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Title: BTK INHIBITOR COMBINATIONS FOR TREATING MULTIPLE MYELOMA

Abstract: Disclosed herein are pharmaceutical combinations, dosing regimen, and methods of administering a combination of a BTK inhibitor (e.g., ibrutinib), an immunomodulatory agent, and a steroid for the treatment of a hematologic malignancy.
BTK INHIBITOR COMBINATIONS FOR TREATING MULTIPLE MYELOMA

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/212,518, filed August 31, 2015, which is incorporated herein by reference in its entirety.

BACKGROUND

[0001] Bruton's tyrosine kinase (Btk), a member of the Tec family of non-receptor tyrosine kinases, is a key signaling enzyme expressed in all hematopoietic cells types except T lymphocytes and natural killer cells. Btk plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[0002] 1-((R)-3-[(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-l-one is also known by its IUPAC name as 1-((3R)-3-[(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-i]pyrimidin-1-yl)piperidin-1-yl]prop-2-en-1-one or 2-Propen-1-one, 1-[(3R)-3-[(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-i]pyrimidin-1-yl]-1-piped dinyl-, and has been given the USAN name, ibrutinib. The various names given for ibrutinib are used interchangeably herein. Ibrutinib is an inhibitor of Btk.

SUMMARY

[0003] Disclosed herein are pharmaceutical combinations, dosing regimens, and methods that comprise a combination of a TEC inhibitor, an immunomodulatory agent, and a steroid for the treatment of a hematologic malignancy. Also described herein are methods of administrating a combination of a TEC inhibitor, an immunomodulatory agent, and a steroid for treatment of multiple myeloma. In some instances, the TEC inhibitor is a BTK, ITK, TEC, RLK, or BMX inhibitor. In some instances, the BTK inhibitor is ibrutinib. In some instances, the immunomodulatory agent is pomalidomide. In some instances the steroid is dexamethasone.

[0004] In some embodiments, provided herein is a pharmaceutical combination that comprises a TEC inhibitor, an immunomodulatory agent, and a steroid. In some instances, the TEC inhibitor is a BTK, ITK, TEC, RLK, or BMX inhibitor. In some instances, the TEC inhibitor is an ITK inhibitor. In some instances, the TEC inhibitor is a BTK inhibitor. In some instances, the BTK inhibitor is ibrutinib. In some instances, the immunomodulatory agent is pomalidomide. In some instances, the steroid is dexamethasone. In some instances, the pharmaceutical combination is
administered for the treatment of a hematologic malignancy. In some instances, the hematologic malignancy is multiple myeloma.

[0005] In some instances, provided herein is a dosing regimen for the treatment of a hematologic malignancy in a subject in need thereof comprising administering an immunomodulatory agent, a BTK inhibitor, and a steroid, wherein the immunomodulatory agent, the Btk inhibitor, and the steroid are administered concurrently, simultaneously, and/or co-administered.

[0006] In some instances, provided herein is a dosing regimen for the treatment of a hematologic malignancy in a subject in need thereof comprising administering pomalidomide, ibrutinib, and dexamethasone, wherein pomalidomide, ibrutinib, and dexamethasone are administered concurrently, simultaneously, and/or co-administered.

[0007] In some aspects, provided herein is a method of treating a hematologic malignancy in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination comprising an immunomodulatory agent, a BTK inhibitor, and a steroid, wherein an immunomodulatory agent, a BTK inhibitor, and a steroid are administered concurrently.

[0008] In some aspects, provided herein is a method of treating a hematologic malignancy in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a combination comprising pomalidomide, ibrutinib, and dexamethasone following a dosing regimen wherein the dosing regimen comprises administering pomalidomide, ibrutinib, and dexamethasone concurrently.

DETAILED DESCRIPTION

Certain Terminology

[0009] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which the claimed subject matter belongs. It is to be understood that the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of any subject matter claimed. In this application, the use of the singular includes the plural unless specifically stated otherwise. It must be noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. In this application, the use of "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "include", "includes," and "included," is not limiting.
As used herein, ranges and amounts can be expressed as "about" a particular value or range. About also includes the exact amount. Hence "about 5 µL" means "about 5 µL" and also "5 µL." Generally, the term "about" includes an amount that would be expected to be within experimental error. The term "about" when used before a numerical value indicates that the value may vary within a reasonable range, such as within ±10%, ±5% or ±1% of the stated value.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

As used herein, the terms "individual(s)", "subject(s)" and "patient(s)" mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g., constant or intermittent) of a health care worker (e.g., a doctor, a registered nurse, a nurse practitioner, a physician's assistant, an orderly or a hospice worker).

The terms "co-administration," "simultaneous administration," "concurrently," or the like, and any grammatical version thereof, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time; however, all agents (i.e., all three agents) are administered during the same cycle (even though the administration of the agents is begun, initiated, or occurs on different days of that cycle). In some embodiments, "co-administration," "simultaneously," and concurrently are interchangeable. In some embodiments, the patients have not been administered Btk inhibitor, such as ibrutinib, prior to initiation of the dosing regimen disclosed herein.

The terms "effective amount" or "therapeutically effective amount," as used herein, refer to a sufficient amount of an agent or a compound, or a combination or two or more agents or compounds, or a sufficient amount of an individual agent or compound in a combination of two or more agents or compounds, being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an "effective amount" for therapeutic uses is the amount of the composition including a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms without undue adverse side effects. An appropriate "effective amount" in any individual case may be determined using techniques, such as a dose escalation study. An "effective amount" of a compound disclosed herein is an amount effective to achieve a desired pharmacologic effect or therapeutic improvement without undue adverse side effects. It is
understood that "an effect amount" or "a therapeutically effective amount" can vary from subject to subject, due to variation in metabolism of ibritinib, age, weight, general condition of the subject, the condition being treated, the severity of the condition being treated, and the judgment of the prescribing physician. By way of example only, therapeutically effective amounts may be determined by routine experimentation, including but not limited to a dose escalation clinical trial.

[0015] The terms "enhance" or "enhancing" means to increase or prolong either in potency or duration a desired effect. By way of example, "enhancing" the effect of therapeutic agents refers to the ability to increase or prolong, either in potency or duration, the effect of therapeutic agents on during treatment of a disease, disorder or condition. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of a therapeutic agent in the treatment of a disease, disorder or condition. When used in a patient, amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician.

[0016] "Antibodies" and "immunoglobulins" (Igs) are glycoproteins having the same structural characteristics. The terms are used synonymously. In some instances the antigen specificity of the immunoglobulin may be known.

[0017] The term "antibody" is used in the broadest sense and covers fully assembled antibodies, antibody fragments that can bind antigen (e.g., Fab, F(ab')2, Fv, single chain antibodies, diabodies, antibody chimeras, hybrid antibodies, bispecific antibodies, humanized antibodies, and the like), and recombinant peptides comprising the forgoing.

[0018] The terms "monoclonal antibody" and "mAb" as used herein refer to an antibody obtained from a substantially homogeneous population of antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts.

[0019] "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen-binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab, F(ab')2, and Fv fragments; diabodies; linear antibodies (Zapata et al. (1995) Protein Eng. 10:1057-1062); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments. Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, each with a single antigen-binding site, and a residual "Fc" fragment, whose name reflects its ability to crystallize readily. Pepsin treatment yields an F(ab')2 fragment that has two antigen-combining sites and is still capable of cross-linking antigen.
"Fv" is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy- and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding site on the surface of the $V_H \cdot V_L$ dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (C$_{H1}$) of the heavy chain. Fab fragments differ from Fab' fragments by the addition of a few residues at the carboxy terminus of the heavy chain C$_{H1}$ domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. Fab' fragments are produced by reducing the F(ab')2 fragment's heavy chain disulfide bridge. Other chemical couplings of antibody fragments are also known.

The "light chains" of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of human immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgGl, IgG2, IgG3, IgG4, IgAl, and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known. Different isotypes have different effector functions. For example, human IgGl and IgG3 isotypes have ADCC (antibody dependent cell-mediated cytotoxicity) activity.

The suffix "ene" appended to a group indicates that such a group is a diradical. By way of example only, a methylene is a diradical of a methyl group, that is, it is a -CH$_2$- group; and an ethylene is a diradical of an ethyl group, i.e., -CH$_2$CH$_2$-.

As used herein, Ci-C$_x$ includes Ci-C$_2$, C$_1$C$_3$ ... Ci-C$_x$, i.e., one to two carbon atoms, one to three carbon atoms... one to $x$ carbon atoms.

An "alkyl" group refers to a saturated, branched or straight chain hydrocarbon group. The "alkyl" moiety optionally has 1 to 10 carbon atoms (whenever it appears herein, a numerical
range such as "1 to 10" refers to each integer in the given range; e.g., "1 to 10 carbon atoms" means that the alkyl group is selected from a moiety having 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group of the compounds described herein may be designated as "C₁-C₄ alkyl" or similar designations. By way of example only, "C₁-C₄ alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, and t-butyl. Thus C₁-C₄ alkyl includes C₁-C₂ alkyl and C₁-C₃ alkyl.

Alkyl groups are optionally substituted or unsubstituted. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, ethenyl, propenyl, butenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

"Lower alkyl" having 1 to 6 carbon atoms.

[0027] The term "alkenyl" refers to a hydrocarbon group containing at least one double bond formed by two carbon atoms that is not part of an aromatic group. An example of an alkenyl group is -C(R)=C(R)-R, wherein R refers to the remaining portions of the alkenyl group, which are either the same or different. The alkenyl moiety is optionally branched, straight chain, or cyclic (in which case, it is also known as a "cycloalkenyl" group). Depending on the structure, an alkenyl group includes a monoradical or a diradical (i.e., an alkenylene group). Alkenyl groups are optionally substituted. Non-limiting examples of an alkenyl group include -CH=CH₂, -C(CH₃)=CH₂, -CH=CHCH₃, -C(CH₃)=CHCH₃. Alkenylene groups include, but are not limited to, -CH=CH-, -C(CH₃)=CH-, -CH=CHCH₂-, -CH=CHCH₂CH₂- and -C(CH₃)=CHCH₂-. Alkenyl groups optionally have 2 to 10 carbons, and if a "lower alkenyl" having 2 to 6 carbon atoms.

[0028] The term "alkynyl" refers to a branched or straight chain hydrocarbon group containing at least one triple bond formed by two carbon atoms. An example of an alkynyl group is -C≡C-R, wherein R refers to the remaining portions of the alkynyl group, which is either the same or different. The "R" portion of the alkynyl moiety may be branched, straight chain, or cyclic. Depending on the structure, an alkynyl group includes a monoradical or a diradical (i.e., an alkyne group). Alkynyl groups are optionally substituted. Non-limiting examples of an alkynyl group include, but are not limited to, -C≡CH, -C≡CCH₃, -C≡CCH₂CH₃, -C≡C-, and -C≡CCH₂-. Alkynyl groups optionally have 2 to 10 carbons, and if a "lower alkynyl" having 2 to 6 carbon atoms.

[0029] An "alkoxy" group refers to an (alkyl)O- group, where alkyl is as defined herein.
[0030] An "amide" is a chemical moiety with the formula -C(\(\text{O}\))HNR or -NH-C(\(\text{O}\))R, where R is selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). In some embodiments, an amide moiety forms a linkage between an amino acid or a peptide molecule and a compound described herein, thereby forming a prodrug. Any amine, or carboxyl side chain on the compounds described herein can be amidified. The procedures and specific groups to make such amides are found in sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference for this disclosure.

[0031] The term "ester" refers to a chemical moiety with formula -COOR, where R is selected from alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). Any hydroxy, or carboxyl side chain on the compounds described herein can be esterified. The procedures and specific groups to make such esters are found in sources such as Greene and Wuts, Protective Groups in Organic Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated herein by reference for this disclosure.

[0032] As used herein, the term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (e.g., aryls and cycloalkyls), heterocycles (e.g., heteroaryls and non-aromatic heterocycles), aromatics (e.g., aryls and heteroaryls), and non-aromatics (e.g., cycloalkyls and non-aromatic heterocycles). Rings can be optionally substituted. Rings can be monocyclic or polycyclic.

[0033] As used herein, the term "ring system" refers to one, or more than one ring.

[0034] The term "membered ring" can embrace any cyclic structure. The term "membered" is meant to denote the number of skeletal atoms that constitute the ring. Thus, for example, cyclohexyl, pyridine, pyran and thiopyran are 6-membered rings and cyclopentyl, pyrrole, furan, and thiophene are 5-membered rings.

[0035] The term "fused" refers to structures in which two or more rings share one or more bonds.

[0036] The term "aromatic" refers to a planar ring having a delocalized \(\pi\)-electron system containing 4n+2 \(\pi\) electrons, where n is an integer. Aromatic rings can be formed from five, six, seven, eight, nine, or more than nine atoms. Aromatics can be optionally substituted. The term "aromatic" includes both carbocyclic aryl (e.g., phenyl) and heterocyclic aryl (or "heteroaryl" or "heteroaromatic") groups (e.g., pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups.
As used herein, the term "aryl" refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. Aryl rings can be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups can be optionally substituted. Examples of aryl groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, fluorenyl, and indenyl. Depending on the structure, an aryl group can be a monoradical or a diradical (i.e., an arylene group).

The term "cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and is optionally saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms. Illustrative examples of cycloalkyl groups include the following moieties:

![Cyclic structures](image)

Depending on the structure, a cycloalkyl group is either a monoradical or a diradical (e.g., a cycloalkylene group), and if a "lower cycloalkyl" having 3 to 8 carbon atoms.

The term "heterocycle" refers to heteroaromatic and heteroalicyclic groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocyclic group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Herein, whenever the number of carbon atoms in a heterocycle is indicated (e.g., C-C heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as "C-C heterocycle" refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. It is understood that the heterocyclic ring can have additional heteroatoms in the ring. Designations such as "4-6-membered heterocycle" refer to the total number of atoms that are contained in the ring (i.e., a four, five, or six membered ring, in which at least one atom is a carbon atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). In heterocycles that have two or more heteroatoms, those two or more heteroatoms can be the same...
or different from one another. Heterocycles can be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. Non-aromatic heterocyclic groups include groups having only 4 atoms in their ring system, but aromatic heterocyclic groups must have at least 5 atoms in their ring system. The heterocyclic groups include benzo-fused ring systems. An example of a 4-membered heterocyclic group is azetidinyl (derived from azetidine). An example of a 5-membered heterocyclic group is thiazolyl. An example of a 6-membered heterocyclic group is pyridyl, and an example of a 10-membered heterocyclic group is quinolinyl. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiienyl, tetrahydropyrananyl, dihydropyrananyl, tetrahydrothiopyrananyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidinyl, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrrolinyl, 3-pyrrolinyl, indoliny1, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolananyl, pyrazolinyl, dithianyl, dithiolany1, dihydropryananyl, dihydrothienyl, dihydrofurananyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolinizynyl. Examples of aromatic heterocyclic (heteroaryl) groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furanyl, thiény1, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofurany1, cinnolinyl, indazolyl, indoliziny1, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazo1yl, thiazolyl, furazany1, benzofurazany1, benzothiophenyl, benzothiazolyl, benzoazoxaryl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups, as derived from the groups listed above, are optionally C-attached or N-attached where such is possible. For instance, a group derived from pyrrole includes pyrrol-1-y1 (N-attached) or pyrrol-3-y1 (C-attached). Further, a group derived from imidazole includes imidazol-1-y1 or imidazol-3-y1 (both N-attached) or imidazol-2-y1, imidazol-4-y1 or imidazol-5-y1 (all C-attached). The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. Depending on the structure, a heterocycle group can be a monoradical or a diradical (i.e., a heterocyclene group).

[0040] The terms "heteroaryl" or, alternatively, "heteroaromatic" refers to an aromatic group that includes one or more, such as one to four, ring heteroatoms selected from nitrogen, oxygen and sulfur. Heteroaryl rings can be formed by five, six, seven, eight, nine, or more than nine, e.g., up to fourteen, ring atoms. An N-containing "heteroaromatic" or "heteroaryl" moiety refers to an
aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. 

Illustrative examples of heteroaryl groups include the following moieties:

and the like. Depending on the structure, a heteroaryl group can be a monoradical or a diradical (i.e., a heteroaryl ene group).

[0041] As used herein, the term "non-aromatic heterocycle", "heterocycloalkyl" or "heteroalicyclic" refers to a non-aromatic ring wherein one or more, such as one to four, atoms forming the ring are a heteroatom. A "non-aromatic heterocycle" or "heterocycloalkyl" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, the radicals are fused with an aryl or heteroaryl. Heterocycloalkyl rings can be formed by three, four, five, six, seven, eight, nine, or more than nine, e.g., up to fourteen, ring atoms. Heterocycloalkyl rings can be optionally substituted. In certain embodiments, non-aromatic heterocycles contain one or more carbonyl (=O) or thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of heterocycloalkyls include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane. Illustrative examples of heterocycloalkyl groups, also referred to as non-aromatic heterocycles, include:
The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. Depending on the structure, a heterocycloalkyl group can be a monoradical or a diradical (i.e., a heterocycloalkylene group).

[0042] The term "halo" or, alternatively, "halogen" or "halide" means fluoro, chloro, bromo and iodo.

[0043] The term "haloalkyl," refers to alkyl structures in which at least one hydrogen is replaced with a halogen atom. In certain embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are all the same as one another. In other embodiments in which two or more hydrogen atoms are replaced with halogen atoms, the halogen atoms are not all the same as one another.

[0044] The term "fluoroalkyl," as used herein, refers to alkyl group in which at least one hydrogen is replaced with a fluorine atom. Examples of fluoroalkyl groups include, but are not limited to, -CF₃, -CH₂CF₃, -CF₂CF₃, -CH₂CH₂CF₃ and the like.

[0045] As used herein, the term "heteroalkyl" refers to optionally substituted alkyl radicals in which one or more, such as one to three or one to two, skeletal chain atoms is a heteroatom, e.g., oxygen, nitrogen, sulfur, silicon, phosphorus or combinations thereof. The heteroatom(s) are placed at any interior position of the heteroalkyl group or at the position at which the heteroalkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, -CH₂-O-CH₃, -CH₂-CH₂-O-CH₃, -CH₂-NH-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-N(CH₃)₂-CH₃, -CH₂-CH₂-NH-CH₃, -CH₂-CH₂-N(CH₃)₂-CH₃, -CH₂-S-CH₂-CH₃, -CH₂-CH₂-S(0)-CH₃, -CH₂-CH₂-S(0)₂-CH₃, -CH=CH-0-CH₃, -Si(CH₃)₂-CH₂-Si(CH₃)₂-CH₃, and -CH=CH-N(N(CH₃))₂-CH₃. In addition, in some embodiments, up to two heteroatoms are consecutive, such as, by way of example, -CH₂-NH-OCH₃ and -CH₂-O-Si(CH₃)₂.

[0046] The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, silicon and phosphorus, but are not limited to these atoms. In embodiments in which two or more heteroatoms are present, the
two or more heteroatoms can all be the same as one another, or some or all of the two or more heteroatoms can each be different from the others.

[0047] The term "bond" or "single bond" refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure.

[0048] The term "moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0049] The term "optionally substituted" or "substituted" means that the referenced group may be substituted with one or more additional group(s), by way of example, individually and independently selected from cyano, halo, acyl, nitro, haloalkyl, fluoroalkyl, amino, including mono- and di-substituted amino groups, and the protected derivatives thereof, or L^4R^5, wherein each L^4 is independently selected from a bond, -0-, -C(=0)-, -S-, -S(=0)-, -S(=0) 2-, -NH-, -NR^5-, -NHC(O)-, -C(0)NH-, -S(=0) 2-NH-, -NHS(=0) 2-, -OC(0)NH-, -NHC(O)0-, -(substituted or unsubstituted C_i-C_6 alkylene), or -(substituted or unsubstituted C_2-C_6 alkenylene); and each R^5 is independently selected from H, (substituted or unsubstituted C_i-C_4 alkyl), (substituted or unsubstituted C_2-C_4 cycloalkyl), (substituted or unsubstituted heterocycloalkyl), (substituted or unsubstituted aryl), (substituted or unsubstituted heteroaryl), or (substituted or unsubstituted heteroaryl). The protecting groups that form the protective derivatives of the above substituents include those found in sources such as Greene and Wuts, above.

