (4.0 v) was added to the reactor. The solution was then cooled to 5°C, centrifuged and the cake was washed with water (1.0 v). The cake was dried under vacuum. This gave 66.9 Kg of product. ^{1}H NMR (DMSO-d$_6$) δ 12.11 (br s, 1H), 7.80 (d, *J* = 8.8 Hz, 2H), 7.46-7.39 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.12-7.04 (m, 4H), 6.43 (br s, 2H).

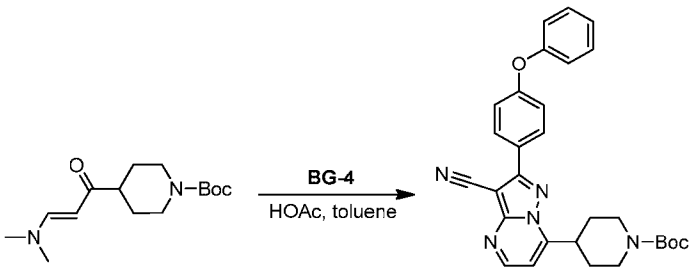
Steps 4 to 6: Synthesis of BG-8



BG-5 BG-6 BG-7 BG-8

[0109] To a mixture of DCM (8.0 v), BG-5 (80.0 Kg, 1.0 eq.), *N,O*-dimethylhydroxylamine hydrochloride (1.2 eq.), HOBt (1.2 eq.) and EDCI (1.2 eq.), TEA (2.6 eq.) was charged dropwise below 15°C. the mixture was stirred at RT until the reaction was completed, centrifuged and the cake was washed with DCM (1.0 v) twice. The filtrate was washed with 20% aqueous NH_4Cl (3 × 4.0 v). The filtrate was concentrated under vacuum to give the crude product BG-6, which was used in the next step without further purification. The residue was dissolved in toluene (5.0 v) and THF (1.0 v), cooled to 10 °C, charged dropwise MeMgBr (1.4 eq.) at 10°C and then stirred at RT until the reaction was completed. The solution was cooled below 10°C. Saturated aqueous NH_4Cl was charged dropwise below 10°C. The mixure was centrifuged, separated, filtrated, and the organic phase was washed with aqueous NaCl twice. The organic phase was concentrated to give the crude product, which was used in the next step without further purification. The residue in DMF (2.5 v) and DMF-DMA (2.5 v) was stirred at 110°C until the reaction was completed. The reaction mixture was cooled, concentrated and then DCM was added. The final mixture was washed with saturated aqueous NH_4Cl. The organic layer was cconcentrated and precipitated by charging hexane. The mixture was ccentrifuged and the cake was collected. The cake was dried under vacuum. This gave 82.2 Kg of the desired product. ^{1}H NMR (DMSO-d_6) δ 7.49 (d, J = 12.6 Hz, 1H), 5.01 (d, J = 12.6 Hz, 1H), 3.99-3.82 (m, 2H), 3.14-2.94 (m, 2H), 2.89-2.61 (m, 6H), 2.49-2.37 (m, 1H), 1.66-1.56 (m, 2H), 1.39 (s, 9H), 1.39-1.20 (m, 2H).

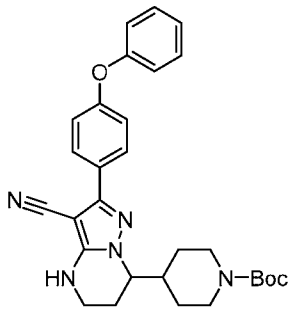
Step 7: Synthesis of BG-9



BG-8 BG-9

[0110] Under nitrogen atmosphere, a mixture of toluene (8.0 v), AcOH (0.5 v), BG-8 (1.2 eq.) and BG-4 (66.9 Kg 1.0 eq.) was heated to 95°C and stirred until the reaction was completed. The mixture was cooled, concentrated and precipitated from methanol. The mixture was centrifuged and the cake was washed with methanol. The cake was dried under vacuum. This gave 107.8 Kg of product.^{1}H NMR (DMSO-d_6) δ 8.78 (d, J = 4.6 Hz, 1H), 8.15-8.07 (m, 2H), 7.51-7.41 (m, 2H), 7.34 (d, J = 4.6 Hz, 1H), 7.27-7.19 (m, 3H), 7.17-7.10 (m, 2H), 4.24-4.02 (m, 2H), 3.81-3.69 (m, 1H), 3.12-3.82 (m, 2H), 2.15-2.04 (m, 2H), 1.76-1.60 (m, 2H), 1.43 (s, 9H).

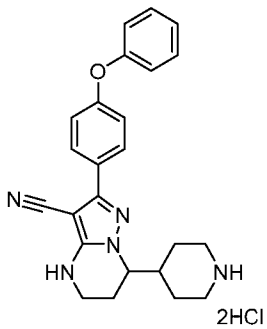
Step 8: Synthesis of BG-10



BG-10

[0111] To a mixture of THF (10.0 v), BG-9 (13.0 Kg, 1.0 eq.) and D-DBTA (1.0 eq) under N_2 was charged Pd/C (10% w/w), hydrogen gas was introduced into the reactor and the hydrogen pressure was maintained to 1.8 MPa. The reactor was heated to 40°C slowly and stirred until the reaction was completed. The mixture was then cooled, filtered, and the cake was washed with THF. The filtrate was collected, and concentrated under vacuum. DCM was added. The residue was washed with aq. $NaHCO_3$, concentrated and precipitated from MTBE and hexane, then centrifuged. The cake was collected and dried under vacuum to give the desired compound (yield:94.8% and purity:98.5%). ^{1}H-NMR (DMSO-d_6) δ 7.82-7.76 (m, 2H), 7.56-7.51 (m, 1H), 7.45-7.37 (m, 2H), 7.21-7.14 (m, 1H), 7.12-7.03 (m, 4H), 4.09-3.91 (m, 3H), 3.30-3.22 (m, 2H), 2.82-2.55 (m, 2H), 2.18-1.99 (m, 2H), 1.98-1.86 (m, 1H), 1.69-1.58 (m, 1H), 1.56-1.45 (m, 1H), 1.38 (s, 9H), 1.32-1.13 (m, 2H).

Step 9: Synthesis of BG-11

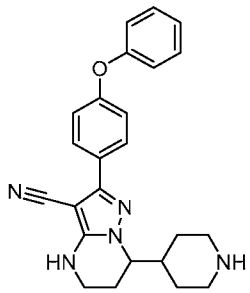


BG-11

[0112] To a solution of BG-10 (100.0 Kg 1.0 eq.) in DCM (6.0 v) was added dropwise HCl in EtOH (20.9% w/w, 2.0 v) under nitrogen atmosphere. The mixture was stirred until the reaction was completed. MTBE (4.0 v) was added to the solution, cooled. The cakes was collected by centrifugation and washed with hexane (2.0 V), then the cake was slurried in hexane (5 v), and centrifuged again. The cake was washed with hexane (2.0 V) and dried under vacuum. This gave 85.2 Kg product. ^{1}H-NMR (DMSO-d_6) δ 9.25-8.85 (m, 2H), 7.84-7.70 (m,

2H), 7.47-7.37 (m, 2H), 7.18 (t, J = 7.4 Hz, 1H), 7.12-7.03 (m, 4H), 5.73 (br s, 2H), 4.12-4.03 (m, 1H), 3.25-3.19 (m, 4H), 2.90-2.73 (m, 2H), 2.28-2.12 (m, 1H), 2.10-2.00 (m, 1H), 1.99-1.86 (m, 1H), 1.84-1.52 (m, 4H).

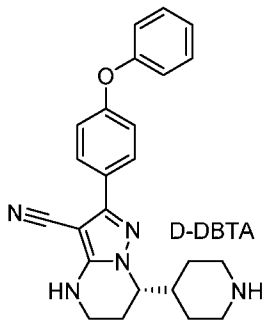
Step 10: Synthesis of BG-11A



BG-11A

[0113] A mixture of BG-11 (85.0 Kg, 1.0 eq) in water (6.0 v) and NaOH (3.0 eq) was stirred until the reaction was completed at RT. The cake was collected and slurried in MTBE (6.0 v). The mixture was then centrifuged to collect the cake. The cake was dried under vacuum. This gave 71.3 Kg product. ^{1}H-NMR (DMSO-d$_6$) δ 7.82-7.74 (m, 2H), 7.54-7.49 (m, 1H), 7.45-7.38 (m, 2H), 7.21-7.14 (m, 1H), 7.12-7.04 (m, 4H), 4.03-3.95 (m, 1H), 3.29-3.21 (m, 2H), 3.00-2.87 (m, 2H), 2.46-2.31 (m, 2H), 2.11-1.83 (m, 3H), 1.58-1.12 (m, 4H).