Overview

[0050] In some embodiments, a pharmaceutical combination is provided. The pharmaceutical combination may comprise three active ingredients: a Btk inhibitor, an immunomodulatory agent (EVlid), and dexamethasone. In some embodiments, the pharmaceutical combination is in separate dosage forms. In some embodiments, the pharmaceutical combination is in three separate dosage forms, wherein each active ingredient is in a separate dosage form from the other active ingredients. In some embodiments, the pharmaceutical combination is in combined dosage forms. In some embodiments, the pharmaceutical combination is administered for the treatment of multiple myeloma. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the multiple myeloma is metastasized multiple myeloma. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the Btk inhibitor is ibrutinib.

[0051] In some embodiments, a dosing regimen for the treatment of multiple myeloma is provided. The dosing regimen may comprise administering to a subject a combination of three
active ingredients, which are a Btk inhibitor, an immunomodulatory agent, and dexamethasone. In some embodiments, the Btk inhibitor is ibrutinib. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the dosing regimen may comprise administering to the subject a combination comprising ibrutinib, pomalidomide, and dexamethasone. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are administered concurrently. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are co-administered. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are administered simultaneously. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are administered in cycles comprising, or consisting of, 28 days. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are administered simultaneously. In some embodiments, pomalidomide is administered on days 1-21 of each cycle. In some embodiments, dexamethasone is administered on days 1, 8, 15, and 22 of each cycle. In some embodiments, ibrutinib is administered on days 1-28 of each cycle. In some embodiments, pomalidomide is administered at a dosage of about 3 mg/day to about 5 mg/day. In some embodiments, pomalidomide is administered at a dosage of about 4 mg/day. In some embodiments, dexamethasone is administered at a dosage of about 20 mg/day to about 60 mg/day. In some embodiments, dexamethasone is administered at a dosage of about 40 mg/day. In some embodiments, ibrutinib is administered orally. In some embodiments, ibrutinib is administered once a day, two times per day, three times per day, four times per day, or five times per day. In some embodiments, ibrutinib is administered at a dosage of about 280 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 400 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 560 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 700 mg/day. In some embodiments, the dosing regimen comprises administration of an additional therapeutic agent. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the multiple myeloma is metastasized multiple myeloma. In some embodiments, the subject has received at least one prior therapy. In some embodiments, the subject has received at least two prior therapies. In some embodiments, the prior therapy comprises lenalidomide. In some embodiments, the prior therapy comprises bortezomib. In some embodiments, the prior therapy comprises carfilzomib. In some embodiments, the prior therapy comprises bortezomib.

[0052] In some embodiments, a method of treating a multiple myeloma in a subject in need thereof is provided. The method comprises administering to the subject a pharmaceutical
combination as described herein. In some embodiments, the pharmaceutical combination may comprise a Btk inhibitor, an immunomodulatory agent (IMiD), dexamethasone, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical combination is in separate dosage forms. In some embodiments, the pharmaceutical combination is in combined dosage forms. In some embodiments, the pharmaceutical combination is administered for the treatment of multiple myeloma. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the multiple myeloma is metastasized multiple myeloma. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the Btk inhibitor is ibrutinib.

[0053] In some embodiments, a method of treating a relapsed or refractory multiple myeloma is provided. The method comprises administering to the subject a pharmaceutical combination as described herein. In some embodiments, the pharmaceutical combination is in separate dosage forms. In some embodiments, the pharmaceutical combination is in combined dosage forms. In some embodiments, the pharmaceutical combination is administered for the treatment of multiple myeloma. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the multiple myeloma is metastasized multiple myeloma. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the Btk inhibitor is ibrutinib.

[0054] In some embodiments, a method of treating multiple myeloma in a subject in need thereof is provided. The method is based upon the dosing regimen as described herein. In some embodiments, The dosing regimen may comprise administering to a subject a combination comprising a Btk inhibitor, an immunomodulatory agent, and dexamethasone. In some embodiments, the Btk inhibitor is ibrutinib. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the dosing regimen may comprise administering to the subject a combination comprising ibrutinib, pomalidomide, and dexamethasone. In some embodiments, the ibrutinib, pomalidomide, and dexamethasone are administered in cycles comprising, or consisting of, 28 days. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are administered simultaneously. In some embodiments, pomalidomide is administered on days 1-21 of each cycle. In some embodiments, dexamethasone is administered on days 1, 8, 15, and 22 of each cycle. In some embodiments, ibrutinib is administered on days 1-28 of each cycle. In some embodiments, pomalidomide is administered at a dosage of about 3 mg/day to about 5 mg/day. In some embodiments, pomalidomide is administered at a dosage of about 4 mg/day. In some embodiments, dexamethasone is administered at a dosage of about
20 mg/day to about 60 mg/day. In some embodiments, dexamethasone is administered at a dosage of about 40 mg/day. In some embodiments, ibrutinib is administered orally. In some embodiments, ibrutinib is administered once a day, two times per day, three times per day, four times per day, or five times per day. In some embodiments, ibrutinib is administered at a dosage of about 280 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 400 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 560 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 700 mg/day. In some embodiments, the dosing regimen comprises administration of an additional therapeutic agent. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the multiple myeloma is metastasized multiple myeloma. In some embodiments, the subject has received at least one prior therapy. In some embodiments, the subject has received at least two prior therapies. In some embodiments, the prior therapy comprises lenalidomide. In some embodiments, the prior therapy comprises carfilzomib. In some embodiments, the prior therapy comprises bortezomib.

In some embodiments, a method of treating a relapsed or refractory multiple myeloma in a subject in need thereof is provided. The method is based upon the dosing regimen as described herein. In some embodiments, the dosing regimen may comprise administering to a subject a combination comprising a Btk inhibitor, an immunomodulatory agent, and dexamethasone. In some embodiments, the Btk inhibitor is ibrutinib. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the invention relates to the co-administration of a first amount of ibrutinib; a second amount of an immunomodulatory agent; and a third amount of dexamethasone, wherein the first amount, second amount, and third amount, taken together, are therapeutically effective. In some embodiments, the dosing regimen may comprise administering to the subject a combination comprising ibrutinib, pomalidomide, and dexamethasone. In some embodiments, the ibrutinib, pomalidomide, and dexamethasone are administered in cycles comprising, or consisting of, 28 days. In some embodiments, ibrutinib, pomalidomide, and dexamethasone are administered simultaneously. In some embodiments, pomalidomide is administered on days 1-21 of each cycle. In some embodiments, dexamethasone is administered on days 1, 8, 15, and 22 of each cycle. In some embodiments, ibrutinib is administered on days 1-28 of each cycle. In some embodiments, pomalidomide is administered at a dosage of about 3 mg/day to about 5 mg/day. In some embodiments, pomalidomide is administered at a dosage of about 4 mg/day. In some embodiments, dexamethasone is administered at a dosage of about
20 mg/day to about 60 mg/day. In some embodiments, dexamethasone is administered at a dosage of about 40 mg/day. In some embodiments, ibrutinib is administered orally. In some embodiments, ibrutinib is administered once a day, two times per day, three times per day, four times per day, or five times per day. In some embodiments, ibrutinib is administered at a dosage of about 280 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 400 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 560 mg/day to about 840 mg/day. In some embodiments, ibrutinib is administered at a dosage of about 700 mg/day. In some embodiments, the dosing regimen comprises administration of an additional therapeutic agent. In some embodiments, the multiple myeloma is relapsed or refractory multiple myeloma. In some embodiments, the multiple myeloma is metastasized multiple myeloma. In some embodiments, the subject has received at least one prior therapy. In some embodiments, the subject has received at least two prior therapies. In some embodiments, the prior therapy comprises lenalidomide. In some embodiments, the prior therapy comprises carfilzomib. In some embodiments, the prior therapy comprises bortezomib.

**Immunomodulatory Agents**

[0055] Immunomodulatory agents (or "immunomodulatory drugs" or IMiDs) are a class of drugs that constitute thalidomide and its analogues. Exemplary immunomodulatory agents include, but are not limited to, pomalidomide (e.g., CC-4047 or Pomalyst®), lenalidomide (i.e., Revlimid®), thalidomide (e.g., Thalomid®), and apremilast.

**Dosing regimen**

[0056] In some embodiments, the dosing regimen comprises administration of a TEC inhibitor, an immunomodulatory agent, and a steroid concurrently in at least one cycle. In some embodiments, the immunomodulatory agent is pomalidomide. In some embodiments, the steroid is dexamethasone. In some embodiments, the TEC inhibitor is an ITK inhibitor. In some embodiments, the TEC inhibitor is a BTK inhibitor. In some instances, the BTK inhibitor is ibrutinib. In some embodiments, the immunomodulatory agent is lenalidomide.

[0057] In some embodiments, each cycle comprises or consists of 28 days. In some embodiments, each cycle comprises or consists of less than 28 days or more than 28 days. For example, each cycle may comprise or consist of 14 days, 15 days, 16 days, 17 days, 18 days, 19 days, 20 days, 21 days, 22 days, 23 days, 24 days, 25 days, 26 days, or 27 days.

[0058] In some embodiments, the immunomodulatory agent is administered on day 1, day 2, day 3, day 4, day 5, day 6, day 7, day 8, day 9, day 10, day 11, day 12, day 13, day 14, day 15, day
16, day 17, day 18, day 19, day 20, and day 21 of each cycle comprising 28 days (i.e., on days 1-21). In some embodiments, the immunomodulatory agent may be administered for less than 21 days of each 28-day cycle. In some embodiments, the immunomodulatory agent may be administered on greater than 21 days of each 28-day cycle. In some embodiments, the immunomodulatory agent is not administered on consecutive days. In some embodiments, this dosing regimen is followed for any number of cycles. In some embodiments, this dosing regimen is followed for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 cycles. In some embodiments, this dosing regimen is followed for more than 12 cycles. In some embodiments, the immunomodulatory agent is pomalidomide.

[0059] In some embodiments, the amount of immunomodulatory agent that is administered is about 1 mg/day; about 2 mg/day; about 3 mg/day; about 4 mg/day; about 5 mg/day; about 6 mg/day; about 7 mg/day; or about 8 mg/day. In some embodiments, less than about 1 mg/day may be administered. In some embodiments, more than about 8 mg/day may be administered. In some embodiments, the amount of immunomodulatory agent administered may vary during each administration, due to physician discretion. In some embodiments, the immunomodulatory agent is pamolidomide.

[0060] In some embodiments, the steroid is administered on day 1, day 8, day 15, and day 22 of each cycle comprising or consisting of 28 days. In some embodiments, the steroid is administered on one day per week (or weekly). In some embodiments, the steroid is administered on more than one day per week. In some embodiments, the steroid is not administered on one day per week, i.e., the steroid may be administered on one day every two weeks or on two days every week. In some embodiments, this dosing regimen is followed for any number of cycles. In some embodiments, this dosing regimen is followed for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 cycles. In some embodiments, this dosing regimen is followed for more than 12 cycles. In some embodiments, the steroid is dexamethasone.

[0061] In some embodiments, the amount of steroid that is administered is about 1 mg/day to about 60 mg/day; about 10 mg/day to about 50 mg/day; or about 20 mg/day to about 40 mg/day. In some embodiments, the amount of steroid that is administered is about 20 mg/day. In some embodiments, the amount of steroid that is administered is about 40 mg/day. In some embodiments, the amount of steroid that is administered is age-dependent. In some embodiments, the steroid is dexamethasone.

[0062] In some embodiments, a dosing regimen described herein is administered to the subject over a period of time of up to 5 years, 4 years, 3 years, 2 years, or 1 year. In some instances, the
combination dosing regime is administered for a period of up to 40 cycles, 35 cycles, 30 cycles, 25 cycles, 20 cycles, 15 cycles, 14 cycles, 13 cycles, 12 cycles, 11 cycles, or 10 cycles. In some instances, the dosing regimen is administered for a period of up to 20 cycles. In some instances, the dosing regimen is administered for a period of up to 15 cycles. In some instances, the dosing regimen is administered for a period of up to 13 cycles. In some instances, the dosing regimen is administered for a period of up to 12 cycles.

[0063] In some embodiments, the amount of a TEC inhibitor that is administered is from 10 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of a TEC inhibitor that is administered is from about 40 mg/day to 900 mg/day, about 40 mg/day to 840 mg/day, about 80 mg/day to 600 mg/day, about 100 mg/day to 500 mg/day, about 140 mg/day to 420 mg/day, or about 560 mg/day to 840 mg/day. In some embodiments, the amount of a TEC inhibitor that is administered per day is about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 180 mg, about 220 mg, about 260 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, 560 mg, 700 mg, or about 840 mg.

[0064] In some embodiments, the amount of an ITK inhibitor that is administered is from 10 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of an ITK inhibitor that is administered is from about 40 mg/day to 900 mg/day, about 40 mg/day to 840 mg/day, about 80 mg/day to 600 mg/day, about 100 mg/day to 500 mg/day, about 140 mg/day to 420 mg/day, or about 560 mg/day to 840 mg/day. In some embodiments, the amount of an ITK inhibitor that is administered per day is about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 180 mg, about 220 mg, about 260 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, 560 mg, 700 mg, or about 840 mg.

[0065] In some embodiments, the amount of a BTK inhibitor that is administered is from 10 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of a BTK inhibitor that is administered is from about 40 mg/day to 900 mg/day, about 40 mg/day to
840 mg/day, about 80 mg/day to 600 mg/day, about 100 mg/day to 500 mg/day, about 140 mg/day to 420 mg/day, or about 560 mg/day to 840 mg/day. In some embodiments, the amount of a BTK inhibitor that is administered per day is about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 180 mg, about 220 mg, about 260 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, 560 mg, 700 mg, or about 840 mg.

[0066] In some embodiments, the amount of ibrutinib that is administered is from 10 mg/day up to, and including, 1000 mg/day. In some embodiments, the amount of ibrutinib that is administered is from about 40 mg/day to 900 mg/day, about 40 mg/day to 840 mg/day, about 80 mg/day to 600 mg/day, about 100 mg/day to 500 mg/day, about 140 mg/day to 420 mg/day, or about 560 mg/day to 840 mg/day. In some embodiments, the amount of ibrutinib that is administered per day is about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 110 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 180 mg, about 220 mg, about 260 mg, about 300 mg, about 350 mg, about 400 mg, about 420 mg, about 560 mg, 700 mg, or about 840 mg. In some embodiments, the amount of ibrutinib that is administered is about 40 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 50 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 60 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 70 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 420 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 560 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 700 mg/day. In some embodiments, the amount of ibrutinib that is administered is about 840 mg/day.

[0067] In some embodiments, the TEC inhibitor (e.g., ITK inhibitor or BTK inhibitor) is administered once per day, twice per day, three times per day, once daily, every other day, once a week, twice a week, three times a week, every other week, three times a month, once a month, or intermittently.
In some embodiments, ibrutinib is administered once per day, twice per day, three times per day, once daily, every other day, once a week, twice a week, three times a week, every other week, three times a month, once a month, or intermittently. In some embodiments, ibrutinib is administered once per day. In some embodiments, ibrutinib is administered as a maintenance therapy.

In some embodiments, ibrutinib is administered daily during each cycle. In some embodiments, each cycle comprises 28 days.

In some embodiments, the TEC inhibitor is administered oral, parenteral (e.g., intravenous, subcutaneous, or intramuscular), buccal, intranasal, rectal or transdermal administration routes. In some embodiments, the TEC inhibitor is administered orally. In some embodiments, the ITK inhibitor is administered orally. In some instances, the BTK inhibitor is administered orally. In some instances, ibrutinib is administered orally.

In the case wherein the patient's status does improve, upon the doctor's discretion the administration of the compounds in some cases is given continuously; alternatively, the dose of drug being administered in some cases is temporarily reduced or temporarily suspended for a certain length of time (i.e., a "drug holiday"). In some embodiments, the length of the drug holiday varies between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, 35 days, 50 days, 70 days, 100 days, 120 days, 150 days, 180 days, 200 days, 250 days, 280 days, 300 days, 320 days, 350 days, or 365 days. The dose reduction during a drug holiday may be from 10% to 100%, including, by way of example only, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 100%. In some embodiments, the drug holiday may be for ibrutinib, pomalidomide, dexamethasone, or a combination thereof.

Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, the dosage or the frequency of administration, or both, in certain cases, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain cases, patients require intermittent treatment on a long-term basis upon any recurrence of symptoms.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, the severity of the disease, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, and the subject
or host being treated. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, or from about 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered simultaneously (or over a short period of time) or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[0074] In some embodiments, the TEC inhibitor, immunomodulatory agent, and steroid are not co-administered with a strong CYP3A inhibitor or a strong CYP3A inducer. Examples of strong CYP3A inhibitors include, but are not limited to, ketoconazole, ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, and nefazodone. Examples of strong CYP3A inducers include, but are not limited to, rifampin, carbamazepine, phenytoin, and St. John's Wort.

[0075] In some embodiments, the TEC inhibitor, immunomodulatory agent, and steroid are not co-administered with a strong CYP1A2 inhibitor, such as fluvoxamine or ciprofloxacin.

[0076] The pharmaceutical composition described herein in some instances is in unit dosage forms suitable for single administration of precise dosages. In unit dosage form, the formulation is divided into unit doses containing appropriate quantities of one or more compound. In some cases, the unit dosage is in the form of a package containing discrete quantities of the formulation. Non-limiting examples are packaged tablets or capsules, and powders in vials or ampoules. In some cases, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers in other cases are used, in which case it is typical to include a preservative in the composition. By way of example only, formulations for parenteral injection presented in unit dosage form, include, but are not limited to ampoules, or in multi-dose containers, with an added preservative.

[0077] In certain embodiments, the invention relates to any of the pharmaceutical compositions or methods described herein, wherein the pharmaceutical composition or method comprises ibrutinib or its use; and the unit dosage of ibrutinib is a capsule comprising 140 mg of ibrutinib. In certain embodiments, the unit dosage of ibrutinib is a capsule comprising 140 mg of ibrutinib, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

[0078] In certain embodiments, the invention relates to any of the pharmaceutical compositions or methods described herein, wherein the pharmaceutical composition or method comprises pomalidomide or its use; and the unit dosage of pomalidomide is a capsule comprising 1 mg, 2 mg, 3 mg, or 4 mg of pomalidomide. In certain embodiments, the unit dosage of pomalidomide
is a capsule comprising 1 mg, 2 mg, 3 mg, or 4 mg of pomalidomide, mannitol, pregelatinized starch, and sodium stearyl fumarate.

[0079] In certain embodiments, the invention relates to any of the pharmaceutical compositions or methods described herein, wherein the pharmaceutical composition or method comprises dexamethasone or its use; and the unit dosage of dexamethasone is a tablet comprising 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, or 6 mg of dexamethasone. In certain embodiments, the invention relates to any of the pharmaceutical compositions or methods described herein, wherein the pharmaceutical composition or method comprises dexamethasone or its use; and the unit dosage of dexamethasone is an elixir comprising 1 mg/mL of dexamethasone. In certain embodiments, the invention relates to any of the pharmaceutical compositions or methods described herein, wherein the pharmaceutical composition or method comprises dexamethasone or its use; and the unit dosage of dexamethasone is an elixir comprising 0.5 mg/5 mL of dexamethasone. In certain embodiments, the invention relates to any of the pharmaceutical compositions or methods described herein, wherein the pharmaceutical composition or method comprises dexamethasone or its use; and the unit dosage of dexamethasone is a solution comprising 0.5 mg/5 mL of dexamethasone.