Step 11: Synthesis of BG-11B

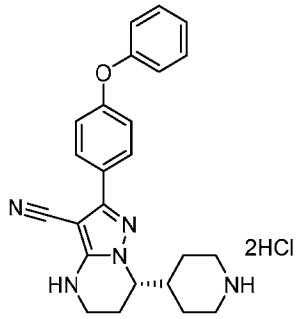


BG-11B

[0114] A mixture of enthanol/water/acetic acid (7:3:1, 46 v) and BG-11A (30 kg, 1.0 eq.) in a reactor was heated to 70±5 °C under nitrogen atmosphere, then a solution of D-DBTA (1.20 eq.) in ethanol/water/acetic acid (7:3:1, 4 v) was added dropwise with the temperature not less than 65°C. The resulting solution was stirred for 16 hrs at 60-65 °C, then cooled to RT. The solid was collected by centrifugation and washed with ethanol (2.0 v). The cake was slurried in the mixed solvent of ethanol/water/AcOH (7:3:1, 20 v) for 16 hrs at 55 °C and cooled to RT. The solid was collected by centrifugation, washed with ethanol (2.0 v). The cake was dried under vacuum (Yield: 37.9%).^{1}H-NMR (DMSO-d$_6$) δ 8.76 (br s, 2H), 7.99-7.89 (m, 4H), 7.83-

7.75 (m, 2H), 7.66-7.57 (m, 3H), 7.52-7.45 (m, 4H), 7.45-7.39 (m, 2H), 7.21-7.14 (m, 1H), 7.13-7.03 (m, 4H), 5.64 (s, 2H), 4.08-4.00 (m, 1H), 3.29-3.19 (m, 4H), 2.85-2.72 (m, 2H), 2.21-1.40 (m, 7H).

Step 12: Synthesis of BG-11C



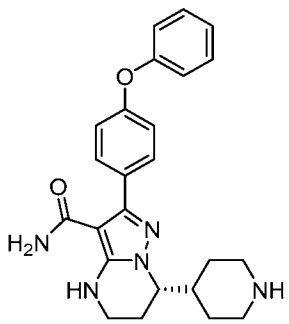
BG-11C

[0115] To a mixture of dichloromethane (15.0 v) and 20.0% aqueous KOH (3.0 v) was added bachwise BG-11B (48.0 kg, 1.0 eq.) under nitrogen atmosphere at RT. After the reaction was completed, the organic layer was collected and the water layer was extracted with dichloromethane (5.0 v). The organic layers were combined. Con. HCl (0.36 v) was added to the above organic layers at RT. The resulting mixture was stirred until the reaction was completed. The solid was collected by centrifugation and washed with dichloromethane (1.0 v). The collected solid was slurried with MTBE (6.0 v). The solid was collected by centrifugation and washed with MTBE (1.0 v), then was dried under vacuum. This gave 31.5 Kg product (Yield:100 %).

Step 12: Synthesis of BG-11D (Alternative intermediate)

[0116] ACN (5.0 v), soft water (10.0 v), KOH (5.0 eq) was charged to a reactor and stirred for at least 15 min. BG-11B (1.0 eq) was charge to the reactor in portion-wise. The mixture was stirred until the reaction was completed. The cake was collected by centrifugation, slurried in ACN (1.0 v) and soft water (5.0 v), and dried under vacuum to give the product.

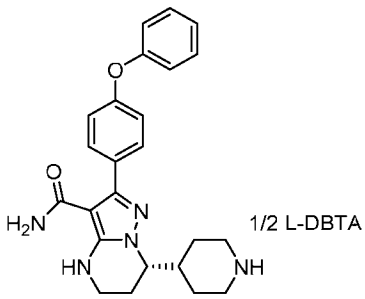
Step 13: Synthesis of BG-12



BG-12

[0117] A solution of BG-11C (15.0 Kg 1.0 eq.) in MsOH (2.5 v) was stirred at 85°C under nitrogen atmosphere until the reaction was completed. After cooling to 5 °C. purified water (4.0 v) was added dropwise to the system and kept the temperature not more than 35°C (temperature increased obviously). The resulting solution was stirred for 16 hrs at 30°C, and then washed with DCM (2×3.0 v). The aqueous phase was collected. DCM (6.0 v) was added to the aqueous phase, the mixture was cooled to 5°C. The pH value was adjusted to 11~12 with 20% aqueous NaOH (temperature increased obviously) with stirring with the temperature not more than 30 °C. The organic phase was separated and collected. The aqueous was extracted with DCM (3.0 v). The organic layers were combined and concentrated. MTBE (4.0 v) was added to the residue. The mixture was then concentrated and precipitated from *n*-heptane. The solid was collected by centrifugation and dried in a vacuum oven. This gave 12.55 Kg product (Yield: 94.9%). ^{1}H-NMR (DMSO-d_6) δ 7.52-7.46 (m, 2H), 7.45-7.38 (m, 2H), 7.21-7.13 (m, 1H), 7.12-7.03 (m, 4H), 6.64 (s, 1H), 3.99-3.90 (m, 1H), 3.29-3.22 (m, 2H), 3.03-2.90 (m, 2H), 2.48-2.36 (m, 2H), 2.03 (dd, J = 13.9, 5.6 Hz, 2H), 2.14-1.99 (m, 1H), 1.97-1.85 (m, 1H), 1.65-1.15 (m, 3H).

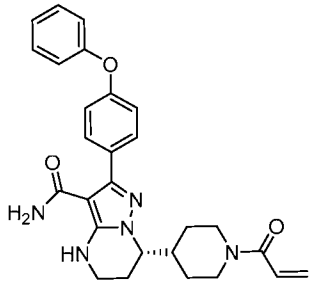
Step 14: Synthesis of BG-13



BG-13

[0118] A mixture of MeOH (13.5 v), purified water (4.5 v) and BG-12 (8.5 Kg, 1.0 eq.) in a reactor was heated to 50°C under N_2 atmosphere. To the mixture was charged dropwise a solution of L-DBTA (0.7 eq) in MeOH/purified water (1.5 v/0.5 v) while keeping the temperature at 50 °C. After addition, the mixture was stirred for at least 2 hrs at 50 °C, and then cooled to RT and stirred for at least 16 hrs at RT. The cake was collected by Centrifugation and was washed with MeOH (2.0 v). The cake was dried in a vacuum oven. This gave 9.08 Kg product (Yield: 74.8%).

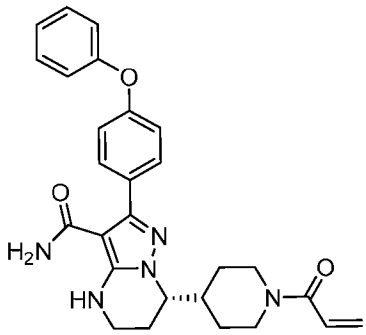
Step 15: Synthesis of (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide **(Compound 1)**



[0119] Under N_2 atmosphere, ACN (12.0 v), water (12.5 v), BG-13 (8.0 Kg, 1.0 eq), and $NaHCO_3$ (2.5 eq.) were added to a reactor. The mixture was then cooled to -5~0 °C. To the mixture, the solution of acryloyl chloride (1.1 eq.) in MeCN (0.5 v) was added dropwise and stirred until the reaction was completed. EA (6.0 v) was then added to the reactor, and stirred. The organic phase was collected. The aqueous layer was further extracted with EA (3.0 v). The organic phases were combined and washed with brine. The organic layer was collected and concentrated.

[0120] The residue was purified by silica gel (2 wt) column, eluted with 3% w/w methanol in DCM (21.0 v). The **Compound 1** solution was collected and concentrated under vacuum. The residue was precipitated from EA/MTBE (2.0 v). The cake was collected by centrifugation as the product.

Step 15: Synthesis of (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl) -4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3-carboxamide (**Compound 1**, alternative method)



[0121] A mixture of CH_3CN (10.0 v), purified water (5.0 v), NaOH (1.5 eq.) and BG-13 (1.0 eq.) was stirred to get a clear solution. EtOAc (6.0 v) was then charged to the reaction and separated. The organic phase was collected and washed with 15% brine (3.0 v) twice. The organic phase prepared above was concentrated and the solvent was swapped to CH_3CN (residue volume: NMT 5.0 v). CH_3CN (7.5 v) and purified water (12.5 v) were charged and cooled to 15-20°C. L-(+)-tartaric acid (0.5 eq) and $NaHCO_3$ (2.5 eq.) were charged to the reaction mixture. A solution of acryloyl chloride (1.1 eq.) in CH_3CN (0.5 v) was charged drop-wise to the reaction mixture. After the reaction was completed, EtOAc (6.0 v) was charged to

the reaction mixture and organic layer was collected. Aqueous phase was further extracted with EA (3.0 v). The organic layers were combined, washed with 15% brine (5.0 v) and concentrated. The solvent was swapped to DCM (volume of residue: 1.5-2.0 v) and purified by silica gel column (silica gel: 100-200 mush, 2.0 w/ w; eluent: 3% w/ w MeOH in DCM (about 50 v). The collected solution was concentrated and swapped to EtOAc (4.0 v). MTBE (6.4 v) was charged drop-wise to residue at 50°C. The mixture was then cooled to 5°C and the cake was collected centrifugation.

Step 16: Preparation of Crystalline Form A of **Compound 1**

[0122] The above cake was dissolved in 7.0 volumes of DCM, and then swapped to solvent EA. After recrystallization from EA/MTBE, the cakes was collected by centrifugation, and was dried under vacuum. This gave 4.44 Kg product (Yield: 70.2%).

[0123] The product was then characterized by X-ray powder diffraction (XRPD) pattern method, which was generated on a PANalytical Empyrean X-ray powder diffractometer with the XRPD parameters as follows: X-Ray wavelength (Cu, kα, Kα1 (Å): 1.540598, Kα2(Å): 1.544426; Kα2/Kα1 intensity ratio: 0.50); X-Ray tube setting (45 Kv, 40mA); divergence slit (automatic); scan mode (Continuous); scan range (°2TH) (3°-40); step size (°2TH) (0.0131); scan speed (°/min) (about 10). The XRPD result found the resultant product as a crystalline shown in **FIG. 6.**

[0124] The proton nuclear magnetic resonance (^{1}H-NMR) shown as in **FIG. 7** was collected on a Bruker 400M NMR Spectrometer in DMSO-d_6. ^{1}H-NMR (DMSO-d_6) δ 7.50 (d, J = 8.6 Hz, 2H), 7.46-7.38 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.85-6.72 (m, 1H), 6.67 (s, 1H), 6.07 (dd, J = 16.8, 2.2 Hz, 1H), 5.64 (dd, J = 10.4 Hz, 2.2 Hz, 1H), 4.55-4.38 (m, 1H), 4.17-3.94 (m, 2H), 3.33-3.22 (m, 2H), 3.08-2.88 (m, 1H), 2.67-2.51 (m, 1H), 2.36-2.15 (m, 1H), 2.12-1.82 (m, 2H), 1.79-1.65 (m, 1H), 1.63-1.49 (m, 1H), 1.38-1.08 (m, 2H).

[0125] The carbon nuclear magnetic resonance (^{13}C-NMR) shown as in **FIG. 8** was collected on a Bruker 400M NMR Spectrometer in DMSO-d_6. ^{13}C-NMR spectra for Crystalline Form A of **Compound 1**.

Example 2 Safety and activity of BTK inhibitor in combination with PD-1 inhibitor in patients with B-cell lymphoid malignancies

Methodology

[0126] First-in-human, open-label, multicenter, phase 1b trial was study to evaluate safety, tolerability, and preliminary efficacy (see **FIG. 1**) of Compound 1 in combination with Mab 1 in subjects with B-cell malignancies, including relapsed/refractory chronic lymphocytic

leukemia (CLL)/small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL), GCB DLBCL or DLBCL with undetermined subtype, follicular lymphoma (FL), marginal zone lymphoma (MZL), hairy cell leukemia (HCL), transformed FL, Richter's transformation, primary central nervous system lymphoma (PCNSL), secondary CNS lymphoma (SCNSL) of breast or testicular origin, and transformed lymphoma. The study was divided into dose escalation and a dose expansion.

[0127] Study Treatment

[0128] **Compound 1** was administrated orally every day (320 mg QD or 160 mg BID) with or without food. **Mab 1** was administrated intravenously (2.0 mg/kg, 5.0 mg/kg, or 200mg flat dose, depending on assigned dose level cohort) every 21 days (Q3W). When the 2 study drugs were administrated on the same day (except on the days both PK samples are collected), **Compound 1** was administered at least 30 minutes before **Mab 1** infusion. All cycles included 21 days.

[0129] For dose escalation, Cycle 1 included 28 days and all subsequent cycles included 21 days. **Compound 1** was administered on Cycle 1 Day 1 and then continuously every day. **Mab 1** was administrated on Cycle 1 Day 8 and then on Day 1 of all subsequent cycles. The period for DLT assessment was 21 days from Cycle 1 Day 8 to Cycle 1 Day 28.

[0130] For dose expansion, all cycles included 21 days. On Day 1 of each cycle, **Compound 1** and **Mab 1** were administrated on the same day, except for 10 subjects of the CNS lymphoma cohort (Cohort 4B) as described below.

[0131] For PCNSL and SCNSL (Cohort 4A and 4B), 10 subjects (Cohort 4A) initially received single-agent **Mab 1** for 4 cycles at 200 mg intravenously Q3W. On Day 1 of Cycle 5 and thereafter, the 10 subjects received combination Compound 1 and **Mab 1** at the RP2D defined by the dose escalation. For Cohort 4B, 10 subjects with PCNSL and SCNSL received combination **Compound 1** and **Mab 1** at the RP2D defined by the dose escalation starting at Day 1 of Cycle 1 and all cycles thereafter. When the 2 drugs were administered on the same day (except on the days both PK samples to be collected), Compound 1 was administered at least 30 minutes before Mab 1 infusion. All cycles included 21 days.

[0132] Dose Escalation

[0133] The purpose of dose escalation is to determine the MTD for this study. During dose escalation, three dose levels were explored in the following order:

• Dose level 1: Compound 1 320 mg QD in combination with Mab 1 2.0 mg/kg Q3W. If Dose Level 3 cleared, subjects were converted to dose level 3 dosing. Dose level -1 (applicable only if dose level 1 exceeds MTD): Compound 1 160 mg QD in combination with

Mab 1 2.0 mg/kg Q3W. Further reductions of Compound 1 or Mab 1 dose levels may be allowed until a safe dose combination is identified.

• Dose level 2: Compound 1 320 mg QD with Mab 1 5.0 mg/kg Q3W. If dose level 3 cleared, subjects were converted to dose level 3 dosing.

• Dose level 3: Compound 1 160 mg BID with Mab 1 200 mg flat dose Q3W.

[0134] Dose escalation followed the same principles as stipulated for a standard 3+3 dose escalation design, with each cohort evaluated for safety based on the number of dose-limiting toxicities (DLTs) observed. Evaluation of a cohort of at least 3 subjects completing the DLT assessment at any given dose level is required prior to determining the next dose level and dose regimen for the subsequent cohort. Three subjects in the cohort is sufficient if no DLTs are observed within the DLT window for all 3 subjects. More than 3 subjects are required per cohort depending on the number of observed DLTs as follows:

• < 6 subjects enrolled in the cohort:

1 subject experiences a DLT during the DLT assessment period: the cohort must enroll a minimum of 6 subjects evaluable for DLT.

≥ 2 subjects experience a DLT during the DLT assessment period: the MTD is considered to have been exceeded, and no additional subjects will be treated at the current or higher doses.

• ≥ 6 subjects enrolled in the cohort:

1 subject experiences a DLT during the DLT assessment period: the cohort is considered tolerable and to not exceed the MTD.

≥ 33% of subjects (i.e., 2 out of 6) experience a DLT during the DLT assessment period: the MTD is considered to have been exceeded, and no additional subjects will be treated at the current or higher doses.

[0135] Dose Expansion

[0136] In the dose expansion, there were 4 dose expansion cohorts at the RP2D for the combination of Mab 1 and Compound 1:

• Cohort 1 (n = 20): GCB DLBCL

• Cohort 2 (n = 20): non-GCB DLBCL

• Cohort 3 (n = 20): Transformed lymphoid malignancy

• Cohort 4: Primary CNS lymphoma or SCNSL of breast or testicular origin

  - Cohort 4A (n = 10): begin with 4 cycles of single-agent Compound 1 at 200 mg Q3W, combination of Compound 1 and Mab 1 starting Cycle 5
  - Cohort 4B (n = 10): combination of Compound 1 and Mab 1 starting Cycle 1

[0137] The cohorts for the dose expansion were defined in Inclusion Criterion 2. The dose and schedule of combination Compound 1 and Mab-1 were the RP2D as determined by the SMC for the non-CNS disease types (Cohorts 1 to 3). The dose and schedule of single-agent Mab 1 were 200 mg IV Q3W for Cohort 4, followed by the RP2D for the combination. Approximately 20 subjects were enrolled in each dose expansion part. Cohorts 1, 2, 3, and 4A opened simultaneously once the RP2D has been determined. Cohort 4B may not be enrolled until Cohort 4A has been completed.

[0138] Dose-Limiting Toxicity

[0139] A dose-Limiting Toxicity (DLT) is a toxicity or adverse event (AE) occurring during the DLT assessment period (21 days from Cycle 1 Day 8 to Cycle 1 Day 28), which cannot be primarily attributed to a cause other than Compound 1 and/or Mab 1 (such as disease progression, underlying illness, concurrent illness, or concomitant medication) and meets 1 of the following criteria:

1) Non-hematologic Grade 4 (or Grade 3 lasting > 3 days) toxicity excluding:
   a. Laboratory abnormalities deemed by investigators as being not of serious nature
   b. Grade 3 tumor flare
   c. Grade 3 infusion-related event that resolves to Grade 1 within 28 days
   d. Grade 3 nausea or vomiting
   e. Grade 3 hypertension

2) Grade 4 neutropenia lasting > 7 days, not attributable to leukemic or lymphomatous infiltration of the bone marrow

3) Grade 4 thrombocytopenia lasting > 7 days, not attributable to leukemic or lymphomatous infiltration of the bone marrow

4) Any toxicity that requires drug hold of 1 or both investigational agents for more than 2 weeks.

Methods

[0140] Primary endpoint

• Dose escalation: The MTD and/or recommended Phase 2 dose (RP2D) of Mab 1 in combination with Compound 1, as determined based on the incidence of protocol-defined dose-limiting toxicities, safety, tolerability, and PK profile.

• Dose expansion: The safety and tolerability of combination Compound 1 and Mab 1 (Cohorts 1 to 3, and 4B), or single agent Mab 1 followed by combination Compound 1 and Mab 1 (Cohort 4A) in previously treated subjects with B-cell malignancies, as assessed by the occurrence and severity of AEs (Common Terminology Criteria for Adverse Events [CTCAE], version 4).