[0080] The foregoing ranges are merely suggestive, as the number of variables in regard to an individual treatment regime is large, and considerable excursions from these recommended values are not uncommon. Such dosages may be altered depending on a number of variables, not limited to the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[0081] Toxicity and therapeutic efficacy of such therapeutic regimens are determined in some instances by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD50 and ED50. Compounds exhibiting high therapeutic indices are preferred. In some instances, the data obtained from cell culture assays and animal studies are used in formulating a range of dosage for use in human. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with minimal toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.
Btk Inhibitor Compounds and Pharmaceutically Acceptable Salts Thereof

[0082] The Btk inhibitor compound described herein (i.e., ibrutinib) is selective for Btk and kinases having a cysteine residue in an amino acid sequence position of the tyrosine kinase that is homologous to the amino acid sequence position of cysteine 481 in Btk. The Btk inhibitor compound can form a covalent bond with Cys 481 of Btk (e.g., via a Michael reaction).

[0083] In some embodiments, the Btk inhibitor is a compound of Formula (A) having the structure:

![Formula (A)](image)

wherein:

A is N;

R₁ is phenyl-O-phenyl or phenyl-S-phenyl;

R₂ and R₃ are independently H;

R₄ is L₃-X-L₄-G, wherein,

L₃ is optional, and when present is a bond, optionally substituted or unsubstituted alkyl, optionally substituted or unsubstituted cycloalkyl, optionally substituted or unsubstituted alkenyl, optionally substituted or unsubstituted alkynyl;

X is optional, and when present is a bond, -0-, -C(=0)-, -S-, -S(=0)-, -S(=0)₂-, -NH-, -NR₉-, -NHC(O)-, -C(0)NH-, -NR₉C(0)-, -C(0)NR₉-, -S(=0)₂NH-, -NHS(=0)₂-, -S(=0)₂NR₉-, -NR₉S(=0)₂-, -OC(0)NH-, -NHC(O)O-, -OC(0)NR₉-, -NHC(O)NR₉-, -CH=NO-, -ON=CH-, -NR₉O(0)NR₉-, heteroaryl-, aryl-, -NR₁₀C(=NR₁₁)NR₁₀-, -NR₁₀C(=NR₁₁)-, -C(=NR₁₁)NR₁₀-, -OC(=NR₁₁)-, or -C(=NR₁₁)O-;

L₄ is optional, and when present is a bond, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heterocycle;

or L₃, X and L₄ taken together form a nitrogen containing heterocyclic ring;

G is

![G structures](image), wherein,
R6. R7 and R8 are independently selected from the group consisting of H, halogen, CN, OH, substituted or unsubstituted alkyl or substituted or unsubstituted heteroalkyl or substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl; each R9 is independently selected from the group consisting of H, substituted or unsubstituted lower alkyl, and substituted or unsubstituted lower cycloalkyl; each R10 is independently H, substituted or unsubstituted lower alkyl, or substituted or unsubstituted lower cycloalkyl; or two R10 groups can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or R10 and R11 can together form a 5-, 6-, 7-, or 8-membered heterocyclic ring; or each R11 is independently selected from the group consisting of H and substituted or unsubstituted alkyl; or a pharmaceutically acceptable salt thereof. In some embodiments, L3, X and L4 taken together form a nitrogen containing heterocyclic ring. In some embodiments, the nitrogen containing heterocyclic ring is a piperidine group. In some embodiments, G is

In some embodiments, the compound of Formula (A) is l-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one.

[0084] "Ibrutinib" or "l-((R)-3-(4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)prop-2-en-1-one" or "l-((3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-<i>]<i>pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one" or "2-Propen-1-one, l-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-<i>]<i>pyrimidin-1-yl]l-piperidinyl-" or ibrutinib or any other suitable name refers to the compound with the following structure:

[0085] A wide variety of pharmaceutically acceptable salts may be formed from ibrutinib and includes:
[0086] - acid addition salts formed by reacting ibrutinib with an organic acid, which includes aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxyl alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, amino acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like;

[0087] - acid addition salts formed by reacting ibrutinib with an inorganic acid, which includes hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like.

[0088] The term "pharmaceutically acceptable salts" in reference to ibrutinib refers to a salt of ibrutinib, which does not cause significant irritation to a mammal to which it is administered and does not substantially abrogate the biological activity and properties of the compound.

[0089] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms (solvates). Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of product formation or isolation with pharmaceutically acceptable solvents such as water, ethanol, methanol, methyl tert-butyl ether (MTBE), diisopropyl ether (DIPE), ethyl acetate, isopropyl acetate, isopropyl alcohol, methyl isobutyl ketone (MIBK), methyl ethyl ketone (MEK), acetone, nitromethane, tetrahydrofuran (THF), dichloromethane (DCM), dioxane, heptanes, toluene, anisole, acetonitrile, and the like. In one aspect, solvates are formed using, but limited to, Class 3 solvent(s). Categories of solvents are defined in, for example, the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), "Impurities: Guidelines for Residual Solvents, Q3C(R3), (November 2005). Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. In some embodiments, solvates of ibrutinib, or pharmaceutically acceptable salts thereof, are conveniently prepared or formed during the processes described herein. In some embodiments, solvates of ibrutinib are anhydrous. In some embodiments, ibrutinib, or pharmaceutically acceptable salts thereof, exist in unsolvated form. In some embodiments, ibrutinib, or pharmaceutically acceptable salts thereof, exist in unsolvated form and are anhydrous.

[0090] In yet other embodiments, ibrutinib, or a pharmaceutically acceptable salt thereof, is prepared in various forms, including but not limited to, amorphous phase, crystalline forms, milled forms and nano-particulate forms. In some embodiments, ibrutinib, or a pharmaceutically
acceptable salt thereof, is amorphous. In some embodiments, ibrutinib, or a pharmaceutically acceptable salt thereof, is amorphous and anhydrous. In some embodiments, ibrutinib, or a pharmaceutically acceptable salt thereof, is crystalline. In some embodiments, ibrutinib, or a pharmaceutically acceptable salt thereof, is crystalline and anhydrous.

[0091] In some embodiments, ibrutinib is prepared as outlined in US Patent no. 7,514,444, incorporated by reference.

[0092] In some embodiments, the Btk inhibitor is PCI-45292, PCI-45466, AVL-101 (Avila Therapeutics/Celgene Corporation), AVL-263 (Avila Therapeutics/Celgene Corporation), AVL-292 (Avila Therapeutics/Celgene Corporation), AVL-291 (Avila Therapeutics/Celgene Corporation), CNX 774 (Avila Therapeutics), BMS-488516 (Bristol-Myers Squibb), BMS-509744 (Bristol-Myers Squibb), CGI-1746 (CGI Pharma/Gilead Sciences), CGI-560 (CGI Pharma/Gilead Sciences), CTA-056, GDC-0834 (Genentech), HY-11066 (also, CTK417891, HMS3265G21, HMS3265G22, HMS3265H21, HMS3265H22, 439574-61-5, AG-F-54930), ONO-4059 (Ono Pharmaceutical Co., Ltd.), ONO-WG37 (Ono Pharmaceutical Co., Ltd.), PLS-123 (Peking University), RN486 (Hoffmann-La Roche), HM71224 (Hanmi Pharmaceutical Company Limited) and LFM-A13.

[0093] In some embodiments, the Btk inhibitor is 4-((tert-butyl)-N-(2-methyl-3-(4-methyl-6-((4-(morpholine-4-carbonyl)phenyl)amino)-5-oxo-4,5-dihydropyrazin-2-yl)phenyl)benzamide (CGI-1746); 7-benzyl-1-(3-(piperidin-1-yl)propyl)-2-(4-(pyridin-4-yl)phenyl)-1H-imidazo[4,5-g]quinoxalin-6(5H)-one (CTA-056); (R)-N-(3-(6-(4-(1,4-dimethyl-3-oxopiperazin-2-yl)phenylamino)-4-methyl-5-oxo-4,5-dihydropyrazin-2-yl)-2-methylphenyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxamide (GDC-0834); 6-cyclopropyl-8-fluoro-2-(2-hydroxymethyl-3-([1-methyl-5-[5-(4-methyl-piperazin-1-y1)pyridin-2-ylamino]-6-oxo-1,6-dihydro-pyridin-3-yl]-phenyl)-2H-isoquinolin-1-one (RN-486); N-[5-[5-(4-acetyl)piperazin-1-carbonyl)-4-methoxy-2-methylphenyl)sulfanyl-1,3-thiazol-2-yl]-4-((3,3-dimethylbutan-2-ylamino)methyl]benzamide (BMS-509744, HY-11092); or N-(5-((5-(4-Acetyl)piperazin-1-carbonyl)-4-methoxy-2-methylphenyl)thio)thiazol-2-yl)-4-(((3-methylbutan-2-yl)amino)methyl]benzamide (HY1 1066); or a pharmaceutically acceptable salt thereof.

[0094] In some embodiments, the Btk inhibitor is:
acceptable salt thereof.

**Additional TEC Family Kinase Inhibitors**

[0095] BTK is a member of the Tyrosine-protein kinase (TEC) family of kinases. In some embodiments, the TEC family comprises BTK, ITK, TEC, RLK and BMX. In some embodiments, a TEC family kinase inhibitor inhibits the kinase activity of BTK, ITK, TEC, RLK and BMX. In some embodiments, a TEC family kinase inhibitor is a BTK inhibitor, which is disclosed elsewhere herein. In some embodiments, a TEC family kinase inhibitor is an ITK inhibitor. In some embodiments, a TEC family kinase inhibitor is a TEC inhibitor. In some embodiments, a TEC family kinase inhibitor is a RLK inhibitor. In some embodiments, a TEC family kinase inhibitor is a BMK inhibitor.

[0096] In some embodiments, the ITK inhibitor covalently binds to Cysteine 442 of ITK. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2002/0500071, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2005/070420, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO2005/079791, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO2007/076228, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2007/058832, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2004/016610, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2004/016611, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2004/016600, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2004/016615, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk
inhibitor compound described in WO 2005/026175, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2006/065946, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2007/027594, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2007/017455, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2008/025820, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2008/025821, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2008/025822, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 201 1/017219, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 201 1/090760, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2009/158571, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2009/051822, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in US 201 1/0281850, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2014/082085, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2014/093383, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in US 8759358, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2014/105958, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in US 2014/0256704, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in US 2014/0315909, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in US 2014/0303161, which is incorporated by reference in its entirety. In some embodiments, the Itk inhibitor is an Itk inhibitor compound described in WO 2014/145403, which is incorporated by reference in its entirety.
In some embodiments, the Itk inhibitor has a structure selected from the group consisting of:

Hematologic Malignancies

[0098] Disclosed herein are pharmaceutical combinations, methods, and dosing regimen for administering a combination of three active ingredients: a TEC inhibitor, an immunomodulatory
agent, and a steroid for the treatment of a hematologic malignancy. In some embodiments, the hematologic malignancy is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some embodiments, the hematological malignancy is a treatment naive hematological malignancy. In some embodiments, the hematological malignancy is a relapsed or refractory hematological malignancy.

[00099] In some embodiments, the hematologic malignancy is a T-cell malignancy. In some embodiments, the T-cell malignancy is peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, or treatment-related T-cell lymphomas.

[00100] In some embodiments, the hematologic malignancy is a B-cell proliferative disorder. In some embodiments, the cancer is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, or prolymphocytic leukemia (PLL). In some embodiments, the cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, or lymphomatoid granulomatosis. In some embodiments, DLBCL is further divided into subtypes: activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), germinal center diffuse large B-cell lymphoma (GCB DLBCL), and Double-Hit (DH) DLBCL. In some embodiments, ABC-DLBCL is characterized by a CD79B mutation. In some embodiments, ABC-DLBCL is characterized by a CD79A mutation. In some embodiments, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some embodiments, the cancer is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia.

[00101] In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is diffuse large B-cell lymphoma (DLBCL). In some embodiments, the cancer is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL). In some embodiments, the cancer is
follicular lymphoma (FL). In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is chronic lymphocytic leukemia (CLL). In some embodiments, the cancer is small lymphocytic lymphoma (SLL). In some embodiments, the cancer is non-CLL/SLL lymphoma. In some embodiments, the cancer is high risk CLL or high risk SLL. In some embodiments, the cancer is PLL. In some embodiments, the cancer is Waldenstrom's macroglobulinemia.

[00102] In some embodiments, a cancer is a treatment-naive cancer. In some instances, a treatment-naive cancer is a cancer that has not been treated by a therapy, such as for example by a TEC inhibitor, an immunomodulatory agent, and/or by an additional therapeutic agent disclosed elsewhere herein. In some embodiments, a treatment-naive cancer is a hematologic cancer.

[00103] In some embodiments, the treatment-naive hematologic cancer is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy. In some embodiments, the treatment-naive hematologic cancer is a B-cell malignancy. In some embodiments, the B-cell malignancy is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, or lymphomatoid granulomatosis. In some embodiments, the treatment-naive hematologic cancer is CLL. In some embodiments, the treatment-naive hematologic cancer is SLL. In some embodiments, the treatment-naive hematologic cancer is DLBCL. In some embodiments, the treatment-naive hematologic cancer is mantle cell lymphoma. In some embodiments, the treatment-naive hematologic cancer is FL. In some embodiments, the treatment-naive hematologic cancer is Waldenstrom's macroglobulinemia. In some embodiments, the treatment-naive hematologic cancer is multiple myeloma. In some embodiments, the treatment-naive hematologic cancer is Burkitt's lymphoma. In some embodiments, the treatment-naive hematologic cancer is PLL.
In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., ITK inhibitor or a BTK inhibitor), a proteasome inhibitor, and a steroid for the treatment of a hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of multiple myeloma.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of CLL.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of SLL.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of PLL.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of DLBCL.
In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of MCL.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of Waldenstrom's macroglobulinemia.

In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent, and a steroid for the treatment of a hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of multiple myeloma.

In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of CLL.

In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of SLL.

In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of PLL.
[00117] In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of DLBCL.

[00118] In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of MCL.

[00119] In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of Waldenstrom's macroglobulinemia.

[00120] In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, a proteasome inhibitor, and a steroid for the treatment of a hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

[00121] In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of multiple myeloma.

[00122] In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of CLL.

[00123] In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of SLL.
In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of PLL.

In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of DLBCL.

In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of MCL.

In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of Waldenstrom's macroglobulinemia.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor such as ibrutinib), immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of a treatment-naive hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

Relapsed or Refractory Hematologic Malignancy

In some embodiments, the hematologic cancer is a relapsed or refractory hematologic cancer. In some embodiments, the relapsed or refractory hematologic cancer is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, T-cell malignancy, or a B-cell malignancy.

In some embodiments, the relapsed or refractory hematologic cancer is a T-cell malignancy. In some embodiments, the relapsed or refractory T-cell malignancy is peripheral T-

[00131] In some embodiments, the relapsed or refractory hematologic cancer is a B-cell proliferative disorder. In some embodiments, the relapsed or refractory cancer is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, or prolymphocytic leukemia (PLL). In some embodiments, the cancer is follicular lymphoma, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, or lymphomatoid granulomatosis. In some embodiments, the relapsed or refractory DLBCL is further divided into subtypes: activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), germinal center diffuse large B-cell lymphoma (GCB DLBCL), and Double-Hit (DH) DLBCL. In some embodiments, ABC-DLBCL is characterized by a CD79B mutation. In some embodiments, ABC-DLBCL is characterized by a CD79A mutation. In some embodiments, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some embodiments, the cancer is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia.

[00132] In some embodiments, the cancer is relapsed or refractory multiple myeloma. In some embodiments, the cancer is relapsed or refractory diffuse large B-cell lymphoma (DLBCL). In some embodiments, the cancer is relapsed or refractory activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL). In some embodiments, the cancer is relapsed or refractory follicular lymphoma (FL). In some embodiments, the cancer is relapsed or refractory multiple myeloma. In some embodiments, the cancer is relapsed or refractory chronic lymphocytic leukemia (CLL). In some embodiments, the cancer is relapsed or refractory small lymphocytic lymphoma (SLL). In some embodiments, the cancer is relapsed or refractory non-CLL/SLL lymphoma. In some
embodiments, the cancer is relapsed or refractory high risk CLL or high risk SLL. In some embodiments, the cancer is relapsed or refractory PLL. In some embodiments, the cancer is relapsed or refractory MCL. In some embodiments, the cancer is relapsed or refractory Waldenstrom’s macroglobulinemia.

[00133] In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., ITK inhibitor or a BTK inhibitor), a proteasome inhibitor, and a steroid for the treatment of a relapsed or refractory hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

[00134] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory multiple myeloma.

[00135] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory CLL.

[00136] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory SLL.

[00137] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory PLL.
[00138] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory DLBCL.

[00139] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory MCL.

[00140] In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory Waldenstrom's macroglobulinemia.

[00141] In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor and an immunomodulatory agent (e.g., pomalidomide) for the treatment of a relapsed or refractory hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

[00142] In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory multiple myeloma.

[00143] In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory CLL.
In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory SLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory PLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory DLBCL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory MCL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory Waldenstrom's macroglobulinemia.

In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent, and a steroid for the treatment of a relapsed or refractory hematologic malignancy selected from the group consisting of multiple myeloma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.
In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory multiple myeloma.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory CLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory SLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory PLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory DLBCL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory MCL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of relapsed or refractory Waldenstrom's macroglobulinemia.

In some embodiments, the relapsed or refractory hematologic cancer is a relapsed or refractory ibrutinib-resistant hematologic cancer. In some embodiments, described herein methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent, and a steroid for the treatment of a relapsed or refractory ibrutinib-resistant hematologic malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

Metastasized Hematologic Malignancy

[00158] In some embodiments, the hematologic cancer is a metastasized hematologic cancer. In some embodiments, the metastasized hematologic cancer is a leukemia, a lymphoma, a myeloma, a non-Hodgkin's lymphoma, a Hodgkin's lymphoma, a T-cell malignancy, or a B-cell malignancy.

[00159] In some embodiments, the metastasized hematologic cancer is a T-cell malignancy. In some embodiments, the T-cell malignancy is peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma, angioimmunoblastic lymphoma, cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma (ATLL), blastic NK-cell lymphoma, enteropathy-type T-cell lymphoma, hematosplenic gamma-delta T-cell lymphoma, lymphoblastic lymphoma, nasal NK/T-cell lymphomas, or treatment-related T-cell lymphomas.

[00160] In some embodiments, the metastasized hematologic cancer is a B-cell proliferative disorder. In some embodiments, the metastasized hematologic cancer is chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, a non-CLL/SLL lymphoma, or prolymphocytic leukemia (PLL). In some embodiments, the metastasized hematologic cancer is follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, or lymphomatoid granulomatosis. In some embodiments, DLBCL is further divided into subtypes: activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL), germinal center diffuse large B-cell lymphoma (GCB DLBCL), and Double-Hit (DH) DLBCL. In some embodiments, ABC-DLBCL is characterized by a CD79B mutation. In some embodiments, ABC-DLBCL is characterized by a CD79A mutation. In some embodiments, the ABC-DLBCL is characterized by a mutation in MyD88, A20, or a combination thereof. In some embodiments, the cancer is acute or chronic myelogenous (or myeloid) leukemia, myelodysplastic syndrome, or acute lymphoblastic leukemia.
In some embodiments, the metastasized hematologic cancer is diffuse large B-cell lymphoma (DLBCL). In some embodiments, the metastasized hematologic cancer is activated B-cell diffuse large B-cell lymphoma (ABC-DLBCL). In some embodiments, the metastasized hematologic cancer is follicular lymphoma (FL). In some embodiments, the metastasized hematologic cancer is multiple myeloma. In some embodiments, the metastasized hematologic cancer is chronic lymphocytic leukemia (CLL). In some embodiments, the metastasized hematologic cancer is small lymphocytic lymphoma (SLL). In some embodiments, the metastasized hematologic cancer is non-CLL/SLL lymphoma. In some embodiments, the metastasized hematologic cancer is high risk CLL or high risk SLL. In some embodiments, the metastasized hematologic cancer is PLL. In some embodiments, the metastasized hematologic cancer is MCL. In some embodiments, the metastasized hematologic cancer is Waldenstrom's macroglobulinemia.