[0141] Secondary endpoints

- The antitumor activity of the combination of Compound 1 and Mab 1 (Cohorts 1 to 3, and 4A), or single-agent Mab 1, followed by combination Compound 1 and Mab 1 (Cohort 4B) in previously treated subjects with specified B-cell malignancies, as determined by overall response rate (ORR, defined as the proportion of subjects who had complete response [CR] or partial response [PR] by standard disease-specific response criteria), duration of response ([DOR]; defined as the time from the date that a confirmed objective response is first documented to the date of progressive disease [PD] or death due to any cause for those subjects with a confirmed PR or CR), and progression-free survival ([PFS]; defined as the time from the first dose of study medication to objective disease progression or death).
- The PK profiles of Mab 1 and Compound 1.
- The incidence of development of anti-drug antibody to Mab 1 when given in combination with Compound 1.

Results

[0142] Patient disposition at the current cutoff is shown in **FIG. 2**. The median follow up is about 5.1 months (rang 0.4-14.1); 5.1 (1.6-14.1) and 4.2 (0.4-14.4) for indolent and aggressive lymphoma, respectively.

[0143] The patients and disease characteristics are listed in **Table 1-A**. The best response is listed in **Table 1-B**.

[0144] The DLT assessment period is 21 days from Cycle 1 Day 8 to Cycle 1 Day 28. In cohort 2, two events of hemolysis, 1 of which met criteria for DLT, see **Table 2**. Both events were in patients with WM and additional patients with WM were excluded form enrollment in trail, and no further DLT events following WM exclusion.

[0145] Table 1-A Patients and Disease Characteristics

Characteristic	Indolent (n = 13)	Aggressive (n = 12)	Total (N = 25)
Age, years, median (range)	62 (47-76)	62.5 (27-71)	62 (27-76)
ECOG performances status, n (%)			
0	7 (53.8)	3 (25)	10 (40)
1	3 (23.1)	7 (58.3)	10 (40)
2	3 (23.1)	1 (8.3)	4 (16)
3	0	1 (8.3)	1 (4)
Follow-up, months, median (range)	5.1 (1.6-14.1)	4.2 (0.4-14.1)	5.1 (0.4-14.1)
Number of prior therapies, median range)	4 (1-6)	4 (1-6)	4 (1-6)
Bulky disease,* n (%)	1 (7.7)	1 (8.3)	2 (8)
Dose 1 (Compound 1 320mg QD, Mab-1 2.0mg/kg Q3W)	7 (53.8)	8 (66.7)	15 (60)
Dose 2 (Compound 1 320mg QD, Mab-1 5.0mg/kg Q3W)	6 (46.2)	4 (33.3)	10 (40)

ECOG, Eastern Cooperative Oncology Group; GBC, germinal center B-cell; LDH, lactate dehydroganase; Q3W, every 3 weeks; QD, once daily.
* Any lymph node >10 cm in maximum diameter.

[0146] Table 1-B Best Response

Response	Indolent n (%)	Aggressive n (%)	Total n (%)
Efficacy evaluable, n	12	12	24
Best Response, n (%)			
ORR	**4 (33.3)**	**4 (33.3)**	**8 (33.3)**
CR	1 (8.3)	1 (8.3)	2 (8.3)
VGPR	1 (8.3)	–	1 (4.2)
PR/PR-L	1 (8.3)	3 (25)	4 (16.7)
MR	1 (8.3)	–	1 (4.2)
SD	4 (33.3)	3 (25)	7 (29.2)
PD	2 (16.7)	5 (41.7)	7 (29.2)
Discontinuation or NE or ND*	2 (16.7)	0	2 (8.3)

CR, complete response; MR, minor response; ND, not defined; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; VGPR, very good partial response.
*Patient discontinued for reason other than PD before 1st response assessment or response assessment was NE or scheduled response assessment was not done.

[0147] Table 2 Dose-Limiting Toxicity

Dose Level	Enrolled	Cohort Status	DLTs
Dose 1 (2.0 mg/kg Q3W)	15	Complete	None
Dose 2 (5.0 mg/kg Q3W)	10	Complete	1 Hemolysis (WM)
Dose 3 (200 mg flat Q3W)	0	Open	(patients have yet to receive drug)

DLT, dose-limiting toxicity; WM, Waldenström's macroglobulinemia.

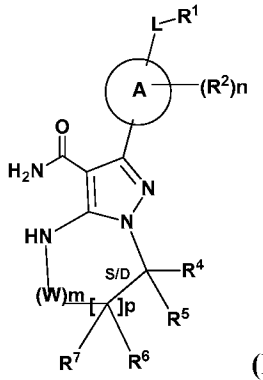
[0148] The combination of **Compound 1** and **Mab 1** was found to achieve maximum improvement in SPD (sum of the products of lymph node diameters by CT scan) in patients with indolent and aggressive lymphoma, respectively, as shown in **FIG. 3A** and **3B**. Also, the combination was found to extend the life of some of the patents enrolled with indolent and aggressive lymphoma, respectively, as shown in **FIG. 4A** and **FIG. 4B**., and to elongate progression-free survival in patients with indolent and aggressive lymphoma, respectively, as shown in **FIG. 5A** and **FIG. 5B**. In conclusion, the potent and selective BTK inhibitor in combination with the checkpoint PD1 inhibitor have a manageable toxicity profile in patients with in a wide variety of B-cell malignancies, including indolent and aggressive lymphomas.

[0149] The foregoing examples and description of certain embodiments should be taken as illustrating, rather than as limiting the present invention as defined by the claims. As will be readily appreciated, numerous variations and combinations of the features set forth above can be utilized without departing from the present invention as set forth in the claims. All such variations are intended to be included within the scope of the present invention. All references cited are incorporated herein by reference in their entireties.

CLAIMS

1. A method for the prevention, delay of progression or treatment of indolent or aggressive B-cell lymphomas in an individual in need thereof, comprising administering a therapeutically effective amount of a Btk inhibitor, in combination with a therapeutically effective amount of an anti-PD-1 antibody,

wherein the Btk inhibitor is a compound of Formula **(I)**,



(I)

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

A is a 5- or 6-membered aromatic ring comprising 0-3 heteroatoms of N, S or O;

each W is independently $-(CH_2)-$ or -C(O)-;

L is a bond, CH_2, NR^{12}, O, or S;

S/D is a single or double bond, and when a double bond, R^5 and R^7 are absent;

m is 0, or an integer of 1-4;

n is 0, or an integer of 1-4, wherein when n is more than 1, each R^2 may be different;

p is 0, or an integer of 1-2, wherein when p is 0, m is non-zero, and when p is more than 1, each R^6 and each R^7 may be different;

R^1, R^4, R^5, R^6,and R^7 are each independently H, halogen, heteroalkyl, alkyl,alkenyl, cycloalkyl, aryl, saturated or unsaturated heterocyclyl, heteroaryl, alkynyl, -CN, $-NR^{13}R^{14}$, $-OR^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-C(=NR^{13})NR^{14}R^{15}$, $-NR^{13}COR^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}CO_2R^{14}$, $-SO_2R^{13}$, $-NR^{13}SO_2NR^{14}R^{15}$, or $-NR^{13}SO_2R^{14}$, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, heteroaryl, aryl, and saturated or unsaturated heterocyclyl are optionally substituted with at least one substituent R^{16},wherein (R^4 and R^5), or (R^4 and R^6), or (R^6 and R^7), or (R^6 and R^6 when p is 2), together with the atoms to which they are attached, can form a ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings optionally substituted with at least one substituent R^{16};

R^2 is halogen, alkyl, -S-alkyl, -CN, $-NR^{13}R^{14}$, $-OR^{13}$, $-COR^{13}$, $-CO_2R^{13}$, $-CONR^{13}R^{14}$, $-C(=NR^{13})NR^{14}R^{15}$, $-NR^{13}COR^{14}$, $-NR^{13}CONR^{14}R^{15}$, $-NR^{13}CO_2R^{14}$, $-SO_2R^{13}$, $-NR^{13}SO_2NR^{14}R^{15}$, or $-NR^{13}SO_2R^{14}$;

R^{12} is H or lower alkyl;

R^{13}, R^{14} and R^{15} are each independently H, heteroalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, saturated or unsaturated heterocyclyl, aryl, or heteroaryl; wherein (R^{13} and R^{14}), and/or (R^{14} and R^{15}) together with the atom(s) to which they are attached, each can form a ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings optionally substituted with at least one substituent R^{16};

R^{16} is halogen, subsituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, subsituted or unsubstituted alkynyl, subsituted or unsubstituted cycloalkyl, subsituted or unsubstituted aryl, subsituted or unsubstituted heteroaryl, subsituted or unsubstituted heterocyclyl, oxo, -CN, -OR^a, -NR^aR^b, -COR^a, -CO_2R^a, -$CONR^aR^b$, -$C(=NR^a)NR^bR^c$, -NR^aCOR^b, -$NR^aCONR^aR^b$, -$NR^aCO_2R^b$, -SO_2R^a, -SO_2aryl, -$NR^aSO_2NR^bR^c$, or -$NR^aSO_2R^b$, wherein R^a, R^b, and R^c are independently hydrogen, halogen, subsituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, subsituted or unsubstituted alkynyl, subsituted or unsubstituted cycloalkyl, subsituted or unsubstituted aryl, subsituted or unsubstituted heteroaryl, subsituted or unsubstituted heterocyclyl, wherein (R^a and R^b), and/or (R^b and R^c) together with the atoms to which they are attached, can form a ring selected from cycloalkyl, saturated or unsaturated heterocycle, aryl, and heteroaryl rings.

2. The method of Claim 1, wherein the anti-PD-1 antibody is a monoclonal antibody.

3. The method of Claim 2, wherein the anti-PD-1 antibody is a monoclonal antibody or a fragment thereof, comprising a heavy chain variable region (Vh) amino acid sequence of SEQ ID No 24, a light chain variable region (Vl) amino acid sequence of SEQ ID No 26, and an IgG4 constant domain amino acid sequence of SEQ ID NO 88.

4. The method of Claim 1, wherein the indolent or aggressive B-cell lymphoma is indolent B-cell lymphomas or aggressive lymphoma, indolent or aggressive Hodgkin's B-cell lymphoma, or indolent or aggressive non-Hodgkin's B-cell lymphoma.

5. The method of Claim 4, wherein the B-cell lymphoma is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), mantle cell lymphoma (MCL), non-germinal center B-cell diffuse large B-cell lymphoma (non-GCB DLBCL), germinal center B-cell diffuse large B-cell lymphoma (GCB DLBCL) or DLBCL with undetermined subtype, follicular lymphoma (FL) or transformed FL, marginal zone lymphoma (MZL), Hairy cell leukemia (HCL), Richter's transformation, primary central nervous system lymphoma (PCNSL), secondary central nervous system lymphoma (SCNSL) of breast or testicular origin, transformed lymphoma, or a combination of two or more thereof.

6. The method of Claim 4, wherein the B-cell lymphoma is CLL, SLL, MCL, non-GCB DLBCL, GCB DLBCL, FL, transformed FL, MZL, HCL, or Richter's transformation.

7. The method of Claim 1, wherein the BTK inhibitor is (S)-7-(1-acryloylpiperidin-4-yl)-2-(4-phenoxyphenyl)-4,5,6,7-tetra-hydropyrazolo[1,5-a]pyrimidine-3-carboxamide, or a pharmaceutically acceptable salt thereof.

8. The method of Claim 7, wherein the BTK inhibitor is administrated at a dose of 320 mg QD or 160 mg BID.

9. The method of Claim 8, wherein the BTK inhibitor is administrated with or without food.

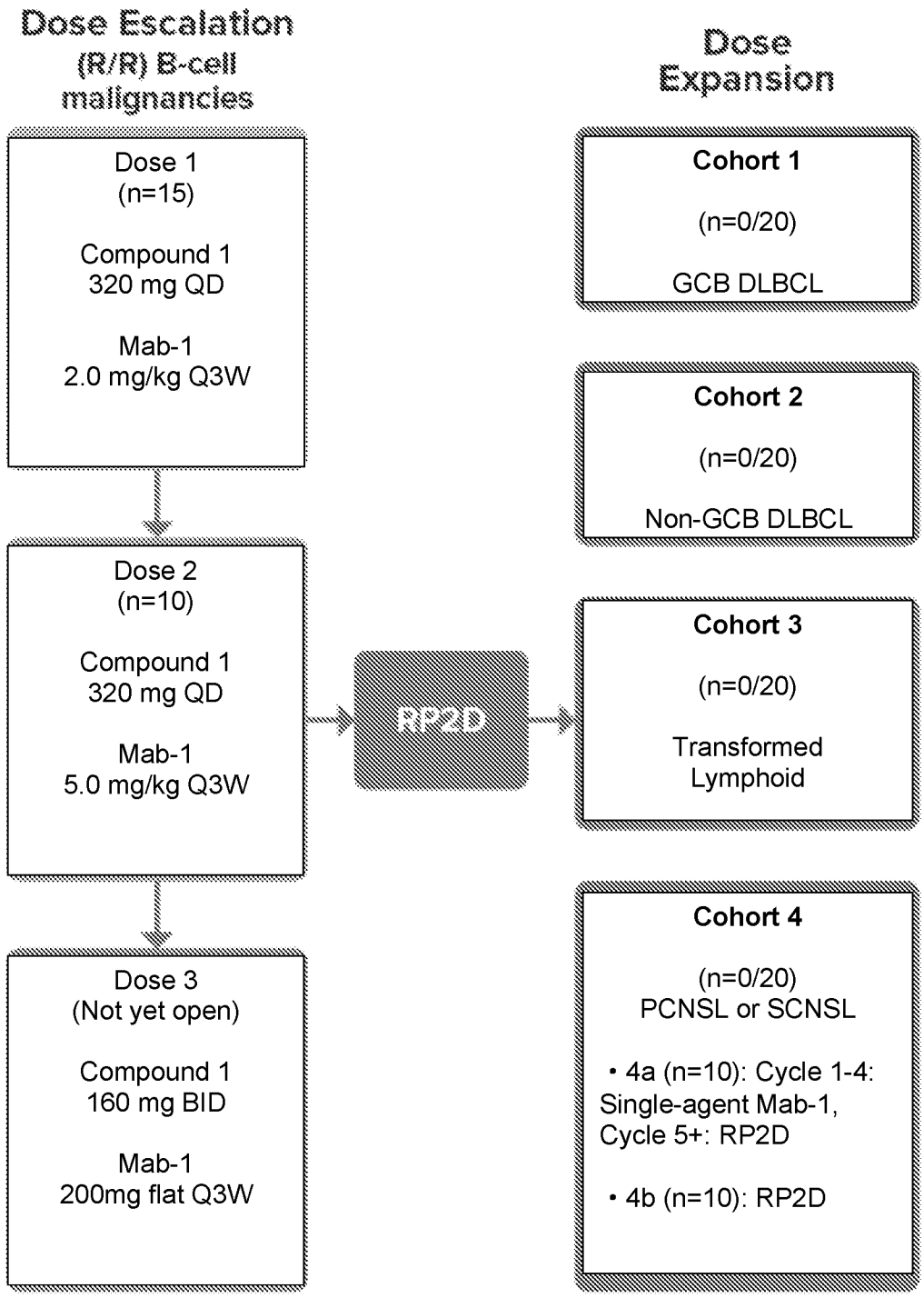
10. The method of Claim 3, wherein the anti-PD-1 antibody is administrated at a dose of 2 mg/kg Q3W to 200 mg/kg Q3W.

11. The method of Claim 10, wherein the anti-PD-1 antibody is administrated at a dose of 2 mg/kg Q3W, 5 mg/kg Q3W, or 200 mg flat Q3W.

12. The method of Claim 11, wherein the anti-PD-1 antibody is administered at a dose of 200 mg flat dose every 21 days

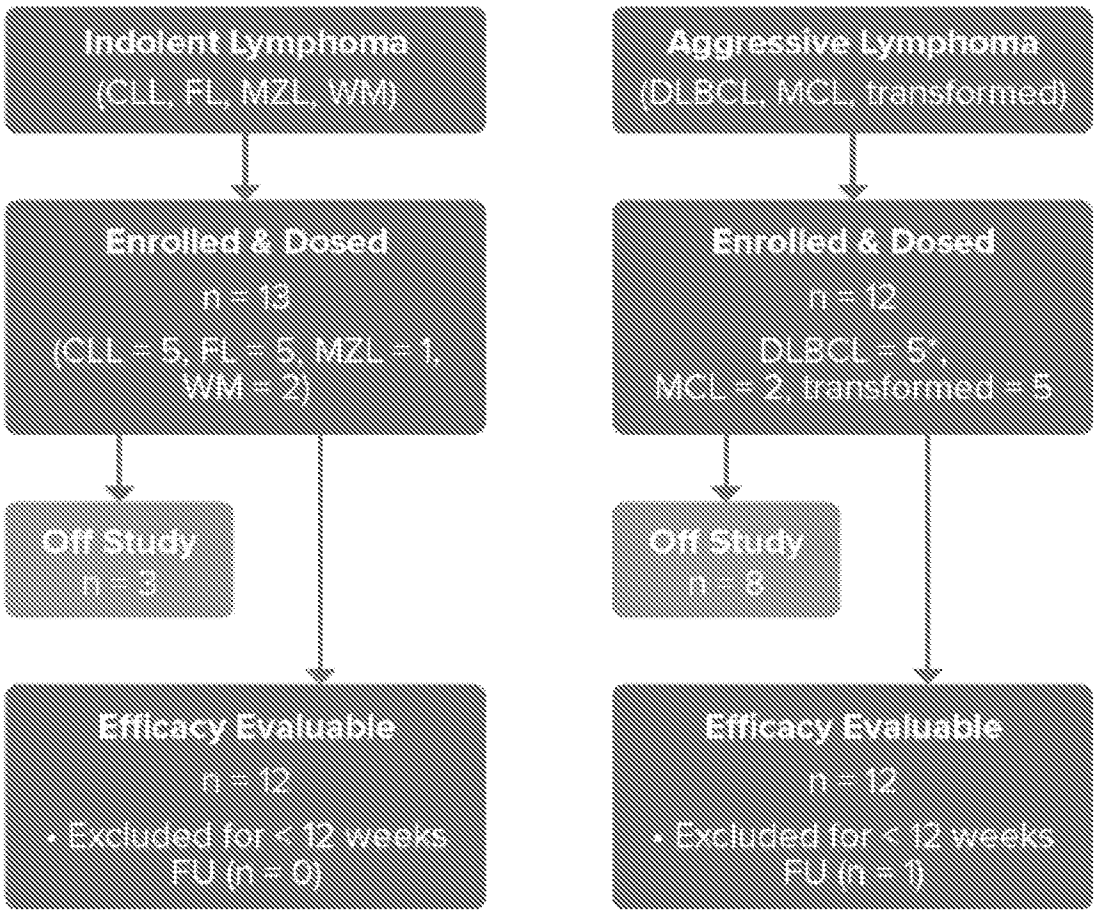
13. The method of Claim 3, wherein the anti-PD-1 antibody is administered intravenously.