In some embodiments, described herein methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., ITK inhibitor or a BTK inhibitor), an immunomodulatory agent, and a steroid for the treatment of a metastasized hematologic malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

In some embodiments, described herein are methods and dosing regimen for administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized multiple myeloma.

In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent, and a steroid for the treatment of a metastasized hematologic malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-

[00165] In some embodiments, described herein methods and dosing regimen for administering a combination of a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized multiple myeloma.

[00166] In some embodiments, described herein methods and dosing regimen for administering a combination of ibritinib, an immunomodulatory agent, and a steroid for the treatment of a metastasized hematologic malignancy selected from the group consisting of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), high risk CLL, non-CLL/SLL lymphoma, prolymphocytic leukemia (PLL), follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia, 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, and lymphomatoid granulomatosis.

[00167] In some embodiments, described herein are methods and dosing regimen for administering a combination of ibritinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized multiple myeloma.

[00168] In some embodiments, described herein are methods and dosing regimen for administering a combination of ibritinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized CLL.
In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized SLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized PLL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized DLBCL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized MCL.

In some embodiments, described herein are methods and dosing regimen for administering a combination of ibrutinib, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone) for the treatment of metastasized Waldenstrom's macroglobulinemia.

Multiple Myeloma

Multiple myeloma is a B cell malignancy characterized by the latent accumulation in bone marrow of secretory plasm cells with a low proliferative index and an extended life span. In some embodiments, treatment for multiple myeloma includes steroids, chemotherapy, proteasome inhibitors, immunomodulatory drugs, and stem cell transplants. In some embodiments, when plasma cells which are protein making cells become cancerous, these cells switch into the production of a single protein refer to as myeloma protein. In some instances, a myeloma protein is an abnormal immunoglobulin fragment or immunoglobulin light chain that is produced in excess by an abnormal clonal proliferation of plasma cells. In some embodiments, myeloma protein is also called M protein, M component, spike protein, or paraprotein.

In some embodiments, a subject with multiple myeloma has a genomic aberration. In some embodiments, the genomic aberration is a chromosomal abnormality. In some embodiments, the chromosomal abnormality is t(4;14), t(14;16), t(6;14), t(l 1:14), deletion 17pl3, deletion 13, chromosome 1 abnormalities, hyperdiploidy.

Disclosed herein, in certain embodiments, are dosing regimens and methods for treatment of multiple myeloma comprising administering to a subject in need thereof a combination comprising a TEC inhibitor such as ITK or BTK inhibitor, an immunomodulatory
agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone). In some instances, also described herein include dosing regimens and methods for treatment of multiple myeloma comprising a combination comprising an ITK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone). In some instances, additionally described herein include dosing regimens and methods for treatment of multiple myeloma comprising a combination comprising a BTK inhibitor, an immunomodulatory agent (e.g., pomalidomide), and a steroid (e.g., dexamethasone). In some instances, further described herein include dosing regimens and methods for treatment of multiple myeloma comprising a combination comprising ibrutinib, pomalidomide, and dexamethasone.

**Additional Therapeutic Agents**

[00177] Disclosed herein include methods and dosing regimen of administering a combination of a TEC inhibitor (e.g., an ITK inhibitor or a BTK inhibitor), an immunomodulatory agent, a steroid, and an additional therapeutic agent. In some embodiments, the additional therapeutic agent is a chemotherapeutic agent, analgesic, a proteosome inhibitor, a targeted therapy, or a combination thereof. In some embodiments, the additional therapeutic agent is a B cell receptor pathway inhibitor. In some embodiments, the B cell receptor pathway inhibitor is a CD79A inhibitor, a CD79B inhibitor, a CD19 inhibitor, a Lyn inhibitor, a Syk inhibitor, a PI3K inhibitor, a Blnk inhibitor, a PLCy inhibitor, a PKCβ inhibitor, or a combination thereof. In some embodiments, the additional therapeutic agent is an antibody, B cell receptor signaling inhibitor, a PI3K inhibitor, an IAP inhibitor, an mTOR inhibitor, a radioimmunotherapeutic, a DNA damaging agent, a proteosome inhibitor, a histone deacetylase inhibitor, a protein kinase inhibitor, a hedgehog inhibitor, an Hsp90 inhibitor, a telomerase inhibitor, a Jak1/2 inhibitor, a protease inhibitor, a PKC inhibitor, a PARP inhibitor, or a combination thereof.

[00178] In some embodiments, the additional therapeutic agent comprises an analgesic such as acetaminophen.

[00179] In some embodiments, the additional therapeutic agent is an agent selected from the group consisting of: an inhibitor of LYN, an inhibitor of SYK, an inhibitor of JAK, an inhibitor of PI3K, an inhibitor of PLCy, an inhibitor of MAPK, an inhibitor of MEK and an inhibitor of NFKB.

[00180] In some embodiments, the additional therapeutic agent is an agent selected from the group consisting of: bendamustine, bortezomib, idelalisib (GS-1 101), vorinostat, everolimus, panobinostat, temsirolimus, romidepsin, vorinostat, fludarabine, cyclophosphamide, mitoxantrone, pentostatine, prednisone, etopside, and procarbazine.
In some embodiments the additional therapeutic agent is bendamustine. In some embodiments, bortezomib is administered in combination with rituximab.

In some embodiments, the additional therapeutic agent is bendamustine. In some embodiments, bortezomib is administered in combination with rituximab.

In some embodiments, the additional therapeutic agent is a multi-agent therapeutic regimen. In some embodiments the additional therapeutic agent comprises the HyperCVAD regimen (cyclophosphamide, vincristine, doxorubicin, methotrexate and cytarabine). In some embodiments, the HyperCVAD regimen is administered in combination with rituximab.

In some embodiments the additional therapeutic agent comprises the R-CHOP regiment (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

In some embodiments the additional therapeutic agent comprises the FCR regimen (FCR (fludarabine, cyclophosphamide, rituximab).

In some embodiments the additional therapeutic agent comprises the FCMR regimen (fludarabine, cyclophosphamide, mitoxantrone, rituximab).

In some embodiments the additional therapeutic agent comprises the FMR regimen (fludarabine, mitoxantrone, rituximab).

In some embodiments the additional therapeutic agent comprises the PCR regimen (pentostatin, cyclophosphamide, rituximab).

In some embodiments the additional therapeutic agent comprises the PEPC regimen (prednisone, etoposide, procarbazine, cyclophosphamide).

In some embodiments the additional therapeutic agent comprises radioimmunotherapy with $^{90}$Y-ibritumomab tiuxetan or $^{131}$I-tositumomab.

In some embodiments, the additional therapeutic agent is an autologous stem cell transplant.

In some embodiments, the additional therapeutic agent is selected from the group consisting of: Nitrogen Mustards such as for example, bendamustine, chlorambucil, chlormethine, cyclophosphamide, ifosfamide, melphalan, prednimustine, trofosfamide; Alkyl Sulfonates like busulfan, busulfan, treosulfan; Ethylene Imines like carboquone, thiotepa, triaziquone; Nitrosoureas like carmustine, fotemustine, lomustine, nimustine, ranimustine, semustine, streptozocin; Epoxides such as for example, etoglucid; Other Alkylation Agents such as for example dacarbazine, mitobronitol, pipobroman, temozolomide; Folic Acid Analogues such as for example methotrexate, perimetrexed, pralatrexate, raltrexed; Purine Analogs such as for example cladribine, clofarabine, fludarabine, mercaptopurine, nelarabine, tioguanine;
Pyrimidine Analogs such as for example azacitidine, capecitabine, carmofur, cytarabine, decitabine, fluorouracil, gemcitabine, tegafur; Vinca Alkaloids such as for example vinblastine, vincristine, vindesine, vinflunine, vinorelbine; Podophyllotoxin Derivatives such as for example etoposide, teniposide; Colchicine derivatives such as for example demecolcine; Taxanes such as for example docetaxel, paclitaxel, paclitaxel poliglumex; Other Plant Alkaloids and Natural Products such as for example trabectedin; Actinomycines such as for example dactinomycin; Antracyclines such as for example aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, pirarubicin, valrubicin, zorubincin; Other Cytotoxic Antibiotics such as for example bleomycin, ixabepilone, mitomycin, plicamycin; Platinum Compounds such as for example carboplatin, cisplatin, oxaliplatin, satraplatin; Methylhydrazines such as for example procarbazine; Sensitizers such as for example aminolevulinic acid, efaproxiral, methyl aminolevulinate, porfimer sodium, temoporfin; Protein Kinase Inhibitors such as for example dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazonanib, sorafenib, sunitinib, temsirolimus; Other Antineoplastic Agents such as for example alitretinoin, altretamine, amzacrine, anagrelide, arsenic trioxide, asparaginase, bexarotene, bortezomib, celecoxib, denileukin diftitox, estramustine, hydroxycarbamide, irinotecan, lonidamine, masoprocol, miltefosine, mitoguazone, mitotane, oblimersen, pegaspargase, pentostatin, romidepsin, sitimagene ceradenovec, tiazofurine, topotecan, tretinoin, vorinostat; Estrogens such as for example diethylstilbenes, ethinylestradiol, fosfestril, polyestradiol phosphate; Progestogens such as for example gestonorone, medroxyprogesterone, megestrol; Gonadotropin Releasing Hormone Analogs such as for example buserelin, goserelin, leuprorelin, triptorelin; Anti-Estrogens such as for example fulvestrant, tamoxifen, toremifene; Anti-Androgens such as for example bicalutamide, flutamide, nilutamide, , Enzyme Inhibitors, aminogluthimide, anastrozole, exemestane, formestane, letrozole, vorozole; Other Hormone Antagonists such as for example abarelix, degarelix; Immunostimulants such as for example histamine dihydrochloride, mifamurtide, pidotimod, plerixafor, roquinimex, thymopentin; Immunosuppressants such as for example everolimus, gusperimus, leflunomide, mycophenolic acid, sirolimus; Calcineurin Inhibitors such as for example ciclosporin, tacrolimus; Other Immunosuppressants such as for example azathioprine, lenalidomide, methotrexate, thalidomide; and Radiopharmaceuticals such as for example, iobenguane.

[00193] In some embodiments, the additional therapeutic agent is selected from the group consisting of: interferons, interleukins, Tumor Necrosis Factors, and Growth Factors, or the like.
In some embodiments, the additional therapeutic agent is selected from the group consisting of: ancestim, filgrastim, lenograstim, molgramostim, pegfilgrastim, sargramostim; Interferons such as for example interferon alfa natural, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, interferon alfa-nl, interferon beta natural, interferon beta-la, interferon beta-lb, interferon gamma, peginterferon alfa-2a, peginterferon alfa-2b; Interleukins such as for example aldesleukin, oprelvekin; Other Immunostimulants such as for example BCG vaccine, glatiramer acetate, histamine dihydrochloride, immunocyanin, lentinan, melanoma vaccine, mifamurtide, pegademase, pidotimod, plerixafor, poly I:C, poly ICLC, roquinimex, tasonermin, thymopentin; Immunosuppressants such as for example abatacept, abetimus, alefacect, antilymphocyte immunoglobulin (horse), antithymocyte immunoglobulin (rabbit), eculizumab, efalizumab, everolimus, gusperimus, leflunomide, muromab-CD3, mycophenolic acid, natalizumab, sirolimus; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, etanercept, golimumab, infliximab; Interleukin Inhibitors such as for example anakinra, basiliximab, canakinumab, daclizumab, mepolizumab, rilonacept, tocilizumab, ustekinumab; Calcineurin Inhibitors such as for example ciclosporin, tacrolimus; and Other Immunosuppressants such as for example azathioprine, lenalidomide, methotrexate, thalidomide.

In some embodiments, the additional therapeutic agent is selected from the group consisting of: Adalimumab, Alemtuzumab, Basiliximab, Bevacizumab, Cetuximab, Certolizumab pegol, Daclizumab, Eculizumab, Efalizumab, Gemtuzumab, Ibritumomab tiuxetan, Infliximab, Muromonab-CD3, Natalizumab, Panitumumab, Ranibizumab, Tositumomab, and Trastuzumab, or the like, or a combination thereof.

In some embodiments, the additional therapeutic agent is selected from the group consisting of: Monoclonal Antibodies such as for example alemtuzumab, bevacizumab, catumaxomab, cetuximab, edrecolomab, gemtuzumab, panitumumab, trastuzumab; Immunosuppressants, eculizumab, efalizumab, muromab-CD3, natalizumab; TNF alpha Inhibitors such as for example adalimumab, afelimomab, certolizumab pegol, golimumab, infliximab; Interleukin Inhibitors, basiliximab, canakinumab, daclizumab, mepolizumab, tocilizumab, ustekinumab; Radiopharmaceuticals, ibritumomab tiuxetan, tositumomab; Others Monoclonal Antibodies such as for example abagovomab, adecatumumab, alemtuzumab, anti-CD30 monoclonal antibody Xmab2513, anti-MET monoclonal antibody MetMab, apolizumab, apomab, arcitumomab, basiliximab, bisppecific antibody 2B1, blinatumomab, brentuximab vedotin, capromab pendetide, cixutumumab, claudiximab, conatumumab, daetuzumab, denosumab, eculizumab, epratuzumab, epratuzumab, ertuxomab, etaracizumab, figitumumab, ...
fresolimumab, galiximab, ganitumab, gemtuzumab ozogamicin, glematatumumab, ibritumomab, inotuzumab ozogamicin, ipilimumab, lexatumumab, lintuzumab, lintuzumab, lucatumumab, mapatumumab, matuzumab, milatuzumab, monoclonal antibody CC49, necitumumab, nimotuzumab, oregonomab, pertuzumab, ramacurimab, ranibizumab, sipilizumab, sonpecizumab, tanezumab, tositumomab, trastuzumab, tucotuzumab celmoleukin, veltuzumab, visilizumab, volociximab, and zalutumumab.

[00197] In some embodiments, the additional therapeutic agent is selected from the group consisting of: agents that affect the tumor micro-environment such as cellular signaling network (e.g., phosphatidylinositol 3-kinase (PI3K) signaling pathway, signaling from the B-cell receptor and the IgE receptor). In some embodiments, the additional therapeutic agent is a PI3K signaling inhibitor or a syc kinase inhibitor. In one embodiment, the syc inhibitor is R788. In another embodiment is a PKCγ inhibitor such as by way of example only, enzastaurin.

[00198] Examples of agents that affect the tumor micro-environment include PI3K signaling inhibitor, syc kinase inhibitor, Protein Kinase Inhibitors such as for example dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazonanib, sorafenib, sunitinib, temsirolimus; Other Angiogenesis Inhibitors such as for example GT-1 11, JI-101, R1530; Other Kinase Inhibitors such as for example AC220, AC480, ACE-041, AMG 900, AP24534, Any-614, AT7519, AT9283, AV-951, axitinib, AZD1 152, AZD7762, AZD8055, AZD8931, bafetinib, BAY 73-4506, BGJ398, BGT226, BI 811283, BI6727, BIBF 1120, BIBW 2992, BMS-690154, BMS-777607, BMS-863233, BSK-461364, CAL-101, CEP-1 1981, CYC1 16, DCC-2036, dinaciclib, dovitinib lactate, E7050, EMD 1214063, ENMD-2076, fostamatinib disodium, GSK2256098, GSK690693, INCB18424, INNO-406, JNJ-26483327, JX-594, KX2-391, linifanib, LY2603618, MGCD265, MK-0457, MK1496, MLN8054, MLN8237, MP470, NMS-1116354, NMS-1286937, ON 01919.Na, OSI-027, OSI-930, Btk inhibitor, PF-00562271, PF-02341066, PF-03814735, PF-04217903, PF-04554878, PF-04691502, PF-3758309, PHA-739358, PLC3397, prodinapotide, R547, R763, ramucirumab, regorafenib, R05185426, SAR103168, SCH 727965, SGI-1 176, SGX523, SNS-314, TAK-593, TAK-901, TKI258, TLN-232, TTP607, XL147, XL228, XL281R05 126766, XL418, XL765.

[00199] In some embodiments, the additional therapeutic agent is selected from the group consisting of: inhibitors of mitogen-activated protein kinase signaling, e.g., U0126, PD98059, PD184352, PD0325901, ARRY-142886, SB239063, SP600125, BAY 43-9006, wortmannin, or LY294002; Syk inhibitors; mTOR inhibitors; and antibodies (e.g., rituxan).
In some embodiments, the additional therapeutic agent is selected from the group consisting of: Adriamycin, Daclomycin, Bleomycin, Vinblastine, Cisplatin, acicivin; aclorubicin; acodazole hydrochloride; acronine; adozelesin; aldesleukin; altretamine; ambomycin; ametantrone acetate; aminoglutethimide; amsacrine; anastrozole; anthramycin; asparaginase; asperlin; azacitidine; azetepa; azotomycin; batimastat; benzodepa; bicalutamide; bisantrene hydrochloride; bisnafide dimesylate; bizelesin; bleomycin sulfate; brequinar sodium; bropirimine; busulfan; cactinomycin; calusterone; caracemide; carbetimer; carboplatin; carmustine; carubicin hydrochloride; carzelesin; cedefingol; chlorambucil; cirolemycin; cladribine; crisnatol mesylate; cyclophosphamide; cytarabine; dacarbazine; daunorubicin hydrochloride; decitabine; dexormaplatin; dezaguanine; dezaguanine mesylate; diaziqune; doxorubicin; doxorubicin hydrochloride; droloxifene; droloxifene citrate; dromostanolone propionate; duazomycin; edatrexate; eflornithine hydrochloride; elsamitracin; enloplatin; enprome; epipropidine; epirubicin hydrochloride; erbuolozole; esorubicin hydrochloride; estramustine; estramustine phosphate sodium; etanidazole; etoposide; etoposide phosphate; etoprine; fadrozole hydrochloride; fazarabine; fenretinide; florouracil; fluorouracil; fosquidone; fostiretic acid; gemcitabine; gemcitabine hydrochloride; hydroxyurea; idarubicin hydrochloride; ifosfamide; iiimofosine; interferon II (including recombinant interferon II, or rIL2), interferon alfa-2a; interferon alfa-2b; interferon alfa-nl; interferon alfa-n3; interferon beta-1 a; interferon gamma-1 b; iproplatin; irinotecan hydrochloride; lanreotide acetate; letrozole; leuprolide acetate; liarozole hydrochloride; lometrexol sodium; lomustine; losoxantrone hydrochloride; masoprocol; maytansine; mechlorethamine hydrochloride; megestrol acetate; melengestrol acetate; melphalan; menogaril; mercaptopurine; methotrexate; methotrexate sodium; metoprine; meturedepa; mitindomide; mitocarcin; mitocromin; mitogillin; mitomalcin; mitomycin; mitosper; mitoxantrone hydrochloride; mycophenolic acid; nocodazoie; nogalamycin; ormaplatin; oxisuran; pegasparagase; pelomiycin; pentamustine; peplomycin sulfate; perfosfamide; pipobroman; piposulfan; piroxantrone hydrochloride; plicamycin; plomestane; porfimer sodium; porfiromycin; prednimustine; procarbazine hydrochloride; puromycin; puromycin hydrochloride; pyrazofurin; riboprine; rogetimide; safingol; safingol hydrochloride; semustine; simtrazene; sparfosate sodium; sparsomycin; spirogermanium hydrochloride; spiromustine; spiroplatin; streptonigrin; streptozocin; sulofenur; talisomycin; tecogalan sodium; tegafur; teloantrone hydrochloride; temoporfin; teniposide; teroxirone; testolactone; thiamiprine; thioguanine; thiotepa; tiazofurin; tirapazamine; toremifene citrate; treteleost acetate; triciribine phosphate; trimetrexate;
trimetrexate glucuronate; triptorelin; tubulozole hydrochloride; uracil mustard; uredepa; vaproetide; verteporfin; vinblastine sulfate; vincristine sulfate; vindesine; vindesine sulfate; vinepidine sulfate; vinglycinate sulfate; vinleurosine sulfate; vinorelbine tartrate; vinrosidine sulfate; vinzolidine sulfate; vorozole; zeniplatin; zinostatin; and zorubicin hydrochloride.