14. The method of Claim 3, wherein the BTK inhibitor is administered at least 30 minutes before the anti-PD-1 antibody if administered on the same day.



BID, twice daily; GCB DLBCL, germinal center B-cell diffuse B-cell lymphoma; PCNSL, primary central nervous system lymphoma; Q3W, every 3 weeks; QD, once daily; RP2D, recommended Phase 2 dose; SCNSL, secondary central nervous system lymphoma.

FIG. 1



CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FU, follow-up; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrøm's macroblobulinemia.
*3 non-GBC; 2 GBC.

FIG. 2

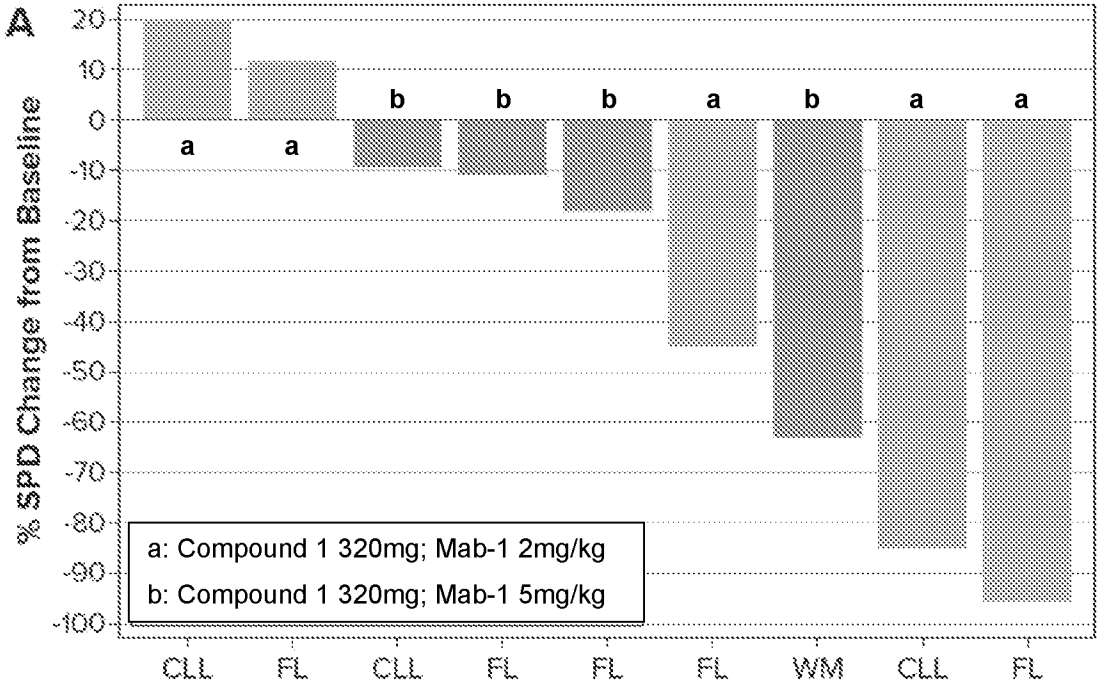


Figure 3A

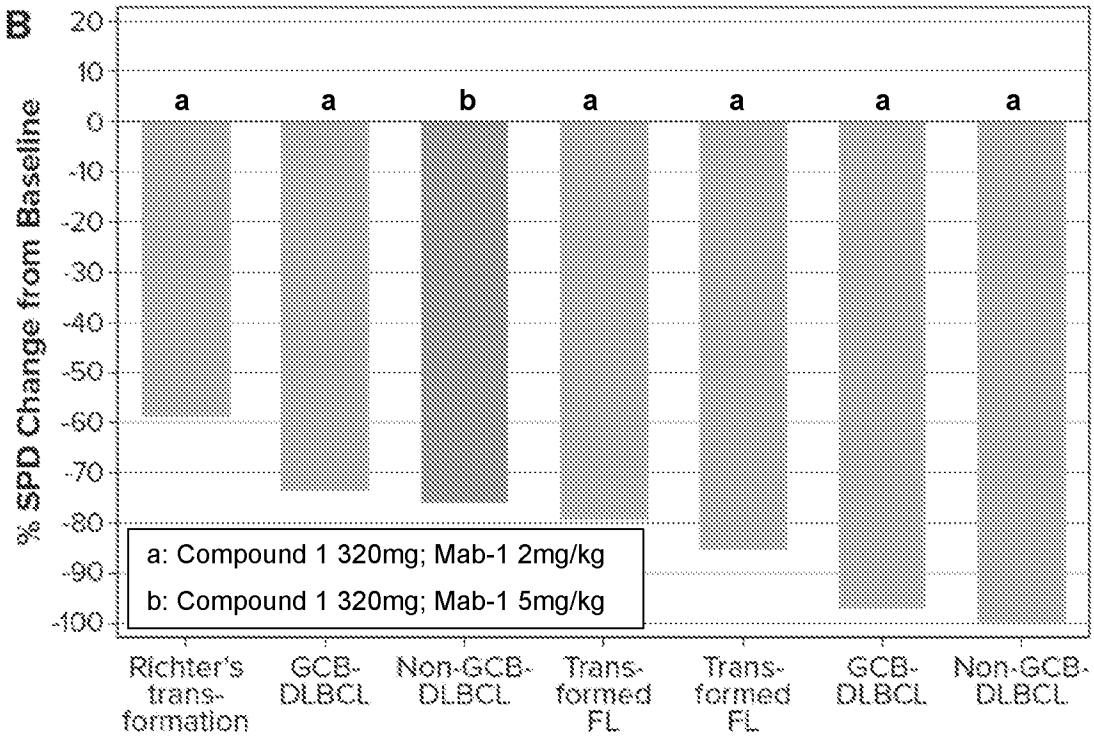


Figure 3B

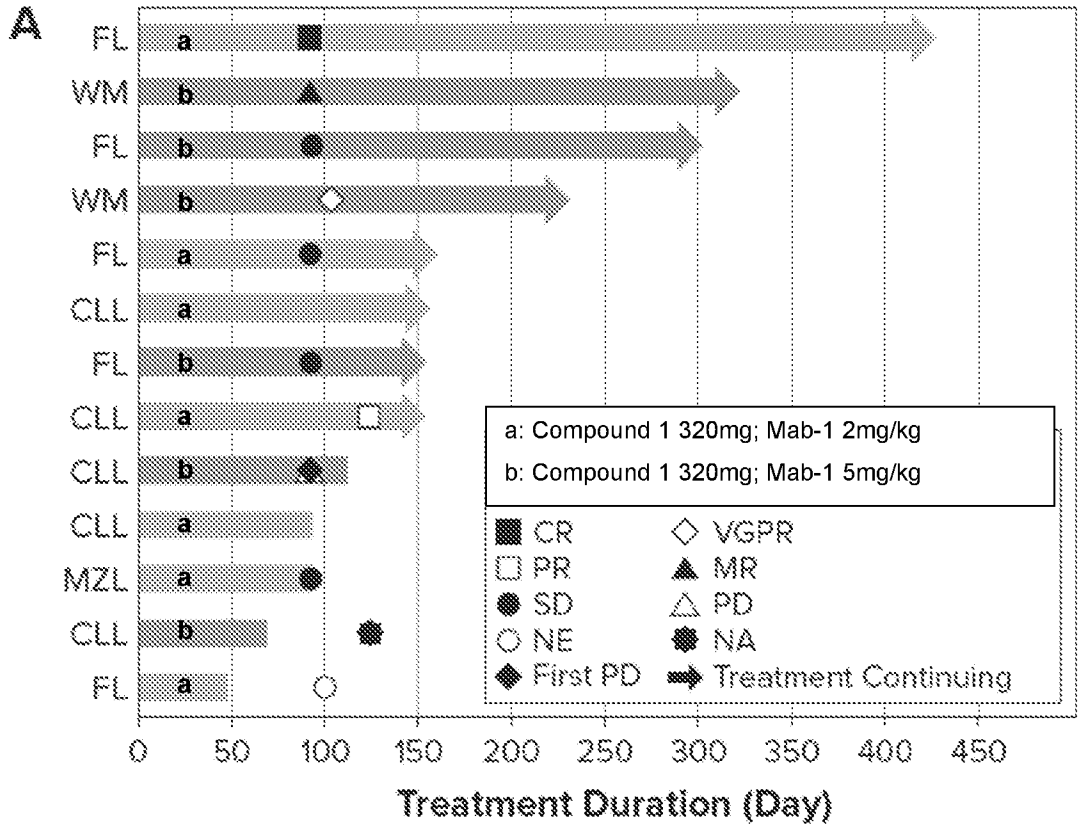

A
FL
WM
FL
WM
FL
CLL
FL
CLL
CLL
CLL
MZL
CLL
FL
a
b
a: Compound 1 320mg; Mab-1 2mg/kg
b: Compound 1 320mg; Mab-1 5mg/kg
CR
PR
SD
NE
First PD
VGPR
MR
PD
NA
Treatment Continuing
0 50 100 150 200 250 300 350 400 450
Treatment Duration (Day)