[00201] In some embodiments, the additional therapeutic agent is selected from the group consisting of: 20-epi-l, 25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelenin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azaseteron; azatxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorlns; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambscidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentantheraquiones; cycloplatam; cypemycin; cytarabine ofosfate; cytolytic factor; cytosinat; dactliliximab; decitabine; dehydrodideaminin B; deslorelin; dexifosamide; dexrazoxane; dexverapamil; diaziquone; didemmin B; didox; diethylorpermine; dihydro-5-azacytidine; 9-dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epiristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelahtine; flusterone; fludarabine; fluorodaunorunic hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam;
heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-such as for example growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leunocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; masin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A+mycobacterium cell wall sk; mopedamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1 -based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone+pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitrooxide antioxidant; nitrullyn; 06-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondasetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxauromycin; palauamine; palmitoyl rhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegasparagase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; piciibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; prednisone; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; ras antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP
inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone Bl; ruboxyl; safingol;
saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived
inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators;
single chain antigen-binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium
phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D;
spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division
inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal
peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine;
tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium;
telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine;
thaliblastine; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin
receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine;
titanocene bichloride; topsentin; toremifene; totipotent stem cell factor; translation inhibitors;
tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; turosteride; tyrosine kinase inhibitors;
tyrophostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor;
urokinase receptor antagonists; vaproteide; variolin B; vector system, erythrocyte gene therapy;
velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone;
zeniplatin; zilascorb; and zinostatin stilamaler.

[00202] In some embodiments, the additional therapeutic agent is selected from the group
consisting of: alkylating agents, antimetabolites, natural products, or hormones, e.g., nitrogen
mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil, etc.), alkyl sulfonates (e.g.,
busulfan), nitrosoureas (e.g., carmustine, lomusitine, etc.), and triazines (decarbazine, etc.).
Examples of antimetabolites include but are not limited to folic acid analog (e.g., methotrexate),
or pyrimidine analogs (e.g., Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine,
pentostatin).

[00203] In some embodiments, the additional therapeutic agent is selected from the group
consisting of: nitrogen mustards (e.g., mechloroethamine, cyclophosphamide, chlorambucil,
meiphalan, etc.), ethylenimine and methylmelamines (e.g., hexamethylmelamine, thiotepa), alkyl
sulfonates (e.g., busulfan), nitrosoureas (e.g., carmustine, lomusitine, semustine, streptozocin,
etc.), and triazines (decarbazine, etc.). Examples of antimetabolites include, but are not limited to
folic acid analog (e.g., methotrexate), or pyrimidine analogs (e.g., fluorouracil, floxouridine,
Cytarabine), purine analogs (e.g., mercaptopurine, thioguanine, pentostatin.)
In some embodiments, the additional therapeutic agent is selected from the group consisting of: agents that act by arresting cells in the G2-M phases due to stabilized microtubules, e.g., Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1, Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminooepothilone B (also known as BMS-3 10705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-1 12378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamidine, Tubulysin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-3 13 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of Medicine), A-204197 (Abbott), T-
607 (Tuiarik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeside, Caribaelin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-OY-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

[00205] In some embodiments, the additional therapeutic agent is not a strong CYP3A inhibitor or a strong CYP3A inducer. Examples of strong CYP3A inhibitors include, but are not limited to, ketoconazole, ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, and nefazodone. Examples of strong CYP3A inducers include, but are not limited to, rifampin, carbamazepine, phenytoin, and St. John's Wort.

[00206] In some embodiments, the additional therapeutic agent is not a strong CYP1A2 inhibitor, such as fluvoxamine or ciprofloxacin.

**Pharmaceutical Compositions/Formulations**

[00207] Disclosed herein, in certain embodiments, are pharmaceutical compositions or combinations for treating a B cell proliferative disorder in an individual in need thereof comprising a TEC inhibitor (e.g., an ITK inhibitor, a BTK inhibitor, e.g., a covalent BTK inhibitor), an immunomodulatory agent, and a steroid, and optionally a pharmaceutically acceptable excipient. Also disclosed herein, in certain embodiments, are compositions or combinations for treating a B cell proliferative disorder in an individual in need thereof comprising a covalent Btk inhibitor (e.g., an irreversible covalent BTK inhibitor, e.g., ibrutinib), an immunomodulatory agent, and a steroid, and optionally a pharmaceutically acceptable excipient. In some embodiments, the B cell proliferative disorder is refractory to the covalent BTK inhibitor (e.g., an irreversible covalent BTK inhibitor, e.g., ibrutinib). In some embodiments, the B cell proliferative disorder is relapsed or refractory to an immunomodulatory agent. In some embodiments, the B cell proliferative disorder is relapsed or refractory to an immunomodulatory agent (i.e., lenalidomide). In some embodiments, the B cell proliferative disorder is relapsed or refractory to a proteosome inhibitor (i.e., bortezomib and/or or carfilzomib). In some embodiments, the B cell proliferative disorder is relapsed or refractory to
an immunomodulatory agent (e.g., lenalidomide) and a proteosome inhibitor (e.g., bortezomib). In some embodiments, the B cell proliferative disorder is relapsed or refractory to an immunomodulatory agent (e.g., lenalidomide) and a proteosome inhibitor (e.g., carfilzomib). In some embodiments, the B cell proliferative disorder is relapsed or refractory. In some embodiments, the B cell proliferative disorder is multiple myeloma.

[00208] In some embodiments, the covalent BTK inhibitor is a compound of Formula (A). In some embodiments, the covalent Btk inhibitor is (R)-1 -(3-(4-amino-3-(4-phenoxy phenyl)- 1H-pyrazolo[3,4-d]pyrimidin- 1-yl)piperidin- 1-yl)prop-2-en- 1-one (i.e., PCI-32765/ibrutinib).

[00209] Pharmaceutical compositions or combinations of a covalent Btk inhibitor (e.g., an irreversible covalent Btk inhibitor, e.g., ibrutinib), a proteasome inhibitor, and a steroid are formulated in a conventional manner using one or more physiologically acceptable carriers including excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack_Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[00210] A pharmaceutical composition or combinations, as used herein, refers to a mixture of a covalent Btk inhibitor (e.g., an irreversible covalent Btk inhibitor, e.g., ibrutinib), a proteasome inhibitor, and a steroid with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

[00211] Pharmaceutical compositions or combinations are optionally manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[00212] In certain embodiments, compositions or combinations also include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases
and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[00213] In other embodiments, compositions or combinations also include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[00214] The term "pharmaceutical combination" as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that the active ingredients, e.g., a compound described herein and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term "non-fixed combination" means that the active ingredients, e.g., a compound described herein and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g., the administration of three or more active ingredients.

[00215] The pharmaceutical formulations described herein are administered by any suitable administration route, including but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, intramuscular), intranasal, buccal, topical, rectal, or transdermal administration routes.

[00216] The pharmaceutical compositions or combinations described herein are formulated into any suitable dosage form, including but not limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by an individual to be treated, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations. In some embodiments, the compositions are formulated into capsules. In some embodiments, the compositions are formulated into solutions (for example, for IV administration).

[00217] The pharmaceutical solid dosage forms described herein optionally include a compound described herein and one or more pharmacologically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating
agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof.

[00218] In still other aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the compositions. In some embodiments, the compositions are formulated into particles (for example for administration by capsule) and some or all of the particles are coated. In some embodiments, the compositions are formulated into particles (for example for administration by capsule) and some or all of the particles are microencapsulated. In some embodiments, the compositions are formulated into particles (for example for administration by capsule) and some or all of the particles are not microencapsulated and are uncoated.

[00219] In certain embodiments, compositions provided herein also include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpipridinium chloride.

[00220] In some embodiments, "anti-foaming agents" reduce foaming during processing which result in coagulation of aqueous dispersions, bubbles in the finished film, or generally impair processing. Exemplary anti-foaming agents include silicon emulsions or sorbitan sesquoleate.

[00221] In some embodiments, "antioxidants" include, for example, butylated hydroxytoluene (BHT), sodium ascorbate, ascorbic acid, sodium metabisulfite and tocopherol. In certain embodiments, antioxidants enhance chemical stability where required.

[00222] In some embodiments, formulations described herein benefit from antioxidants, metal chelating agents, thiol containing compounds and other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

[00223] "Binders" impart cohesive qualities and include, e.g., alginic acid and salts thereof; cellulose derivatives such as carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®),
ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®); microcrystalline dextrose; amylose; magnesium aluminum silicate; polysaccharide acids; bentonites; gelatin; polyvinylpyrrolidone/vinyl acetate copolymer; crospovidone; povidone; starch; pregelatinized starch; tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitol®), and lactose; a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, polyvinylpyrrolidone (e.g., Polyvidone® CL, Kollidon® CL, Polyplasdone® XL-10), larch arabogalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[00224] In some embodiments, a "carrier" or "carrier materials" include any commonly used excipients in pharmaceutics and should be selected on the basis of compatibility with compounds disclosed herein, such as, compounds of ibrutinib, and the release profile properties of the desired dosage form. Exemplary carrier materials include, e.g., binders, suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, diluents, and the like. "Pharmaceutically compatible carrier materials" may include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, polyvinylpyrrolidone (PVP), cholesterol, cholesterol esters, sodium caseinate, soy lecithin, taurocholic acid, phosphotidylcholine, sodium chloride, tricalcium phosphate, dipotassium phosphate, cellulose and cellulose conjugates, sugars (e.g., sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, and the like. See, e.g., Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999).

[00225] "Dispersing agents," and/or "viscosity modulating agents" include materials that control the diffusion and homogeneity of a drug through liquid media or a granulation method or blend method. In some embodiments, these agents also facilitate the effectiveness of a coating or eroding matrix. Exemplary diffusion facilitators/dispersing agents include, e.g., hydrophilic polymers, electrolytes, Tween® 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents such as, for example, hydroxypropyl celluloses (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcelluloses (e.g., HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose,
hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), vinyl pyrrolidone/vinyl acetate copolymer (S630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)), polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyvinylpyrrolidone/vinyl acetate copolymer (S-630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose, polysorbate-80, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, celluloses, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone, caromers, polyvinyl alcohol (PVA), alginites, chitosans and combinations thereof. Plasticizers such as cellulose or triethyl cellulose can also be used as dispersing agents. Dispersing agents particularly useful in liposomal dispersions and self-emulsifying dispersions are dimyristoyl phosphatidyl choline, natural phosphatidyl choline from eggs, natural phosphatidyl glycerol from eggs, cholesterol and isopropyl myristate.

[00226] Combinations of one or more erosion facilitator with one or more diffusion facilitator are also used in the present compositions.

[00227] The term "diluent" refers to chemical compounds that are used to dilute the compound of interest prior to delivery. In some embodiments, diluents are also used to stabilize compounds because they provide a more stable environment. Salts dissolved in buffered solutions (which also can provide pH control or maintenance) are utilized as diluents in the art, including, but not limited to a phosphate buffered saline solution. In certain embodiments, diluents increase bulk of the composition to facilitate compression or create sufficient bulk for homogenous blend for capsule filling. Such compounds include e.g., lactose, starch, mannitol, sorbitol, dextrose, microcrystalline cellulose such as Avicel®; dibasic calcium phosphate, dicalcium phosphate dihydrate; tricalcium phosphate, calcium phosphate; anhydrous lactose, spray-dried lactose; pregelatinized starch, compressible sugar, such as Di-Pac® (Amstar); mannitol,
hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose-based diluents, confectioner's sugar; monobasic calcium sulfate monohydrate, calcium sulfate dihydrate; calcium lactate trihydrate, dextrates; hydrolyzed cereal solids, amylose; powdered cellulose, calcium carbonate; glycine, kaolin; mannitol, sodium chloride; inositol, bentonite, and the like.

[00228] The term "disintegrate" includes both the dissolution and dispersion of the dosage form when contacted with gastrointestinal fluid. "Disintegration agents or disintegrants" facilitate the breakup or disintegration of a substance. Examples of disintegration agents include a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PHI 05, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00229] "Drug absorption" or "absorption" typically refers to the process of movement of drug from site of administration of a drug across a barrier into a blood vessel or the site of action, e.g., a drug moving from the gastrointestinal tract into the portal vein or lymphatic system.

[00230] An "enteric coating" is a substance that remains substantially intact in the stomach but dissolves and releases the drug in the small intestine or colon. Generally, the enteric coating comprises a polymeric material that prevents release in the low pH environment of the stomach but that ionizes at a higher pH, typically a pH of 6 to 7, and thus dissolves sufficiently in the small intestine or colon to release the active agent therein.

[00231] "Erosion facilitators" include materials that control the erosion of a particular material in gastrointestinal fluid. Erosion facilitators are generally known to those of ordinary skill in the art. Exemplary erosion facilitators include, e.g., hydrophilic polymers, electrolytes, proteins, peptides, and amino acids.
"Filling agents" include compounds such as lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

"Flavoring agents" and/or "sweeteners" useful in the formulations described herein, include, e.g., acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor, caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cynamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhetinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glycyrrhizinate (Magnasweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrone, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sylitol, sucralose, sorbitol, Swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof.

"Lubricants" and "glidants" are compounds that prevent, reduce or inhibit adhesion or friction of materials. Exemplary lubricants include, e.g., stearic acid, calcium hydroxide, talc, sodium stearyl fumerate, a hydrocarbon such as mineral oil, or hydrogenated vegetable oil such as hydrogenated soybean oil (Sterotex®), higher fatty acids and their alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, glycerol, t alc, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chloride, leucine, a polyethylene glycol (e.g., PEG-4000) or a methoxypolyethylene glycol such as Carbowax™, sodium oleate, sodium benzoate, glyceryl behenate, polyethylene glycol, magnesium or sodium lauryl sulfate, colloidal silica such as Syloid™, Cab-O-Sil® , a starch such as corn starch, silicone oil, a surfactant, and the like.

A "measurable serum concentration" or "measurable plasma concentration" describes the blood serum or blood plasma concentration, typically measured in mg, μg, or ng of therapeutic agent per mL, dL, or L of blood serum, absorbed into the bloodstream after
administration. As used herein, measurable plasma concentrations are typically measured in ng/mL or µg/mL.

[00236] "Pharmacodynamics" refers to the factors which determine the biologic response observed relative to the concentration of drug at a site of action.

[00237] "Pharmacokinetics" refers to the factors which determine the attainment and maintenance of the appropriate concentration of drug at a site of action.

[00238] "Plasticizers" are compounds used to soften the microencapsulation material or film coatings to make them less brittle. Suitable plasticizers include, e.g., polyethylene glycols such as PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, triethyl cellulose and triacetin. In some embodiments, plasticizers can also function as dispersing agents or wetting agents.

[00239] "Solubilizers" include compounds such as triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, sodium lauryl sulfate, sodium doccurate, vitamin E TPGS, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cyclodextrins, ethanol, n-butanol, isopropyl alcohol, cholesterol, bile salts, polyethylene glycol 200-600, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide and the like.

[00240] "Stabilizers" include compounds such as any antioxidation agents, buffers, acids, preservatives and the like.

[00241] "Steady state," as used herein, is when the amount of drug administered is equal to the amount of drug eliminated within one dosing interval resulting in a plateau or constant plasma drug exposure.

[00242] "Suspending agents" include compounds such as polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, vinyl pyrrolidone/vinyl acetate copolymer (S630), polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose acetate stearate, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate,
polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00243] "Surfactants" include compounds such as sodium lauryl sulfate, sodium docusate, Tween 60 or 80, triacetin, vitamin E TPGS, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, poloxamers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like. Some other surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40. In some embodiments, surfactants may be included to enhance physical stability or for other purposes.

[00244] "Viscosity enhancing agents" include, e.g., methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose acetate stearate, hydroxypropylmethyl cellulose phthalate, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof.

[00245] "Wetting agents" include compounds such as oleic acid, glycercyl monostearate, sorbitan monooleate, sorbitan monolaurate, tethanolamine oleate, polyoxyethylene sorbitanmonooleate, polyoxyethylene sorbitan monolaurate, sodium docusate, sodium oleate, sodium lauryl sulfate, sodium docessate, triacetin, Tween 80, vitamin E TPGS, ammonium salts and the like.

**Dosage Forms**

[00246] In some embodiments, the compositions described herein is formulated for administration to a subject via any conventional means including, but not limited to, oral, parenteral (e.g., intravenous, subcutaneous, or intramuscular), buccal, intranasal, rectal or transdermal administration routes. In some embodiments, the composition is formulated for administration in a combined dosage form. In some embodiments, the composition is formulated for administration in a separate dosage forms. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms "individual(s)", "subject(s)" and "patient(s)" are used interchangeably herein, and mean any mammal. In some embodiments, the mammal is a human. In some embodiments, the mammal is a non-human. None of the terms require or are limited to situations characterized by the supervision (e.g., constant or intermittent) of a health care worker (e.g., a doctor, a registered nurse, a nurse practitioner, a physician's assistant, an orderly or a hospice worker).

[00247] Moreover, the pharmaceutical compositions described herein, which include ibrutinib and/or an anticancer agent can be formulated into any suitable dosage form, including but not
limited to, aqueous oral dispersions, liquids, gels, syrups, elixirs, slurries, suspensions and the like, for oral ingestion by a patient to be treated, solid oral dosage forms, aerosols, controlled release formulations, fast melt formulations, effervescent formulations, lyophilized formulations, tablets, powders, pills, dragees, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, multiparticulate formulations, and mixed immediate release and controlled release formulations.

[00248] Pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include, for example, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. If desired, disintegrating agents may be added, such as the cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00249] Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00250] Pharmaceutical preparations which are used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

[00251] In some embodiments, the solid dosage forms disclosed herein may be in the form of a tablet, (including a suspension tablet, a fast-melt tablet, a bite-disintegration tablet, a rapid-disintegration tablet, an effervescent tablet, or a caplet), a pill, a powder (including a sterile packaged powder, a dispensable powder, or an effervescent powder) a capsule (including both
soft or hard capsules, e.g., capsules made from animal-derived gelatin or plant-derived HPMC, or "sprinkle capsules"), solid dispersion, solid solution, bioerodible dosage form, controlled release formulations, pulsatile release dosage forms, multiparticulate dosage forms, pellets, granules, or an aerosol. In other embodiments, the pharmaceutical formulation is in the form of a powder. In still other embodiments, the pharmaceutical formulation is in the form of a tablet, including but not limited to, a fast-melt tablet. Additionally, pharmaceutical formulations described herein may be administered as a single capsule or in multiple capsule dosage form. In some embodiments, the pharmaceutical formulation is administered in two, or three, or four, capsules or tablets.

[00252] In some embodiments, solid dosage forms, e.g., tablets, effervescent tablets, and capsules, are prepared by mixing particles of ibrutinib and/or an anticancer agent, with one or more pharmaceutical excipients to form a bulk blend composition. When referring to these bulk blend compositions as homogeneous, it is meant that the particles of ibrutinib and/or an anticancer agent, are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms, such as tablets, pills, and capsules. The individual unit dosages may also include film coatings, which disintegrate upon oral ingestion or upon contact with diluent. These formulations can be manufactured by conventional pharmacological techniques.

[00253] Conventional pharmacological techniques include, e.g., one or a combination of methods: (1) dry mixing, (2) direct compression, (3) milling, (4) dry or non-aqueous granulation, (5) wet granulation, or (6) fusion. See, e.g., Lachman et al., The Theory and Practice of Industrial Pharmacy (1986). Other methods include, e.g., spray drying, pan coating, melt granulation, granulation, fluidized bed spray drying or coating (e.g., wurster coating), tangential coating, top spraying, tableting, extruding and the like.

[00254] In some embodiments, the pharmaceutical solid dosage forms described herein include a compound described herein and one or more pharmaceutically acceptable additives such as a compatible carrier, binder, filling agent, suspending agent, flavoring agent, sweetening agent, disintegrating agent, dispersing agent, surfactant, lubricant, colorant, diluent, solubilizer, moistening agent, plasticizer, stabilizer, penetration enhancer, wetting agent, anti-foaming agent, antioxidant, preservative, or one or more combination thereof. In still other aspects, using standard coating procedures, such as those described in Remington's Pharmaceutical Sciences, 20th Edition (2000), a film coating is provided around the formulation of ibrutinib and/or an anticancer agent. In another embodiment, some or all of the particles of ibrutinib and/or an anticancer agent, are not microencapsulated and are uncoated.
[00255] Suitable carriers for use in the solid dosage forms described herein include, but are not limited to, acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, pregelatinized starch, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose acetate stearate, sucrose, microcrystalline cellulose, lactose, mannitol and the like.

[00256] Suitable filling agents for use in the solid dosage forms described herein include, but are not limited to, lactose, calcium carbonate, calcium phosphate, dibasic calcium phosphate, calcium sulfate, microcrystalline cellulose, cellulose powder, dextrose, dextrates, dextran, starches, pregelatinized starch, hydroxypropylmethylcellulose (HPMC), hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate stearate (HPMCAS), sucrose, xylitol, lactitol, mannitol, sorbitol, sodium chloride, polyethylene glycol, and the like.

[00257] In order to release the compound of ibrutinib, a proteasome inhibitor, and/or a steroid from a solid dosage form matrix as efficiently as possible, disintegrants are often used in the formulation, especially when the dosage forms are compressed with binder. Disintegrants help rupturing the dosage form matrix by swelling or capillary action when moisture is absorbed into the dosage form. Suitable disintegrants for use in the solid dosage forms described herein include, but are not limited to, natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel® or sodium starch glycolate such as Promogel® or Exploatab®, a cellulose such as a wood product, methylcrystalline cellulose, e.g., Avicel®, Avicel® PH101, Avicel®PH102, Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose, a cross-linked starch such as sodium starch glycolate, a cross-linked polymer such as crospovidone, a cross-linked polyvinylpyrrolidone, alginate such as alginic acid or a salt of alginic acid such as sodium alginate, a clay such as Veegum® HV (magnesium aluminum silicate), a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanths, sodium starch glycolate, bentonite, a natural sponge, a surfactant, a resin such as a cation-exchange resin, citrus pulp, sodium lauryl sulfate, sodium lauryl sulfate in combination starch, and the like.

[00258] Binders impart cohesiveness to solid oral dosage form formulations: for powder filled capsule formulation, they aid in plug formation that can be filled into soft or hard shell capsules.
and for tablet formulation, they ensure the tablet remaining intact after compression and help assure blend uniformity prior to a compression or fill step. Materials suitable for use as binders in the solid dosage forms described herein include, but are not limited to, carboxymethylcellulose, methylcellulose (e.g., Methocel®), hydroxypropylmethylcellulose (e.g., Hypromellose USP Pharmacoat-603, hydroxypropylmethylcellulose acetate stearate (Aqoate HS-LF and HS), hydroxyethylcellulose, hydroxypropylcellulose (e.g., Klucel®, ethylcellulose (e.g., Ethocel®), and microcrystalline cellulose (e.g., Avicel®), microcrystalline dextrrose, amyllose, magnesium aluminum silicate, polysaccharide acids, bentonites, gelatin, polyvinylpyrrolidone/vinyl acetate copolymer, crospovidone, povidone, starch, pregelatinized starch, tragacanth, dextrin, a sugar, such as sucrose (e.g., Dipac®), glucose, dextrose, molasses, mannitol, sorbitol, xylitol (e.g., Xylitabs®), lactose, a natural or synthetic gum such as acacia, tragacanth, ghatti gum, mucilage of isapol husks, starch, polyvinylpyrrolidone (e.g., Povidone® CL, Kollidon® CL, Polyplasdone® XL-10, and Povidone® K-12), larch arabagalactan, Veegum®, polyethylene glycol, waxes, sodium alginate, and the like.

[00259] In general, binder levels of 20-70% are used in powder-filled gelatin capsule formulations. Binder usage level in tablet formulations varies whether direct compression, wet granulation, roller compaction, or usage of other excipients such as fillers which itself can act as moderate binder. Formulators skilled in art can determine the binder level for the formulations, but binder usage level of up to 70% in tablet formulations is common.

[00260] Suitable lubricants or glidants for use in the solid dosage forms described herein include, but are not limited to, stearic acid, calcium hydroxide, talc, corn starch, sodium stearyl fumerate, alkali-metal and alkaline earth metal salts, such as aluminum, calcium, magnesium, zinc, stearic acid, sodium stearates, magnesium stearate, zinc stearate, waxes, Stearowet®, boric acid, sodium benzoate, sodium acetate, sodium chlorate, leucine, a polyethylene glycol or a methoxypolyethylene glycol such as Carbowax™, PEG 4000, PEG 5000, PEG 6000, propylene glycol, sodium oleate, glycerclyl behenate, glycerclyl palmitostearate, glycerclyl benzoate, magnesium or sodium lauryl sulfate, and the like.

[00261] Suitable diluents for use in the solid dosage forms described herein include, but are not limited to, sugars (including lactose, sucrose, and dextrose), polysaccharides (including dextrates and maltodextrin), polyols (including mannitol, xylitol, and sorbitol), cyclodextrins and the like.

[00262] The term "non water-soluble diluent" represents compounds typically used in the formulation of pharmaceuticals, such as calcium phosphate, calcium sulfate, starches, modified
starches and microcrystalline cellulose, and microcellulose (e.g., having a density of about 0.45 g/cm$^3$, e.g., Avicel, powdered cellulose), and talc.

[00263] Suitable wetting agents for use in the solid dosage forms described herein include, for example, oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, quaternary ammonium compounds (e.g., Polyquat 10®), sodium oleate, sodium lauryl sulfate, magnesium stearate, sodium docusate, triacetin, vitamin E TPGS and the like.

[00264] Suitable surfactants for use in the solid dosage forms described herein include, for example, sodium lauryl sulfate, sorbitan monooleate, polyoxyethylene sorbitan monooleate, polysorbates, poloxamers, bile salts, glyceryl monostearate, copolymers of ethylene oxide and propylene oxide, e.g., Pluronic® (BASF), and the like.

[00265] Suitable suspending agents for use in the solid dosage forms described here include, but are not limited to, polyvinylpyrrolidone, e.g., polyvinylpyrrolidone K12, polyvinylpyrrolidone K17, polyvinylpyrrolidone K25, or polyvinylpyrrolidone K30, polyethylene glycol, e.g., the polyethylene glycol can have a molecular weight of about 300 to about 6000, or about 3350 to about 4000, or about 7000 to about 5400, or vinyl pyrrolidone/vinyl acetate copolymer (S630), sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, polysorbate-80, hydroxyethylcellulose, sodium alginate, gums, such as, e.g., gum tragacanth and gum acacia, guar gum, xanthans, including xanthan gum, sugars, cellulosics, such as, e.g., sodium carboxymethylcellulose, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, polysorbate-80, sodium alginate, polyethoxylated sorbitan monolaurate, polyethoxylated sorbitan monolaurate, povidone and the like.

[00266] Suitable antioxidants for use in the solid dosage forms described herein include, for example, e.g., butylated hydroxytoluene (BHT), sodium ascorbate, and tocopherol.

[00267] It should be appreciated that there is considerable overlap between additives used in the solid dosage forms described herein. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in solid dosage forms described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

[00268] In other embodiments, one or more layers of the pharmaceutical formulation are plasticized. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating
composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

Compressed tablets are solid dosage forms prepared by compacting the bulk blend of the formulations described above. In various embodiments, compressed tablets which are designed to dissolve in the mouth will include one or more flavoring agents. In other embodiments, the compressed tablets will include a film surrounding the final compressed tablet. In some embodiments, the film coating can provide a delayed release of ibrutinib or the second agent, from the formulation. In other embodiments, the film coating aids in patient compliance (e.g., Opadry® coatings or sugar coating). Film coatings including Opadry® typically range from about 1% to about 3% of the tablet weight. In other embodiments, the compressed tablets include one or more excipients.

In some embodiments, a capsule is prepared, for example, by placing the bulk blend of the formulation of ibrutinib or the second agent, described above, inside of a capsule. In some embodiments, the formulations (non-aqueous suspensions and solutions) are placed in a soft gelatin capsule. In other embodiments, the formulations are placed in standard gelatin capsules or non-gelatin capsules such as capsules comprising HPMC. In other embodiments, the formulation is placed in a sprinkle capsule, wherein the capsule may be swallowed whole or the capsule may be opened and the contents sprinkled on food prior to eating. In some embodiments, the therapeutic dose is split into multiple (e.g., two, three, or four) capsules. In some embodiments, the entire dose of the formulation is delivered in a capsule form.

In various embodiments, the particles of ibrutinib, a proteasome inhibitor, and/or a steroid, and one or more excipients are dry blended and compressed into a mass, such as a tablet, having a hardness sufficient to provide a pharmaceutical composition that substantially disintegrates within less than about 30 minutes, less than about 35 minutes, less than about 40 minutes, less than about 45 minutes, less than about 50 minutes, less than about 55 minutes, or less than about 60 minutes, after oral administration, thereby releasing the formulation into the gastrointestinal fluid.

In another aspect, dosage forms may include microencapsulated formulations. In some embodiments, one or more other compatible materials are present in the microencapsulation material. Exemplary materials include, but are not limited to, pH modifiers, erosion facilitators, anti-foaming agents, antioxidants, flavoring agents, and carrier materials such as binders.
suspending agents, disintegration agents, filling agents, surfactants, solubilizers, stabilizers, lubricants, wetting agents, and diluents.

[00273] Materials useful for the microencapsulation described herein include materials compatible with ibrutinib and/or an anticancer agent, which sufficiently isolate the compound of any of ibrutinib or an anticancer agent, from other non-compatible excipients. Materials compatible with compounds of any of ibrutinib or an anticancer agent, are those that delay the release of the compounds of any of ibrutinib or an anticancer agent, in vivo.

[00274] Exemplary microencapsulation materials useful for delaying the release of the formulations including compounds described herein, include, but are not limited to, hydroxypropyl cellulose ethers (HPC) such as Klucl® or Nisso HPC, low-substituted hydroxypropyl cellulose ethers (L-HPC), hydroxypropyl methyl cellulose ethers (HPMC) such as Seppifilm-LC, Pharmacoat®, Metolose SR, Methocel®-E, Opadry YS, PrimaFlo, Benecel MP824, and Benecel MP843, methylcellulose polymers such as Methocel®-A, hydroxypropyl methylcellulose acetate stearate Aqoat (HF-LS, HF-LG, HF-MS) and Metolose®, Ethylcellulosates (EC) and mixtures thereof such as E461, Ethocel®, Aqualon®-EC, Surelease®, Polyvinyl alcohol (PVA) such as Opadry AMB, hydroxyethylcelluloses such as Natrosol®, carboxymethylcelluloses and salts of carboxymethylcelluloses (CMC) such as Aqualon®-CMC, polyvinyl alcohol and polyethylene glycol co-polymers such as Kollicoat IR®, monoglycerides (Myverol), triglycerides (KLX), polyethylene glycols, modified food starch, acrylic polymers and mixtures of acrylic polymers with cellulose ethers such as Eudragit®EPO, Eudragit®L30D-55, Eudragit®FS 30D Eudragit®L100-55, Eudragit®L100, Eudragit® S100, Eudragit® RD100, Eudragit®E100, Eudragit®L12.5, Eudragit®S12.5, Eudragit®NE30D, and Eudragit® NE 40D, cellulose acetate phthalate, sepipfilms such as mixtures of HPMC and stearic acid, cyclodextrins, and mixtures of these materials.

[00275] In still other embodiments, plasticizers such as polyethylene glycols, e.g., PEG 300, PEG 400, PEG 600, PEG 1450, PEG 3350, and PEG 800, stearic acid, propylene glycol, oleic acid, and triacetin are incorporated into the microencapsulation material. In other embodiments, the microencapsulating material useful for delaying the release of the pharmaceutical compositions is from the USP or the National Formulary (NF). In yet other embodiments, the microencapsulation material is Klucl. In still other embodiments, the microencapsulation material is methocel.

[00276] Microencapsulated compounds of any of ibrutinib or an anticancer agent may be formulated by methods known by one of ordinary skill in the art. Such known methods include,
e.g., spray drying processes, spinning disk-solvent processes, hot melt processes, spray chilling methods, fluidized bed, electrostatic deposition, centrifugal extrusion, rotational suspension separation, polymerization at liquid-gas or solid-gas interface, pressure extrusion, or spraying solvent extraction bath. In addition to these, several chemical techniques, e.g., complex coacervation, solvent evaporation, polymer-polymer incompatibility, interfacial polymerization in liquid media, in situ polymerization, in-liquid drying, and desolvation in liquid media could also be used. Furthermore, in some embodiments, other methods such as roller compaction, extrusion/spheronization, coacervation, or nanoparticle coating are also used.

[00277] In one embodiment, the particles of compounds of any of ibrutinib or an anticancer agent are microencapsulated prior to being formulated into one of the above forms. In still another embodiment, some or most of the particles are coated prior to being further formulated by using standard coating procedures, such as those described in Remington’s Pharmaceutical Sciences, 20th Edition (2000).

[00278] In other embodiments, the solid dosage formulations of the compounds of any of ibrutinib and/or an anticancer agent are plasticized (coated) with one or more layers. Illustratively, a plasticizer is generally a high boiling point solid or liquid. Suitable plasticizers can be added from about 0.01% to about 50% by weight (w/w) of the coating composition. Plasticizers include, but are not limited to, diethyl phthalate, citrate esters, polyethylene glycol, glycerol, acetylated glycerides, triacetin, polypropylene glycol, polyethylene glycol, triethyl citrate, dibutyl sebacate, stearic acid, stearol, stearate, and castor oil.

[00279] In other embodiments, a powder including the formulations with a compound of any of ibrutinib and/or an anticancer agent, described herein, may be formulated to include one or more pharmaceutical excipients and flavors. Such a powder may be prepared, for example, by mixing the formulation and optional pharmaceutical excipients to form a bulk blend composition. Additional embodiments also include a suspending agent and/or a wetting agent. This bulk blend is uniformly subdivided into unit dosage packaging or multi-dosage packaging units.

[00280] In still other embodiments, effervescent powders are also prepared in accordance with the present disclosure. Effervescent salts have been used to disperse medicines in water for oral administration. Effervescent salts are granules or coarse powders containing a medicinal agent in a dry mixture, usually composed of sodium bicarbonate, citric acid and/or tartaric acid. When salts of the compositions described herein are added to water, the acids and the base react to liberate carbon dioxide gas, thereby causing “effervescence.” Examples of effervescent salts include, e.g., the following ingredients: sodium bicarbonate or a mixture of sodium bicarbonate
and sodium carbonate, citric acid and/or tartaric acid. Any acid-base combination that results in
the liberation of carbon dioxide can be used in place of the combination of sodium bicarbonate
and citric and tartaric acids, as long as the ingredients were suitable for pharmaceutical use and
result in a pH of about 6.0 or higher.

[00281] In some embodiments, the solid dosage forms described herein is formulated as enteric
coated delayed release oral dosage forms, i.e., as an oral dosage form of a pharmaceutical
composition as described herein which utilizes an enteric coating to affect release in the small
intestine of the gastrointestinal tract. In some embodiments, the enteric coated dosage form is a
compressed or molded or extruded tablet/mold (coated or uncoated) containing granules, powder,
pellets, beads or particles of the active ingredient and/or other composition components, which
are themselves coated or uncoated. In some embodiments, the enteric coated oral dosage form is
also be a capsule (coated or uncoated) containing pellets, beads or granules of the solid carrier or
the composition, which are themselves coated or uncoated.

[00282] In some embodiments, the term “delayed release” as used herein refers to the delivery
so that the release is accomplished at some generally predictable location in the intestinal tract
more distal to that which would have been accomplished if there had been no delayed release
alterations. In some embodiments the method for delay of release is coating. Any coatings should
be applied to a sufficient thickness such that the entire coating does not dissolve in the
gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is
expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an
enteric coating in the methods and compositions described herein to achieve delivery to the lower
gastrointestinal tract. In some embodiments the polymers described herein are anionic carboxylic
polymers. In other embodiments, the polymers and compatible mixtures thereof, and some of
their properties, include, but are not limited to:

[00283] Shellac, also called purified lac, a refined product obtained from the resinous secretion
of an insect. This coating dissolves in media of pH >7;

[00284] Acrylic polymers. The performance of acrylic polymers (primarily their solubility in
biological fluids) can vary based on the degree and type of substitution. Examples of suitable
acrylic polymers include methacrylic acid copolymers and ammonium methacrylate copolymers.
The Eudragit series E, L, S, RL, RS and NE (Rohm Pharma) are available as solubilized in
organic solvent, aqueous dispersion, or dry powders. The Eudragit series RL, NE, and RS are
insoluble in the gastrointestinal tract but are permeable and are used primarily for colonic
targeting. The Eudragit series E dissolve in the stomach. The Eudragit series L, L-30D and S are insoluble in stomach and dissolve in the intestine;

[00285] Cellulose Derivatives. Examples of suitable cellulose derivatives are: ethyl cellulose; reaction mixtures of partial acetate esters of cellulose with phthalic anhydride. The performance can vary based on the degree and type of substitution. Cellulose acetate phthalate (CAP) dissolves in pH > 6. Aquateric (FMC) is an aqueous based system and is a spray dried CAP psuedolatex with particles < 1 μm. Other components in Aquateric can include pluronics, Tweens, and acetylated monoglycerides. Other suitable cellulose derivatives include: cellulose acetate trimellitate (Eastman); methylcellulose (Pharmacoat, Methocel); hydroxypropylmethyl cellulose phthalate (HPMCP); hydroxypropylmethyl cellulose succinate (HPMCS); and hydroxypropylmethylcellulose acetate succinate (e.g., AQOAT (Shin Etsu)). The performance can vary based on the degree and type of substitution. For example, HPMCP such as, HP-50, HP-55, HP-55S, HP-55F grades are suitable. The performance can vary based on the degree and type of substitution. For example, suitable grades of hydroxypropylmethyl cellulose acetate succinate include, but are not limited to, AS-LG (LF), which dissolves at pH 5, AS-MG (MF), which dissolves at pH 5.5, and AS-HG (FIF), which dissolves at higher pH. These polymers are offered as granules, or as fine powders for aqueous dispersions; Poly Vinyl Acetate Phthalate (PVAP). PVAP dissolves in pH > 5, and it is much less permeable to water vapor and gastric fluids.

[00286] In some embodiments, the coating can, and usually does, contain a plasticizer and possibly other coating excipients such as colorants, talc, and/or magnesium stearate, which are well known in the art. Suitable plasticizers include triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflex A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, anionic carboxylic acrylic polymers usually will contain 10-25% by weight of a plasticizer, especially dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. Conventional coating techniques such as spray or pan coating are employed to apply coatings. The coating thickness must be sufficient to ensure that the oral dosage form remains intact until the desired site of topical delivery in the intestinal tract is reached.

[00287] Colorants, detackifiers, surfactants, antifoaming agents, lubricants (e.g., carnuba wax or PEG) may be added to the coatings besides plasticizers to solubilize or disperse the coating material, and to improve coating performance and the coated product.

[00288] In other embodiments, the formulations described herein, which include ibrutinib and/or an anticancer agent, are delivered using a pulsatile dosage form. A pulsatile dosage form is
capable of providing one or more immediate release pulses at predetermined time points after a controlled lag time or at specific sites. Many other types of controlled release systems known to those of ordinary skill in the art and are suitable for use with the formulations described herein. Examples of such delivery systems include, e.g., polymer-based systems, such as polylactic and polyglycolic acid, ployanhydrides and polycaprolactone; porous matrices, nonpolymer-based systems that are lipids, including sterols, such as cholesterol, cholesterol esters and fatty acids, or neutral fats, such as mono-, di- and triglycerides; hydrogel release systems; silastic systems; peptide-based systems; wax coatings, bioerodible dosage forms, compressed tablets using conventional binders and the like. See, e.g., Liberman et al., Pharmaceutical Dosage Forms, 2 Ed., Vol. 1, pp. 209-214 (1990); Singh et al., Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 751-753 (2002); U.S. Pat. Nos. 4,327,725, 4,624,848, 4,968,509, 5,461,140, 5,456,923, 5,516,527, 5,622,721, 5,686,105, 5,700,410, 5,977,175, 6,465,014 and 6,932,983.

[00289] In some embodiments, pharmaceutical formulations are provided that include particles of ibrutinib and/or an anticancer agent, described herein and at least one dispersing agent or suspending agent for oral administration to a subject. The formulations may be a powder and/or granules for suspension, and upon admixture with water, a substantially uniform suspension is obtained.

[00290] In some embodiments, liquid formulation dosage forms for oral administration are aqueous suspensions selected from the group including, but not limited to, pharmaceutically acceptable aqueous oral dispersions, emulsions, solutions, elixirs, gels, and syrups. See, e.g., Singh et al., Encyclopedia of Pharmaceutical Technology, 2nd Ed., pp. 754-757 (2002). In addition the liquid dosage forms may include additives, such as: (a) disintegrating agents; (b) dispersing agents; (c) wetting agents; (d) at least one preservative, (e) viscosity enhancing agents, (f) at least one sweetening agent, and (g) at least one flavoring agent. In some embodiments, the aqueous dispersions can further include a crystalline inhibitor.

[00291] In some embodiments, the aqueous suspensions and dispersions described herein remain in a homogenous state, as defined in The USP Pharmacists’ Pharmacopeia (2005 edition, chapter 905), for at least 4 hours. The homogeneity should be determined by a sampling method consistent with regard to determining homogeneity of the entire composition. In one embodiment, an aqueous suspension can be re-suspended into a homogenous suspension by physical agitation lasting less than 1 minute. In another embodiment, an aqueous suspension is re-suspended into a homogenous suspension by physical agitation lasting less than 45 seconds. In yet another embodiment, an aqueous suspension is re-suspended into a homogenous suspension
by physical agitation lasting less than 30 seconds. In still another embodiment, no agitation is necessary to maintain a homogeneous aqueous dispersion.

[00292] Examples of disintegrating agents for use in the aqueous suspensions and dispersions include, but are not limited to, a starch, e.g., a natural starch such as corn starch or potato starch, a pregelatinized starch such as National 1551 or Amijel®, or sodium starch glycolate such as Promogel® or Explotab®; a cellulose such as a wood product, methylcellulose, e.g., Avicel®, Avicel® PH101, Avicel® PH102, Avicel® PHI 05, Elcema® P100, Emcocel®, Vivacel®, Ming Tia®, and Solka-Floc®, methylcellulose, croscarmellose, or a cross-linked cellulose, such as cross-linked sodium carboxymethylcellulose (Ac-Di-Sol®), cross-linked carboxymethylcellulose, or cross-linked croscarmellose; a cross-linked starch such as sodium starch glycolate; a cross-linked polymer such as crospovidone; a cross-linked polyvinylpyrrolidone; alginate such as alginic acid or a salt of alginic acid such as sodium alginate; a clay such as Veegum® HV (magnesium aluminum silicate); a gum such as agar, guar, locust bean, Karaya, pectin, or tragacanth; sodium starch glycolate; bentonite; a natural sponge; a surfactant; a resin such as a cation-exchange resin; citrus pulp; sodium lauryl sulfate; sodium lauryl sulfate in combination starch; and the like.

[00293] In some embodiments, the dispersing agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, for example, hydrophilic polymers, electrolytes, Tween® 60 or 80, PEG, polyvinylpyrrolidone (PVP; commercially known as Plasdone®), and the carbohydrate-based dispersing agents such as, for example, hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L), hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g., HPMC K100, HPMC K4M, HPMC K15M, and HPMC K100M), carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethyl-cellulose phthalate, hydroxypropylmethyl-cellulose acetate stearate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol (PVA), polyvinylpyrrolidone/vinyl acetate copolymer (Plasdone®, e.g., S-630), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol), poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); and poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Corporation, Parsippany, N.J.)). In other embodiments, the dispersing agent is selected from a group not comprising one of the following agents: hydrophilic polymers; electrolytes;
Tween® 60 or 80; PEG; polyvinylpyrrolidone (PVP); hydroxypropylcellulose and hydroxypropyl cellulose ethers (e.g., HPC, HPC-SL, and HPC-L); hydroxypropyl methylcellulose and hydroxypropyl methylcellulose ethers (e.g., HPMC K100, HPMC K4M, HPMC K15M, HPMC K100M, and PharmacoatUSP 2910 (Shin-Etsu)); carboxymethylcellulose sodium; methylcellulose; hydroxyethylcellulose; hydroxypropylmethylcellulose phthalate; hydroxypropylmethyl-cellulose acetate stearate; non-crystalline cellulose; magnesium aluminum silicate; triethanolamine; polyvinyl alcohol (PVA); 4-(l, 1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde; poloxamers (e.g., Pluronics F68®, F88®, and F108®, which are block copolymers of ethylene oxide and propylene oxide); or poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®).

[00294] Wetting agents suitable for the aqueous suspensions and dispersions described herein are known in the art and include, but are not limited to, cetyl alcohol, glycerol monostearate, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens® such as e.g., Tween 20® and Tween 80® (ICI Specialty Chemicals)), and polyethylene glycols (e.g., Carbowaxes 3350® and 1450®, and Carbopol 934® (Union Carbide)), oleic acid, glyceryl monostearate, sorbitan monooleate, sorbitan monolaurate, triethanolamine oleate, polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan monolaurate, sodium oleate, sodium lauryl sulfate, sodium docusate, tricetin, vitamin E TPGS, sodium taurocholate, simethicone, phosphotidylcholine and the like.

[00295] Suitable preservatives for the aqueous suspensions or dispersions described herein include, for example, potassium sorbate, parabens (e.g., methylparaben and propylparaben), benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl alcohol or benzyl alcohol, phenolic compounds such as phenol, or quaternary compounds such as benzalkonium chloride. Preservatives, as used herein, are incorporated into the dosage form at a concentration sufficient to inhibit microbial growth.

[00296] Suitable viscosity enhancing agents for the aqueous suspensions or dispersions described herein include, but are not limited to, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, Plasdon® S-630, carborner, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the viscosity enhancing agent will depend upon the agent selected and the viscosity desired.

[00297] Examples of sweetening agents suitable for the aqueous suspensions or dispersions described herein include, for example, acacia syrup, acesulfame K, alitame, anise, apple, aspartame, banana, Bavarian cream, berry, black currant, butterscotch, calcium citrate, camphor,
caramel, cherry, cherry cream, chocolate, cinnamon, bubble gum, citrus, citrus punch, citrus cream, cotton candy, cocoa, cola, cool cherry, cool citrus, cyclamate, cynamate, dextrose, eucalyptus, eugenol, fructose, fruit punch, ginger, glycyrrhizinate, glycyrrhiza (licorice) syrup, grape, grapefruit, honey, isomalt, lemon, lime, lemon cream, monoammonium glycyrrhizinate (MagnaSweet®), maltol, mannitol, maple, marshmallow, menthol, mint cream, mixed berry, neohesperidine DC, neotame, orange, pear, peach, peppermint, peppermint cream, Prosweet® Powder, raspberry, root beer, rum, saccharin, safrole, sorbitol, spearmint, spearmint cream, strawberry, strawberry cream, stevia, sucralose, sucrose, sodium saccharin, saccharin, aspartame, acesulfame potassium, mannitol, talin, sucralose, sorbitol, swiss cream, tagatose, tangerine, thaumatin, tutti fruitti, vanilla, walnut, watermelon, wild cherry, wintergreen, xylitol, or any combination of these flavoring ingredients, e.g., anise-menthol, cherry-anise, cinnamon-orange, cherry-cinnamon, chocolate-mint, honey-lemon, lemon-lime, lemon-mint, menthol-eucalyptus, orange-cream, vanilla-mint, and mixtures thereof. In one embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.001% to about 1.0% the volume of the aqueous dispersion. In another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.005% to about 0.5% the volume of the aqueous dispersion. In yet another embodiment, the aqueous liquid dispersion can comprise a sweetening agent or flavoring agent in a concentration ranging from about 0.01% to about 1.0% the volume of the aqueous dispersion.

[00298] In addition to the additives listed above, the liquid formulations can also include inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, sodium lauryl sulfate, sodium doccucate, cholesterol, cholesterol esters, taurocholic acid, phosphatidylcholine, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

[00299] In some embodiments, the pharmaceutical formulations described herein can be self-emulsifying drug delivery systems (SEDDS). Emulsions are dispersions of one immiscible phase in another, usually in the form of droplets. Generally, emulsions are created by vigorous mechanical dispersion. SEDDS, as opposed to emulsions or microemulsions, spontaneously form emulsions when added to an excess of water without any external mechanical dispersion or agitation. An advantage of SEDDS is that only gentle mixing is required to distribute the droplets
throughout the solution. Additionally, water or the aqueous phase can be added just prior to administration, which ensures stability of an unstable or hydrophobic active ingredient. Thus, the SEDDS provides an effective delivery system for oral and parenteral delivery of hydrophobic active ingredients. SEDDS may provide improvements in the bioavailability of hydrophobic active ingredients. Methods of producing self-emulsifying dosage forms are known in the art and include, but are not limited to, for example, U.S. Pat. Nos. 5,858,401, 6,667,048, and 6,960,563, each of which is specifically incorporated by reference.

[00300] It is to be appreciated that there is overlap between the above-listed additives used in the aqueous dispersions or suspensions described herein, since a given additive is often classified differently by different practitioners in the field, or is commonly used for any of several different functions. Thus, the above-listed additives should be taken as merely exemplary, and not limiting, of the types of additives that can be included in formulations described herein. The amounts of such additives can be readily determined by one skilled in the art, according to the particular properties desired.

**Intranasal Formulations**

[00301] Intranasal formulations are known in the art and are described in, for example, U.S. Pat. Nos. 4,476,116, 5,116,817 and 6,391,452, each of which is specifically incorporated by reference. Formulations that include ibrutinib and/or an anticancer agent, which are prepared according to these and other techniques well-known in the art are prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, fluorocarbons, and/or other solubilizing or dispersing agents known in the art. See, for example, Ansel, H. C. et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, Sixth Ed. (1995). Preferably these compositions and formulations are prepared with suitable nontoxic pharmaceutically acceptable ingredients. These ingredients are known to those skilled in the preparation of nasal dosage forms and some of these can be found in REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 21st edition, 2005, a standard reference in the field. The choice of suitable carriers is highly dependent upon the exact nature of the nasal dosage form desired, e.g., solutions, suspensions, ointments, or gels. Nasal dosage forms generally contain large amounts of water in addition to the active ingredient. Minor amounts of other ingredients such as pH adjusters, emulsifiers or dispersing agents, preservatives, surfactants, gelling agents, or buffering and other stabilizing and solubilizing agents may also be present. The nasal dosage form should be isotonic with nasal secretions.
[00302] For administration by inhalation described herein may be in a form as an aerosol, a mist or a powder. Pharmaceutical compositions described herein are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound described herein and a suitable powder base such as lactose or starch.

Buccal Formulations

[00303] Buccal formulations may be administered using a variety of formulations known in the art. For example, such formulations include, but are not limited to, U.S. Pat. Nos. 4,229,447, 4,596,795, 4,755,386, and 5,739,136, each of which is specifically incorporated by reference. In addition, the buccal dosage forms described herein can further include a bioerodible (hydrolysable) polymeric carrier that also serves to adhere the dosage form to the buccal mucosa. The buccal dosage form is fabricated so as to erode gradually over a predetermined time period, wherein the delivery is provided essentially throughout. Buccal drug delivery, as will be appreciated by those skilled in the art, avoids the disadvantages encountered with oral drug administration, e.g., slow absorption, degradation of the active agent by fluids present in the gastrointestinal tract and/or first-pass inactivation in the liver. With regard to the bioerodible (hydrolysable) polymeric carrier, it will be appreciated that virtually any such carrier can be used, so long as the desired drug release profile is not compromised, and the carrier is compatible with ibritinib and/or an anticancer agent, and any other components that may be present in the buccal dosage unit. Generally, the polymeric carrier comprises hydrophilic (water-soluble and water-swellable) polymers that adhere to the wet surface of the buccal mucosa. Examples of polymeric carriers useful herein include acrylic acid polymers and co, e.g., those known as "carbomers" (Carbopol®, which may be obtained from B.F. Goodrich, is one such polymer). Other components may also be incorporated into the buccal dosage forms described herein include, but are not limited to, disintegrants, diluents, binders, lubricants, flavoring, colorants, preservatives, and the like. For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, or gels formulated in a conventional manner.
Transdermal Formulations

[00304] Transdermal formulations described herein may be administered using a variety of devices which have been described in the art. For example, such devices include, but are not limited to, U.S. Pat. Nos. 3,598,122, 3,598,123, 3,710,795, 3,731,683, 3,742,951, 3,814,097, 3,921,636, 3,972,995, 3,993,072, 3,993,073, 3,996,934, 4,031,894, 4,060,084, 4,069,307, 4,077,407, 4,201,211, 4,230,105, 4,292,299, 4,292,303, 5,336,168, 5,665,378, 5,837,280, 5,869,090, 6,923,983, 6,929,801 and 6,946,144, each of which is specifically incorporated by reference in its entirety.

[00305] The transdermal dosage forms described herein may incorporate certain pharmaceutically acceptable excipients which are conventional in the art. In one embodiment, the transdermal formulations described herein include at least three components: (1) a formulation of a compound of ibrutinib and an anticancer agent; (2) a penetration enhancer; and (3) an aqueous adjuvant. In addition, transdermal formulations can include additional components such as, but not limited to, gelling agents, creams and ointment bases, and the like. In some embodiments, the transdermal formulation can further include a woven or non-woven backing material to enhance absorption and prevent the removal of the transdermal formulation from the skin. In other embodiments, the transdermal formulations described herein can maintain a saturated or supersaturated state to promote diffusion into the skin.

[00306] Formulations suitable for transdermal administration of compounds described herein may employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. Still further, transdermal delivery of the compounds described herein can be accomplished by means of iontophoretic patches and the like. Additionally, transdermal patches can provide controlled delivery of ibrutinib, a proteasome inhibitor, and a steroid. The rate of absorption can be slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. Conversely, absorption enhancers can be used to increase absorption. An absorption enhancer or carrier can include absorbable pharmaceutically acceptable solvents to assist passage through the skin. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.
Injectable Formulations

[00307] Formulations that include a compound of ibrutinib and/or an anticancer agent, suitable for intramuscular, subcutaneous, or intravenous injection may include physiologically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propylene glycol, polyethylene-glycol, glycerol, cremophor and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants. Formulations suitable for subcutaneous injection may also contain additives such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

[00308] For intravenous injections, compounds described herein may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. For other parenteral injections, appropriate formulations may include aqueous or nonaqueous solutions, preferably with physiologically compatible buffers or excipients. Such excipients are generally known in the art.

[00309] Parenteral injections may involve bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The pharmaceutical composition described herein may be in a form suitable for parenteral injection as a sterile suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or
triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

Other Formulations

[00310] In certain embodiments, delivery systems for pharmaceutical compounds are employed, such as, for example, liposomes and emulsions. In certain embodiments, compositions provided herein are also include an mucoadhesive polymer, selected from among, for example, carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[00311] In some embodiments, the compounds described herein are administered topically and can be formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compounds can contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[00312] In some embodiments, the compounds described herein are also be formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[00313] In some embodiments, the pharmaceutical compositions are formulated such that the amount of the covalent Btk inhibitor (e.g., an irreversible covalent Btk inhibitor, e.g., ibrutinib) in each unit dosage form is about 140 mg per.

Kits/Article of Manufacture

[00314] Disclosed herein, in certain embodiments, are kits and articles of manufacture for use with one or more methods described herein. Such kits include a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein.
Suitable containers include, for example, bottles, vials, syringes, and test tubes. In one embodiment, the containers are formed from a variety of materials such as glass or plastic.

[00315] The articles of manufacture provided herein contain packaging materials. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, bags, containers, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment.

[00316] For example, the container(s) include ibrutinib, optionally in a composition or in combination with an immunomodulatory agent and a steroid as disclosed herein. Such kits optionally include an identifying description or label or instructions relating to its use in the methods described herein.

[00317] A kit typically includes labels listing contents and/or instructions for use, and package inserts with instructions for use. A set of instructions will also typically be included.

[00318] In one embodiment, a label is on or associated with the container. In one embodiment, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself; a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In one embodiment, a label is used to indicate that the contents are to be used for a specific therapeutic application. The label also indicates directions for use of the contents, such as in the methods described herein.

[00319] In certain embodiments, the pharmaceutical compositions are presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack, for example, contains metal or plastic foil, such as a blister pack. In one embodiment, the pack or dispenser device is accompanied by instructions for administration. In one embodiment, the pack or dispenser is also accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In one embodiment, compositions containing a compound provided herein formulated in a compatible pharmaceutical carrier are also prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.
EXAMPLES
[00320] These examples are provided for illustrative purposes only and not to limit the scope of
the claims provided herein.

Example 1: Combination Treatment of Ibrutinib in Combination with Pomalidomide
(Pomalyst™) and Dexamethasone in Patients with Relapsed or Relapsed and Refractory
Multiple Myeloma (Phase l/2b Study)
[00321] Bruton's tyrosine kinase (BTK) is an enzyme overexpressed in malignant plasma cells
and which may positively regulate the myeloma stem cell-like population.

Study Drugs
[00322] Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration.
[00323] Pomalidomide will be supplied as hard gelatin capsules for PO administration.
[00324] Dexamethasone will be available as scored tablets in various strengths for PO
administration.

Phase 1 Objectives:
[00325] Primary Objectives: To determine the maximum tolerated dose (MTD)/maximum
administered dose (MAD) and the Phase 2b dose of the ibritnib, pomalidomide and
dexamethasone combination. Secondary Objectives: Overall response rate (ORR) defined as >PR
according to the International Myeloma Working Group (IMWG) response criteria; duration of
response (DOR); the clinical benefit rate (CBR) and its duration, defined as >MR according to
the IMWG response criteria; to evaluate the pharmacokinetics (PK) of ibritnib and
pomalidomide when given in combination with dexamethasone.

Phase 2b Objectives
[00326] Primary Objective: To evaluate the effect of ibritnib in combination with
pomalidomide and dexamethasone compared to placebo in combination with pomalidomide and
dexamethasone on progression-free survival (PFS), as assessed by the Independent Review
Committee (IRC), in subjects with relapsed/refractory MM. Secondary Objectives: To compare
the treatment arms as assessed by both IRC and investigator in terms of the following: ORR
(>PR; according to IMWG); DOR (Duration of Response); CBR (>MR according to IMWG and
its duration); Overall survival (OS); Time-to-progression (TTP). In addition, other objectives
include"
  • To evaluate the safety and tolerability of ibritnib in combination with pomalidomide and
dexamethasone.
To evaluate the pharmacokinetics (PK) of ibrutinib and pomalidomide when given in combination with dexamethasone.

Exploratory Objectives:
- To evaluate potential prognostic and predictive biomarkers relative to treatment outcomes (selected sites for Phase 1 and all sites for Phase 2b).
- To assess biomarkers, (including gene expression profiles [GEP], secreted proteins, bone turnover and/or immunophenotypic) in subjects with relapsed/refractory MM (selected sites for Phase 1 and all sites for Phase 2b).

To evaluate and compare the treatment arms in terms of the following:
- Time-to-next-treatment (TTNT) (Phase 2b).
- Patient-reported outcomes (PROs) and disease-related symptoms according to European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Multiple Myeloma (EORTC QLQ-MY20) and Euro QoL 5 dimensions questionnaire (EQ-5D-5L) (Phase 2b).

**Open-Label Sub Study Treatment Arm C (Phase 2b)**

Objectives: To evaluate the efficacy and safety of ibrutinib in combination with pomalidomide and dexamethasone in subjects who either have: Less than a partial response (<PR) following at least 112 days (4 x 28 day cycles) of pomalidomide and dexamethasone (regimen must not have included other anti-cancer agents) and are without evidence of progressive disease (PD); Disease progression following an initial confirmed response of MR or better to the combination of pomalidomide and dexamethasone (regimen must not have included other anti-cancer agents).

**Study Design**

This study will be conducted in two Phases:

Phase 1 will be an open-label, national, multicenter dose-finding study of the ibrutinib, pomalidomide and dexamethasone combination in subjects with relapsed/refractory MM who have received at least two prior lines of therapy, including lenalidomide (LEN) and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of completion of the most recent treatment regimen.

Up to 36 patients will be enrolled in order to determine the MTD/MAD and Phase 2b dose.

In the dose finding portion of the study, up to four cohorts may be explored. The study will follow a 6+3 dose de-escalation design. In Cohort 1, 6 subjects will be administered ibrutinib
840 mg PO daily in combination with pomalidomide 4mg PO Days 1-21 and dexamethasone (age-adjusted dose) PO on Days 1, 8, 15 and 22 of a 28-day cycle. The dose limiting toxicity (DLT) observation period will end following Cycle 2 Day 1 pre-dose assessments. If 2 subjects within the initial cohort of 6 subjects experience a DLT, an additional 3 subjects will be enrolled at the same dose level. If 3 or more of the initial 6 subjects or the 9 subjects experience a DLT, dose de-escalation will occur. If subject incidence of DLTs during the DLT observation period of study treatment is ≤33% (ie ≤1 of 6 or ≤2 of 9), this dose level will be considered safe to proceed to Phase 2 and defined as the Phase 2b dose.

[00332] **Phase 2b** will be conducted as a randomized, double-blind, international, multicenter study of ibrutinib or placebo in combination with pomalidomide and dexamethasone in subjects with relapsed/refractory MM who have received at least two prior lines of therapy, including lenalidomide (LEN) and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of completion of the most recent treatment regimen.

[00333] Approximately 195 subjects will be randomized 1:1 between Arm A (ibrutinib in combination with pomalidomide and dexamethasone) and Arm B (placebo in combination with pomalidomide and dexamethasone) and stratified according to:

- 2-3 vs. ≥ 4 prior therapies
- Last regimen (no IMiD/PI vs. IMiD or PI vs. EViD and PI)
- Age: ≤75 vs. > 75 years

[00334] **Open-Label Sub-Study Treatment Arm C (Phase 2b Only)** will enroll up to 22 subjects to receive open-label ibrutinib in combination with pomalidomide and dexamethasone. For more details regarding inclusion/exclusion criteria refer to

[00335] Subjects eligible for the randomized study portion (Arm A or Arm B) are not eligible for participation in the sub-study (Arm C).

**Inclusion Criteria**

**Disease Related**

1. Subjects with relapsed/refractory MM who have received at least two prior lines of therapy including LEN and either bortezomib or carfilzomib and have demonstrated disease progression on or within 60 days of the completion of the most recent treatment regimen.
• Subjects must have received at least 2 cycles of treatment with LEN and either bortezomib or carfilzomib at the approved dose and schedule (maintenance will be excluded).

2. Measurable disease defined by at least ONE of the following:

• Serum monoclonal protein (SPEP) ≥ 1 g/dL.
• Urine monoclonal protein (UPEP) ≥ 200 mg by 24 hour urine.

Laboratory

• Adequate hematologic function independent of platelet transfusion and growth factor support for at least 7 days prior to Screening and dosing (Phase 1) or randomization/enrollment (Phase 2b), with the exception of pegylated G-CSF (granulocyte-colony stimulating factor pegfilgrastim) and darbopoetin which require at least 14 days, defined as:
  o Absolute neutrophil count ≥1500 cells/mm$^3$ (1.5 x 10$^9$/L).
  o Platelet count >75,000 cells/mm$^3$ (75 x 10$^9$/L).
  o Hemoglobin ≥8.0 g/dL.
• Adequate hepatic and renal function defined as:
  o Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤3.0 x upper limit of normal (ULN).
  o Serum creatinine <3.0 mg/dL AND an estimated Creatinine Clearance ≥30 mL/min (Cockcroft-Gault).
  o Total Bilirubin ≤2.0 mg/dL.
  o PT/INR ≤1.5 x ULN and PTT (aPTT) ≤1.5 x ULN (unless on warfarin, then INR <3.0).

Demographic

• Men and women ≥ 18 years of age.
• Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

Ethical/Other
• **US/Canada Sites Only:** All study participants must be registered into the mandatory Pomalyst REMS™ or RevAid® program, and be willing and able to comply with the requirements of the Pomalyst REMS™ or RevAid® program as appropriate for the country in which the drug is being used.

• **US/Canada Sites Only:** Female subjects of childbearing potential (FCBP)\(^a\) must adhere to the scheduled pregnancy testing as required in the Pomalyst REMS™ or RevAid® program as appropriate for the country in which the drug is being used.

• **Ex-US Sites Only:** Female subjects of childbearing potential (FCBP)\(^a\) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mR7/mL within 10 - 14 days and again within 24 hours prior to starting Cycle 1 of pomalidomide. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

• **US/Canada Sites Only:** Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.

• **Ex-US Sites Only:** Male subjects must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

• FCBP \(^a\) and male subjects who are sexually active must use **TWO acceptable methods** of birth control, one highly effective method of birth control plus one additional effective method of birth control for at least 28 days prior to study treatment and during the study treatment period. For female and male subjects, these birth control requirements must be adhered to for 90 days after the last dose of ibrutinib and pomalidomide, whichever is later. Male subjects must agree to not donate sperm during the study treatment period and up to 90 days after the last dose of ibrutinib and pomalidomide, whichever is later.

[00336] A female of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point; or 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
Exclusion Criteria

Disease-Related

- Primary refractory disease defined as nonresponsive in patients who have never achieved a minimal response or better with any therapy.
- History of plasma cell leukemia, primary amyloidosis, POEMS syndrome within 12 months prior to first administration of study treatment.

Concurrent Conditions

- Recent prior chemotherapy
  - Alkylators (e.g., melphalan, cyclophosphamide) and/or anthracyclines ≤21 days prior to first administration of study treatment.
  - High dose corticosteroids, EVIIDs or proteasome inhibitors <14 days prior to first administration of study treatment.
  - Monoclonal antibody ≤6 weeks prior to first administration of study treatment.
- Prior exposure to Bruton's tyrosine kinase (BTK) inhibitors.
- Prior exposure to pomalidomide (except Treatment Arm C).
- History of serious hypersensitivity reactions to prior thalidomide, lenalidomide or pomalidomide.
- History of other malignancies, except:
  - Malignancy treated with curative intent and with no known active disease present for ≥3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.
- Peripheral neuropathy Grade ≥2 with pain at Screening.
- Concurrent systemic immunosuppressant therapy (e.g., cyclosporine A, tacrolimus, etc., or chronic administration of >20 mg/day of prednisone) within 28 days of the first dose of study treatment.
- Recent infection requiring systemic treatment that was completed < 7 days before the first dose of study treatment and/or uncontrolled active systemic infection.
- Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event, Grade ≤ 1 or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
- Known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- History of stroke or intracranial hemorrhage within 6 months prior to enrollment/randomization.
- Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment/randomization. Those who are PCR positive will be excluded.
- Major surgery within 4 weeks of first dose of study treatment.
- Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
- Currently active, clinically significant hepatic impairment (> mild hepatic impairment according to the Child Pugh classification.
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment/randomization.
- QTc ≥ 470 msec calculated using Fridericia formula (QTcF) at Screening.
- Unable to swallow capsules or malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction.
- Requires treatment with a strong cytochrome P450 (CYP) 3A inhibitor.
- Women who are pregnant or breast-feeding.
- Unwilling or unable to participate in all required study evaluations and procedures.
[00337] Unable to understand the purpose and risks of the study and to provide a signed and
dated informed consent form (ICF) and authorization to use protected health information (in
accordance with national and local subject privacy regulations).

Study Treatment

Phase 1:

[00338] In the dose finding portion of the study, up to four cohorts may be explored and
ibrutinib dose de-escalation will follow the 6+3 design for MTD/MAD and the Phase 2b dose
determination.

[00339] Ibrutinib will be administered orally daily at a designated dose and will be initiated on
Day 1 of the first cycle. Treatment will be continuous (without interruption) until disease
progression or unacceptable toxicity. Pomalidomide will be administered orally daily at a
designated dose on Days 1-21 of each 28-day (4 weeks) cycle until disease progression or
unacceptable toxicity. Dexamethasone will be administered orally (PO) once weekly at an age-
adjusted dose of either 40 mg or 20 mg on Days 1, 8, 15 and 22 of each 28-day (4 weeks) cycle
until disease progression or unacceptable toxicity.

Table 1:

<table>
<thead>
<tr>
<th>Cohort 1 (Dose Level 1)</th>
<th>Ibrutinib (PO)</th>
<th>Pomalidomide (PO)</th>
<th>Dexamethasone (PO)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>840 mg</td>
<td>4 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Cohort 2 (Dose Level -1)</td>
<td>700 mg</td>
<td>4 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Cohort 3 (Dose Level -2)</td>
<td>560 mg</td>
<td>4 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>Cohort 4 (Dose Level -3)</td>
<td>560 mg</td>
<td>3 mg</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

† Dose will be 20 mg weekly in those >75 years of age

Randomized Treatment

Treatment Arm A

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<table>
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<tbody>
<tr>
<td>Ibrutinib</td>
<td>PO daily</td>
</tr>
<tr>
<td>All cycles</td>
<td></td>
</tr>
</tbody>
</table>
Pomalidomide 4 mg PO daily Days 1-21
Dexamethasone Age-adjusted dose, PO on Days 1, 8, 15, and 22

<table>
<thead>
<tr>
<th>Treatment Arm B</th>
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<tbody>
<tr>
<td>All cycles</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>PO daily</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg PO daily Days 1-21</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Age-adjusted dose, PO on Days 1, 8, 15, and 22</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Open-label Sub-study</th>
<th></th>
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<tbody>
<tr>
<td>Treatment Arm C</td>
<td></td>
</tr>
<tr>
<td>All cycles</td>
<td></td>
</tr>
<tr>
<td>Ibrutinib</td>
<td>PO daily</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>4 mg PO daily Days 1-21</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Age-adjusted dose, PO on Days 1, 8, 15, and 22</td>
</tr>
</tbody>
</table>

[00340] If 3 or more subjects in Cohort 1 (see Table 1) experience a dose limiting toxicity (DLT), Cohort 2 will be enrolled. If 3 or more subjects in Cohort 2 experience a DLT, Cohort 3 will be enrolled. If 3 or more subjects in Cohort 3 experience a DLT, Cohort 4 will be enrolled. After the MTD/MAD of ibrutinib is defined and the Phase 2b dose determined, enrollment into Phase 2b will commence.

Phase 2b

[00341] Phase 2b will be conducted in a randomized, double-blind, international, multicenter study. Eligible patients will be randomized in a 1:1 ratio into 2 arms to receive either ibrutinib in combination with pomalidomide and dexamethasone (Treatment Arm A) or placebo in combination with pomalidomide and dexamethasone (Treatment Arm B). The dose of ibrutinib and pomalidomide in all arms will be based upon the MTD/MAD identified in Phase 1. All treatment arms will receive ibrutinib/placebo in combination with pomalidomide and dexamethasone on the same schedule as Phase 1 (28-day cycles) until IRC confirmed disease progression or unacceptable toxicity.
The examples and embodiments described herein are illustrative and various modifications or changes suggested to persons skilled in the art are to be included within this disclosure. As will be appreciated by those skilled in the art, the specific components listed in the above examples may be replaced with other functionally equivalent components, e.g., diluents, binders, lubricants, fillers, and the like.
CLAIMS

WHAT I CLAIMED IS:

1. A pharmaceutical combination comprising:
   a) ibrutinib;
   b) an immunomodulatory agent;
   c) dexamethasone.

2. The pharmaceutical combination of claim 1, wherein the combination is in separate dosage forms.

3. The pharmaceutical combination of claim 1, wherein the combination is in a combined dosage form.

4. The pharmaceutical combination of claim 1, wherein the combination is in three separate dosage forms.

5. The pharmaceutical combination of any one of the claims 1-4, wherein the combination is administered for the treatment of multiple myeloma.

6. The pharmaceutical combination of claim 5, wherein multiple myeloma is relapsed or refractory multiple myeloma.

7. The pharmaceutical combination of any one of claims 5-6, wherein multiple myeloma is metastasized multiple myeloma.

8. The pharmaceutical composition of any one of claims 1-7, wherein the immunomodulatory agent is pomalidomide.

9. A dosing regimen for the treatment of multiple myeloma in a subject in need thereof comprising administering to the subject a combination comprising ibrutinib, pomalidomide, and dexamethasone, wherein ibrutinib, pomalidomide, and dexamethasone are administered concurrently in at least one cycle.

10. The dosing regimen of claim 9, wherein each cycle comprises 28 days.

11. The dosing regimen of any one of claims 9-10, wherein pomalidomide is administered on days 1-21 of each cycle.

12. The dosing regimen of any one of claims 9-11, wherein dexamethasone is administered on days 1, 8, 15, and 22 of each cycle.

13. The dosing regimen of any one of claims 9-12, wherein ibrutinib is administered on days 1-28 of each cycle.
14. The dosing regimen of any one of claims 9-13, wherein pomalidomide is administered orally.
15. The dosing regimen of any one of claims 9-14, wherein pomalidomide is administered at a dosage of about 3 mg/day to about 5 mg/day.
16. The dosing regimen of any one of claims 9-15, wherein pomalidomide is administered at a dosage of about 4 mg/day.
17. The dosing regimen of any one of claims 9-16, wherein dexamethasone is administered orally.
18. The dosing regimen of any one of the claims 9-17, wherein dexamethasone is administered at a dosage of about 20 mg/day to about 60 mg/day.
19. The dosing regimen of any one of claims 9-18, wherein dexamethasone is administered at a dosage of about 40 mg/day.
20. The dosing regimen of any one of claims 9-19, wherein ibrutinib is administered orally.
21. The dosing regimen of any one of claims 9-20, wherein ibrutinib is administered once a day, two times per day, three times per day, four times per day, or five times per day.
22. The dosing regimen of any one of claims 9-21, wherein ibrutinib is administered at a dosage of about 560 mg/day to about 840 mg/day.
23. The dosing regimen of claim 22, wherein ibrutinib is administered at a dosage of about 700 mg/day.
24. The dosing regimen of any of claims 9-23, further comprising administration of an additional therapeutic agent.
25. The dosing regimen of any one of claims 9-24, wherein the multiple myeloma is relapsed or refractory multiple myeloma.
26. The dosing regimen of any one of claims 9-25, wherein the multiple myeloma is metastasized multiple myeloma.
27. The dosing regimen of any one of claims 9-26, wherein the subject has received at least one prior therapy.
28. The dosing regimen of any one of claims 9-27, wherein the subject has received at least two prior therapies.
29. The dosing regimen of any one of claims 25-28, wherein the prior therapy comprises lenalidomide.
30. The dosing regimen of any one of claims 25-29, wherein the prior therapy comprises carfilzomib.
31. The dosing regimen of any one of claims 25-30, wherein the prior therapy comprises bortezomib.

32. Use of a pharmaceutical combination of any one of claims 1-8 in the manufacture of a medicament for the treatment of multiple myeloma.

33. A method of treating a multiple myeloma in a subject in need thereof, comprising co-administering to the subject
a) a first amount of ibrutinib;
b) a second amount of an immunomodulatory agent; and
c) a third amount of dexamethasone,
wherein the first amount, second amount, and third amount, taken together, are therapeutically effective.

34. A method of treating a relapsed or refractory multiple myeloma in a subject in need thereof, comprising co-administering to the subject
a) a first amount of ibrutinib;
b) a second amount of an immunomodulatory agent; and
c) a third amount of dexamethasone,
wherein the first amount, second amount, and third amount, taken together, are therapeutically effective.

35. The method of any one of claims 33-34, wherein the immunomodulatory agent is pomalidomide.

36. The method of claim 35, wherein pomalidomide is administered orally.

37. The method of any one of claims 35-36, wherein the second amount is about 3 mg/day to about 5 mg/day.

38. The method of any one of claims 35-37, wherein the second amount is about 4 mg/day.

39. The method of any one of claims 33-38, wherein dexamethasone is administered orally.

40. The method of any one of claims 33-39 wherein the third amount is about 20 mg/day to about 60 mg/day.

41. The method of any one of claims 33-40, wherein the third amount is about 40 mg/day.

42. The method of any one of claims 33-41, wherein ibrutinib is administered orally.

43. The method of any one of claims 33-42, wherein ibrutinib is administered once a day, two times per day, three times per day, four times per day, or five times per day.

44. The method of any one of claims 33-43, wherein the first amount is about 560 mg/day to about 840 mg/day.
45. The method of claim 44, wherein the first amount is about 700 mg/day.
46. The method of any of claims 33-45, further comprising administration of an additional therapeutic agent.
47. The method of any one of claims 33-46, wherein the multiple myeloma is relapsed or refractory multiple myeloma.
48. The method of any one of claims 33-47, wherein the multiple myeloma is metastasized multiple myeloma.
49. The method of any one of claims 33-48, wherein the subject has received at least one prior therapy.
50. The method of any one of claims 33-49, wherein the subject has received at least two prior therapies.
51. The method of any one of claims 49-50, wherein the prior therapy comprises lenalidomide.
52. The method of any one of claims 49-51, wherein the prior therapy comprises carfilzomib.
53. The method of any one of claims 49-52, wherein the prior therapy comprises bortezomib.
55. A method of treating a relapsed or refractory multiple myeloma in a subject in need thereof, based on a dosing regimen of claims 9-31.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

 INV. A61K31/519 A61K31/454 A61K31/573 A61K35/00

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

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

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

EPO-Internal, BIOSIS, CHEMABS Data, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search

17 November 2016

Date of mailing of the international search report

30/11/2016

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV RIJSWIJK
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

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**INTERNATIONAL SEARCH REPORT**

**Form PCT/ISA/210 (continuation of second sheet) (April 2008) page 2 of 3**
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