FIG. 4A

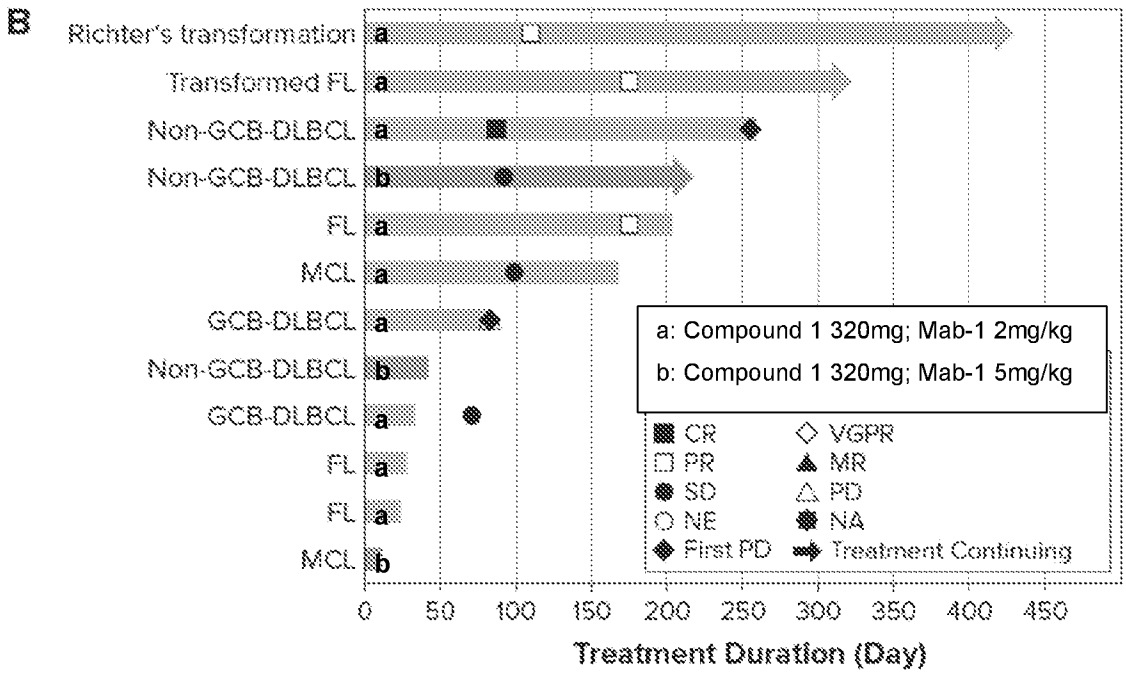

B
Richter's transformation
Transformed FL
Non-GCB-DLBCL
Non-GCB-DLBCL
FL
MCL
GCB-DLBCL
Non-GCB-DLBCL
GCB-DLBCL
FL
FL
MCL
a
b
a: Compound 1 320mg; Mab-1 2mg/kg
b: Compound 1 320mg; Mab-1 5mg/kg
CR
PR
SD
NE
First PD
VGPR
MR
PD
NA
Treatment Continuing
0 50 100 150 200 250 300 350 400 450
Treatment Duration (Day)

FIG. 4B

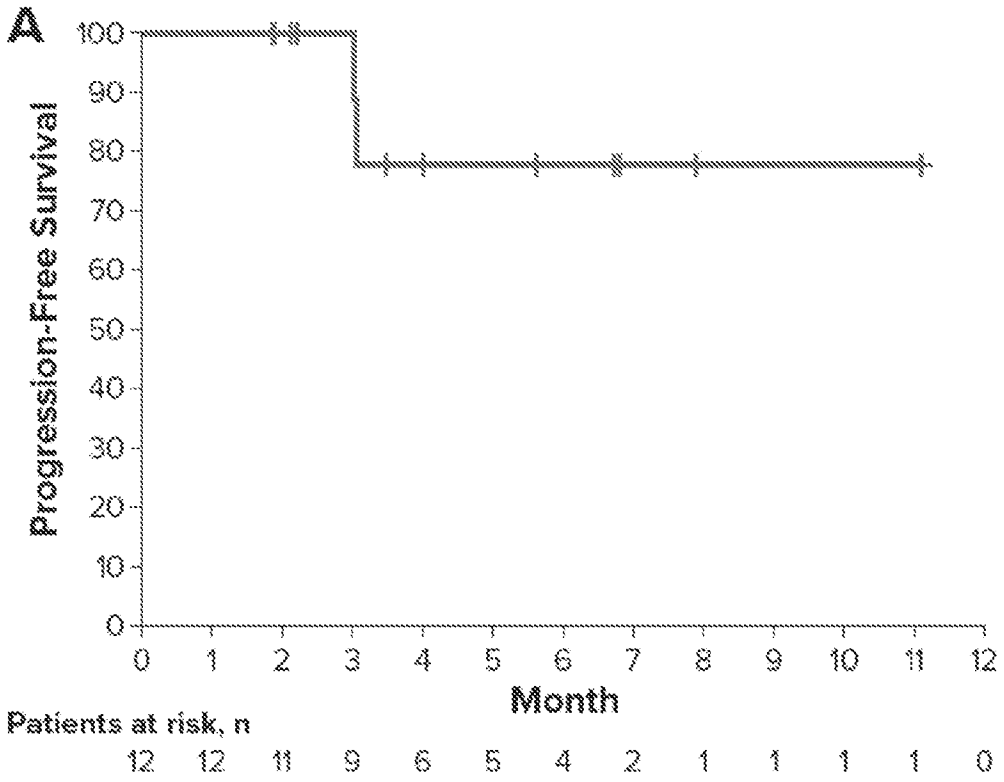

A
Progression-Free Survival
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Month
Patients at risk, n
12 12 11 9 6 5 4 2 1 1 1 1 0

FIG. 5A

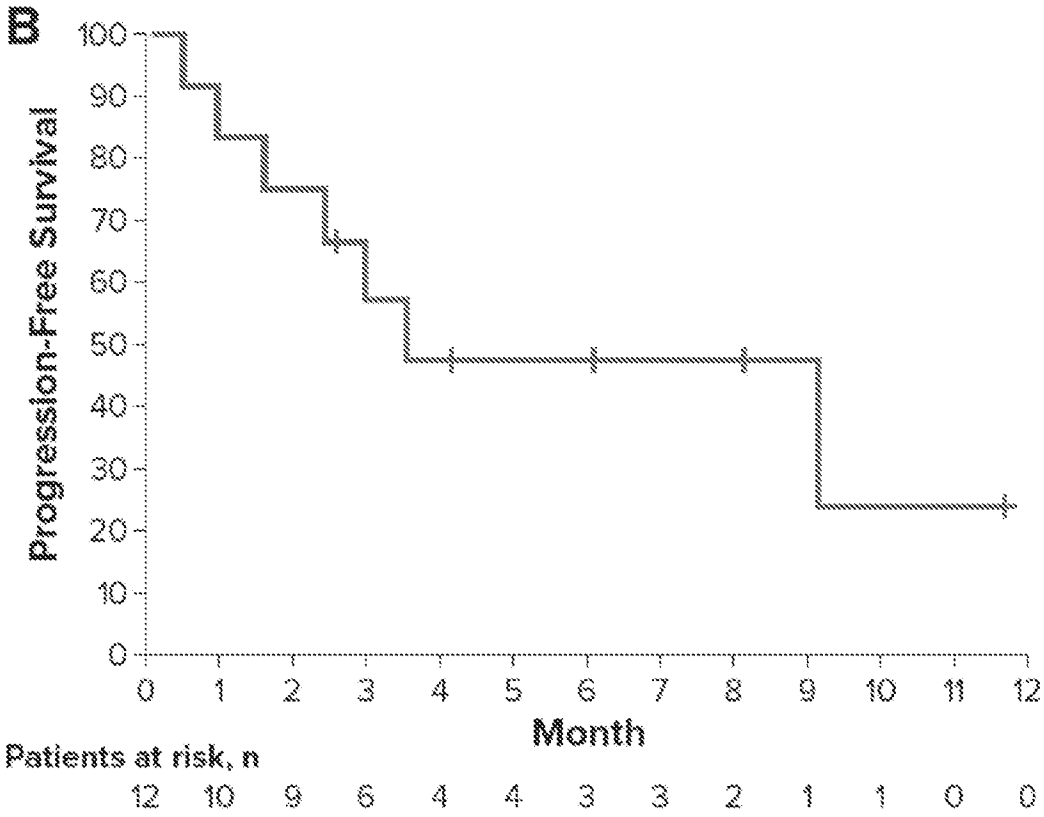

B
Progression-Free Survival
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Month
Patients at risk, n
12 10 9 6 4 4 3 3 2 1 1 0 0

FIG. 5B

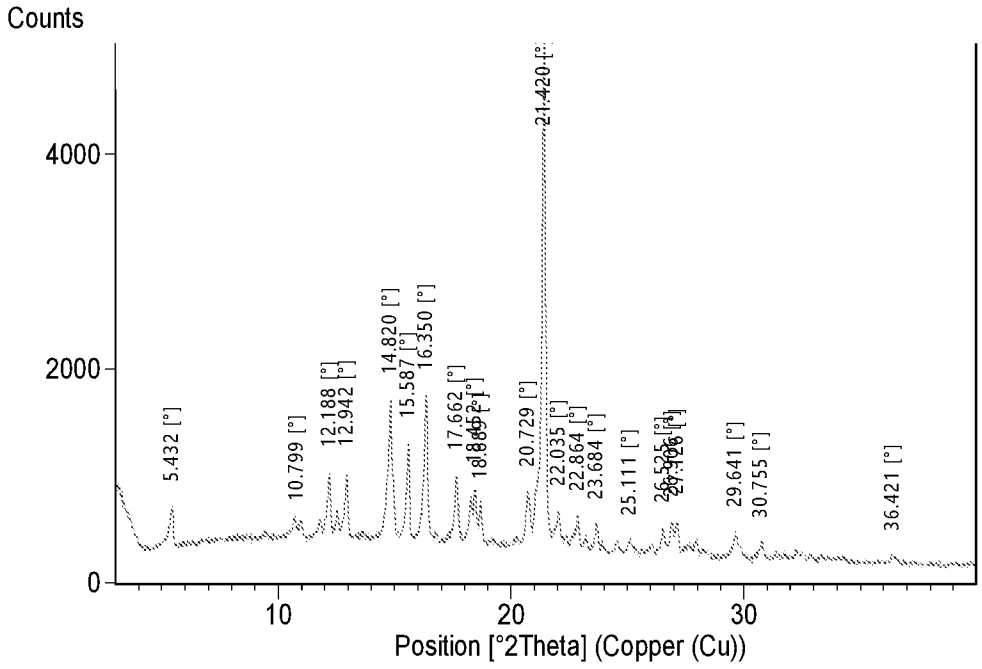

Counts
4000
2000
0
10
20
30
Position [°2Theta] (Copper (Cu))
5.432 [°]
10.799 [°]
12.188 [°]
12.942 [°]
14.820 [°]
15.587 [°]
16.350 [°]
17.662 [°]
20.729 [°]
21.420 [°]
22.035 [°]
22.864 [°]
23.684 [°]
25.111 [°]
29.641 [°]
30.755 [°]
36.421 [°]

FIG. 6

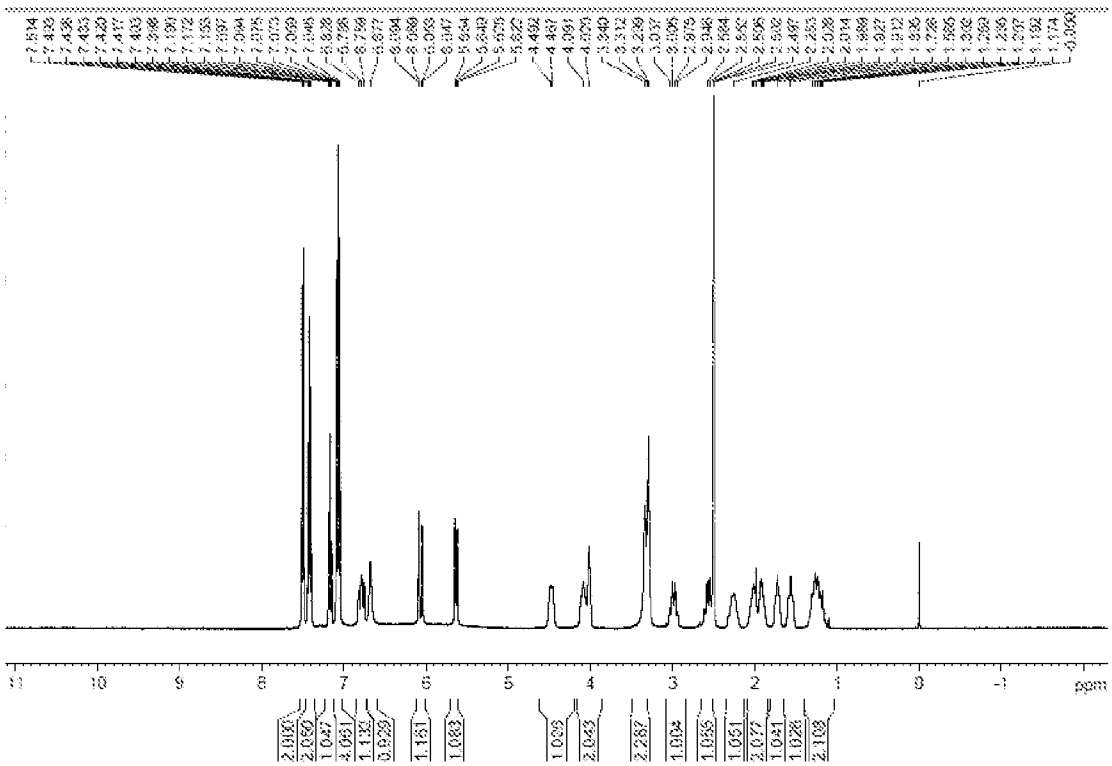

ppm

FIG. 7

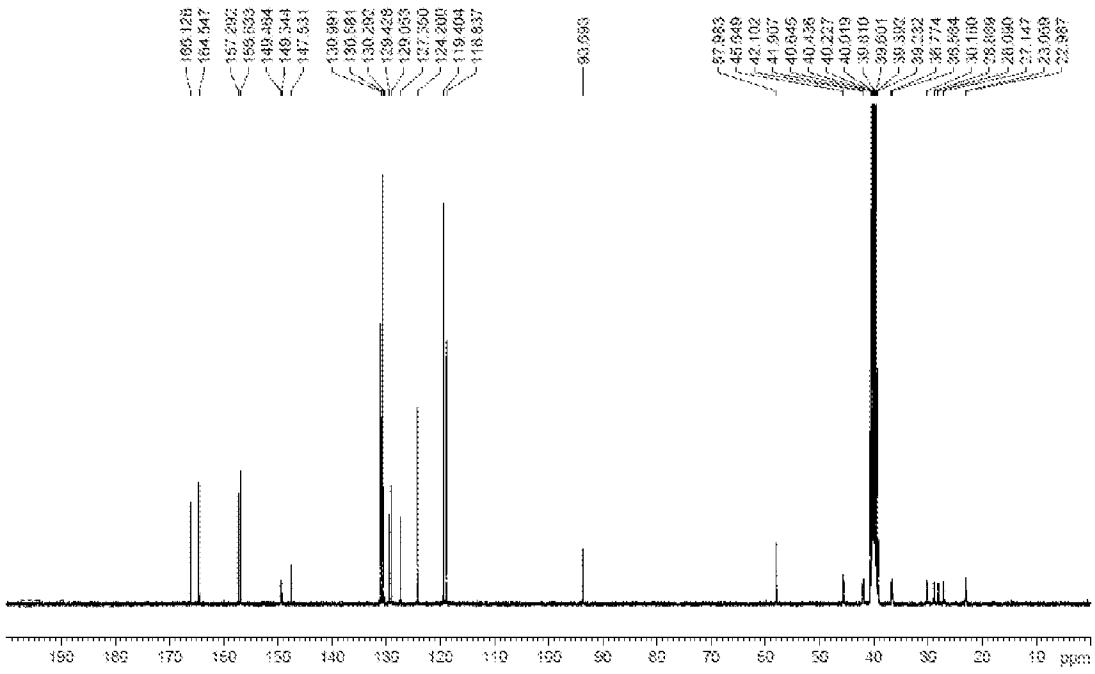

166.128
164.547
157.293
156.533
149.494
149.344
147.531
130.991
130.581
130.286
129.428
129.053
127.350
124.200
119.404
118.837
93.693
87.983
45.649
42.102
41.907
40.645
40.438
40.227
40.019
39.810
39.601
39.392
39.182
38.774
38.564
30.160
28.809
28.090
27.147
23.059
22.987
ppm

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/63068

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 487/20, A61K 31/435, A61K 31/519, C07D 471/20, C07K 16/28 (2019.01)
CPC - C07D 487/04, A61K 31/4188, A61K 31/435, A61K 31/519, A61K 31/55, A61K 31/551, C07D 471/14, C07K 16/2803

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2017/059224 A2 (GILEAD SCIENCE, INC.) 06 April 2017 (06.04.2017) para [0013], [0027], [0029], [0043], [0046], [0049]	1-14
Y	US 2015/0259354 A1 (BEIGENE, LTD.) 17 September 2015 (17.09.2015) abstract, para [0306]	1-14
Y	US 2015/0079109 A1 (BEIGENE, LTD.) 19 March 2015 (19.03.2015) abstract, para [0016], [0020], SEQ ID NOs: 24, 26, 88	3, 10-14
A	WO 2017/046746 A1 (ACERTA PHARMA B.V.) 23 March 2017 (23.03.2017) para [0013], [00175], [001213], [001318]	1

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2019	27 FEB 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/63068

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments: