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(54) Title: MEK INHIBITORS AND USES THEREOF

(57) Abstract: The present disclosure provides MEK inhibitors, compositions thereof, and methods of using the same.



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MEK INHIBITORS AND USES THEREOF

CROSS REFERENCED TO RELATED APPLICATIONS

[0001] This application claims the priority of US provisional application 63/269,131 filed March 10, 2022 and US provisional application number 63/375,870 filed September 16, 2022, each of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

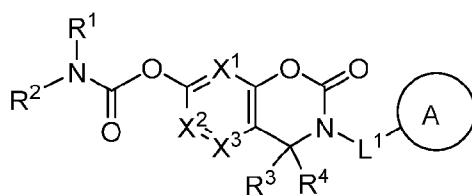
[0002] The present disclosure relates to compounds and methods useful for inhibiting mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK). The disclosure also provides pharmaceutically acceptable compositions comprising compounds of the present disclosure and methods of using said compositions in the treatment of proliferative disorders, such as cancers.

BACKGROUND

[0003] Activation of the p42/44 MAPK signaling pathway comprising mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)-ERK has been implicated in the pathogenesis and progression of various cancers. The MEK-ERK pathway is often activated by mutation of upstream factors, BRAF or Ras, or by the signals of constitutively activated cell-surface receptors. Inhibition of MEK can be a promising strategy for controlling the growth of tumors, for example, the tumors associated with MEK pathway signaling.

SUMMARY

[0004] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as MEK inhibitors. In one aspect, the instant disclosure provides a compound of Formula (I):



(I),

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0005] Another aspect of the disclosure provides a method of treating a disorder mediated by MEK in a subject. The method comprises administering a therapeutically effective amount of a compound described herein to a subject in need thereof to treat the disorder mediated by MEK, as further described in the detailed description.

[0006] Another aspect of the disclosure provides a method of inhibiting MEK activity. The method comprises contacting MEK or a KSR-MEK complex or a RAF-MEK complex with an effective amount of a compound described herein, as further described in the detailed description.

[0007] In some aspects, compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating proliferative disorders, such as the cancers as described herein.

DETAILED DESCRIPTION

[0008] Compounds of the present disclosure, and pharmaceutical compositions thereof, are useful as MEK inhibitors. Without wishing to be bound by any particular theory, it is believed that the compounds of the present disclosure may directly engage kinase suppressor of Ras (KSR) at the MEK interface, and that KSR may remodel the prototypical allosteric pocket of the MEK inhibitor in the KSR-MEK complex. Without wishing to be bound by any particular theory, it is believed that the compounds of the present disclosure may bind the KSR-MEK complex and may disrupt the related RAF-MEK complex.

1. Definitions:

[0009] When introducing elements of the different aspects as described herein, the articles "a," "an," "the," and "said" are intended to mean that there are one or more of the elements. The terms "comprising," "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

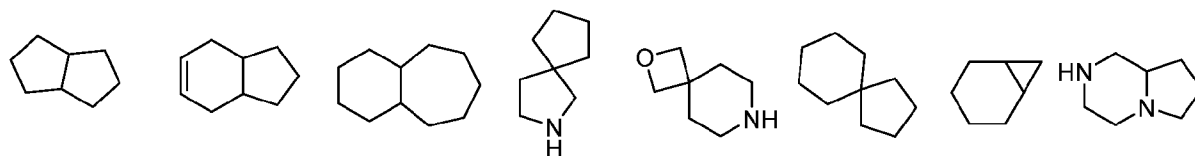
[0010] Compounds of the present disclosure include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this disclosure, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS

version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

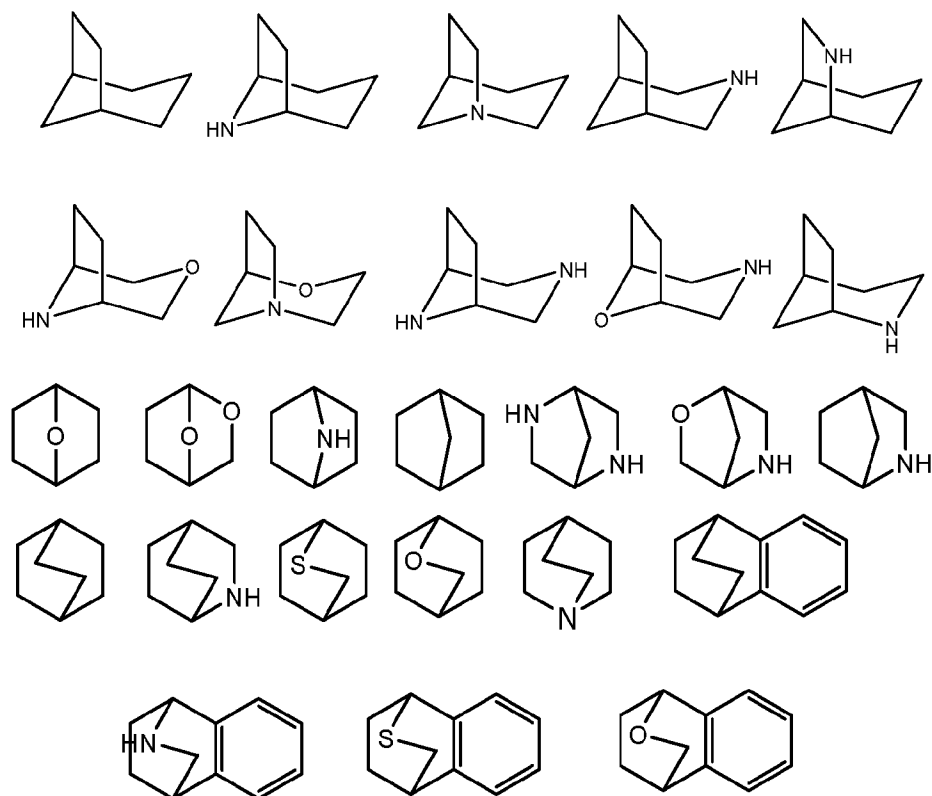
[0011] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (*i.e.*, unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C₃-C₆ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0012] As used herein, the term "bicyclic ring" or "bicyclic ring system" refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term "heterobicyclic" is a subset of "bicyclic" that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. As used herein, the

term “bridged bicyclic” refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a “bridge” is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a “bridgehead” is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bicyclic rings include:



Exemplary bridged bicyclics include:



[0013] The term “lower alkyl” refers to a C₁₋₄ straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and *tert*-butyl.

[0014] The term “lower haloalkyl” refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

[0015] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

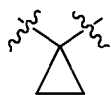
[0016] The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

[0017] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0018] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, *i.e.*, -(CH₂)_n-, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0019] The term “alkenylene” refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0020] As used herein, the term “cyclopropylenyl” refers to a bivalent cyclopropyl group of



the following structure:

[0021] The term “halogen” means F, Cl, Br, or I.

[0022] The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” “aralkoxy,” or “aryloxyalkyl,” refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term “aryl” may be used interchangeably with the term “aryl ring.” In certain embodiments of the present invention, “aryl” refers to an aromatic ring system

which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl,” as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0023] The terms “heteroaryl” and “heteroar-,” used alone or as part of a larger moiety, *e.g.*, “heteroaralkyl,” or “heteroaralkoxy,” refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-,” as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazoliny, quinoxaliny, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring,” “heteroaryl group,” or “heteroaromatic,” any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0024] As used herein, the terms “heterocycle,” “heterocyclyl,” “heterocyclic radical,” and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term “nitrogen” includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0025] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms “heterocycle,” “heterocyclyl,” “heterocyclyl ring,” “heterocyclic group,” “heterocyclic moiety,” and “heterocyclic radical,” are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H* indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono- or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0026] As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0027] As described herein, compounds of the invention may contain “optionally substituted” moieties. In general, the term “substituted,” whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an “optionally substituted” group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term “stable,” as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0028] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(\text{CH}_2)_{0-4}\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{OR}^\circ$; $-\text{O}(\text{CH}_2)_{0-4}\text{R}^\circ$, $-\text{O}-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{CH}(\text{OR}^\circ)_2$; $-(\text{CH}_2)_{0-4}\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{Ph}$, which may be substituted with R° ;

$-(\text{CH}_2)_{0-4}\text{O}(\text{CH}_2)_{0-1}\text{Ph}$ which may be substituted with R° ; $-\text{CH}=\text{CHPh}$, which may be substituted with R° ; $-(\text{CH}_2)_{0-4}\text{O}(\text{CH}_2)_{0-1}\text{-pyridyl}$ which may be substituted with R° ; $-\text{NO}_2$; $-\text{CN}$; $-\text{N}_3$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)_2$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{C}(\text{S})\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{C}(\text{S})\text{NR}^\circ_2$; $-(\text{CH}_2)_{0-4}\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{OR}^\circ$; $-\text{N}(\text{R}^\circ)\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{N}(\text{R}^\circ)\text{C}(\text{O})\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{R}^\circ$; $-\text{C}(\text{S})\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{OSiR}^\circ_3$; $-(\text{CH}_2)_{0-4}\text{OC}(\text{O})\text{R}^\circ$; $-\text{OC}(\text{O})(\text{CH}_2)_{0-4}\text{SR}^\circ$; $-\text{SC}(\text{S})\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{SC}(\text{O})\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{C}(\text{O})\text{NR}^\circ_2$; $-\text{C}(\text{S})\text{NR}^\circ_2$; $-\text{C}(\text{S})\text{SR}^\circ$; $-\text{SC}(\text{S})\text{SR}^\circ$; $-(\text{CH}_2)_{0-4}\text{OC}(\text{O})\text{NR}^\circ_2$; $-\text{C}(\text{O})\text{N}(\text{OR}^\circ)\text{R}^\circ$; $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^\circ$; $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{R}^\circ$; $-\text{C}(\text{NOR}^\circ)\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{SSR}^\circ$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})_2\text{R}^\circ$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})_2\text{OR}^\circ$; $-(\text{CH}_2)_{0-4}\text{OS}(\text{O})_2\text{R}^\circ$; $-\text{S}(\text{O})_2\text{NR}^\circ_2$; $-\text{S}(\text{O})(\text{NR}^\circ)\text{R}^\circ$; $-\text{S}(\text{O})_2\text{N}=\text{C}(\text{NR}^\circ_2)_2$; $-(\text{CH}_2)_{0-4}\text{S}(\text{O})\text{R}^\circ$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{NR}^\circ_2$; $-\text{N}(\text{R}^\circ)\text{S}(\text{O})_2\text{R}^\circ$; $-\text{N}(\text{OR}^\circ)\text{R}^\circ$; $-\text{C}(\text{NH})\text{NR}^\circ_2$; $-\text{P}(\text{O})_2\text{R}^\circ$; $-\text{P}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})\text{R}^\circ_2$; $-\text{OP}(\text{O})(\text{OR}^\circ)_2$; SiR°_3 ; $-(\text{C}_{1-4}$ straight or branched alkylene) $\text{O}-\text{N}(\text{R}^\circ)_2$; or $-(\text{C}_{1-4}$ straight or branched alkylene) $\text{C}(\text{O})\text{O}-\text{N}(\text{R}^\circ)_2$.

[0029] Each R° is independently hydrogen, C_{1-6} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, $-\text{CH}_2$ - $(5-6$ membered heteroaryl ring), or a $5-6$ -membered saturated, partially unsaturated, or aryl ring having $0-4$ heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R° , taken together with their intervening atom(s), form a $3-12$ -membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having $0-4$ heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted by a divalent substituent on a saturated carbon atom of R° selected from $=\text{O}$ and $=\text{S}$; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, $-(\text{CH}_2)_{0-2}\text{R}^\bullet$, $-(\text{haloR}^\bullet)$, $-(\text{CH}_2)_{0-2}\text{OH}$, $-(\text{CH}_2)_{0-2}\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{CH}(\text{OR}^\bullet)_2$; $-\text{O}(\text{haloR}^\bullet)$, $-\text{CN}$, $-\text{N}_3$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{R}^\bullet$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OH}$, $-(\text{CH}_2)_{0-2}\text{C}(\text{O})\text{OR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{SH}$, $-(\text{CH}_2)_{0-2}\text{NH}_2$, $-(\text{CH}_2)_{0-2}\text{NHR}^\bullet$, $-(\text{CH}_2)_{0-2}\text{NR}^\bullet_2$, $-\text{NO}_2$, $-\text{SiR}^\bullet_3$, $-\text{OSiR}^\bullet_3$, $-\text{C}(\text{O})\text{SR}^\bullet$, $-(\text{C}_{1-4}$ straight or branched alkylene) $\text{C}(\text{O})\text{OR}^\bullet$, or $-\text{SSR}^\bullet$.

[0030] Each R^\bullet is independently selected from C_{1-4} aliphatic, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a $5-6$ -membered saturated, partially unsaturated, or aryl ring having $0-4$ heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each R^\bullet is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from $=\text{O}$, $=\text{S}$, $=\text{NNR}^*_2$,

=NNHC(O)R*, =NNHC(O)OR*, =NNHS(O)₂R*, =NR*, =NOR*, -O(C(R^{*})₂)₂₋₃O-, or -S(C(R^{*})₂)₂₋₃S-, or a divalent substituent bound to vicinal substitutable carbons of an "optionally substituted" group is -O(CR^{*})₂₋₃O-, wherein each independent occurrence of R^{*} is selected from hydrogen, C₁₋₆ aliphatic or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0031] When R^{*} is C₁₋₆ aliphatic, R^{*} is optionally substituted with halogen, -R[•], -(haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR[•]₂, or -NO₂, wherein each R[•] is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each R[•] is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0032] An optional substituent on a substitutable nitrogen is independently -R[†], -NR[†]₂, -C(O)R[†], -C(O)OR[†], -C(O)C(O)R[†], -C(O)CH₂C(O)R[†], -S(O)₂R[†], -S(O)₂NR[†]₂, -C(S)NR[†]₂, -C(NH)NR[†]₂, or -N(R[†])S(O)₂R[†]; wherein each R[†] is independently hydrogen, C₁₋₆ aliphatic, unsubstituted -OPh, or an unsubstituted 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of R[†], taken together with their intervening atom(s) form an unsubstituted 3-12-membered saturated, partially unsaturated, or aryl mono- or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when R[†] is C₁₋₆ aliphatic, R[†] is optionally substituted with halogen, -R[•], -(haloR[•]), -OH, -OR[•], -O(haloR[•]), -CN, -C(O)OH, -C(O)OR[•], -NH₂, -NHR[•], -NR[•]₂, or -NO₂, wherein each R[•] is independently selected from C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each R[•] is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0033] In some embodiments, "alkyl" as used alone or as part of a group, refers to saturated monovalent hydrocarbon radicals having straight or branched hydrocarbon chains or, in the event that at least 3 carbon atoms are present, cyclic hydrocarbons or combinations thereof and contains 1 to 20 carbon atoms (C₁-C₂₀ alkyl), 1 to 10 carbon atoms (C₁-C₁₀ alkyl), 1 to 8 carbon atoms (C₁-C₈ alkyl), 1 to 6 carbon atoms (C₁-C₆ alkyl), or 1 to 4 carbon atoms (C₁-C₄ alkyl). In some

embodiments, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

[0034] In some embodiments, “alkoxy” refers to —O-(alkyl), wherein “alkyl” is as defined above.

[0035] In some embodiments, “cycloalkyl” as used alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from 3 to 8 carbon atoms, or from 3 to 6 carbon atoms. In some embodiments, cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

[0036] In some embodiments, halogen or halo is F, Cl, Br, or I.

[0037] As used herein, the term “pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this disclosure include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

[0038] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and N⁺(C₁-C₄alkyl)₄ salts. Representative alkali or alkaline earth metal salts include

sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0039] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (*e.g.*, enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the disclosure. Unless otherwise stated, all tautomeric forms of the compounds of the disclosure are within the scope of the disclosure. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this disclosure. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present disclosure.

[0040] As used herein, the term “provided compound” refers to any MEK inhibitor genus, subgenus, and/or species set forth herein.

[0041] As used herein, the terms “inhibitor” or “MEK inhibitor” or “MEK antagonist” are defined as a compound that binds to and/or inhibits MEK with measurable affinity. In some embodiments, inhibition in the presence of a MEK inhibitor or a MEK antagonist is observed in a dose-dependent manner. In some embodiments, the measured signal (*e.g.*, signaling activity or biological activity) is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% lower than the signal measured with a negative control under comparable conditions. The potency of an inhibitor is usually defined by its IC₅₀ value (half maximal inhibitory concentration or concentration required to inhibit 50% of the agonist response). The lower the IC₅₀ value the

greater the potency of the antagonist and the lower the concentration that is required to inhibit the maximum biological response. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less than about 100 μ M, less than about 50 μ M, less than about 1 μ M, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0042] The terms “measurable affinity” and “measurably inhibit,” as used herein, means a measurable change or inhibition in MEK activity between a sample comprising a compound of the present disclosure, or composition thereof, and MEK, and an equivalent sample comprising MEK, in the absence of said compound, or composition thereof.

[0043] As used herein, the term “effective amount” refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory, or preventative result). An effective amount can be administered in one or more administrations, applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0044] As used herein, the term “treating” includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof. In some embodiments, treatment can be administered after one or more symptoms have developed. In other embodiments, treatment can be administered in the absence of symptoms. For example, treatment can be administered to a susceptible individual prior to the onset of symptoms (*e.g.*, in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment can also be continued after symptoms have resolved, for example, to prevent or delay their recurrence.

[0045] The phrases “disorder mediated by MEK” or “disease mediated by MEK” or “MEK-associated disease or disorder,” as used herein, refer to diseases or disorders associated with, or mediated by MEK or MEK activity. A non-limiting example of a MEK-associated disease or disorder is a MEK-associated cancer.

[0046] As used herein, the term “pharmaceutical composition” refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0047] As used herein, the term “pharmaceutically acceptable carrier” refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The

compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, *see e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0048] As used herein, a “non-ATP competitive” or “ATP non-competitive” MEK inhibitor refers to an inhibitor of MEK that does not bind in the ATP pocket of MEK, or does not displace ATP from the MEK active site, and can form direct contacts when co-bound to the MEK-ATP complex. Non-ATP competitive inhibition by a compound of the invention can be confirmed by art-recognized methods such as enzymology studies, competition assays, biophysical methods, including X-ray co-crystallography. An exemplary non-ATP competitive inhibitor of the invention inhibits recombinant MEK1 or MEK2 with an IC_{50} of from about 1 nM to about 50 μ M. In some embodiments, an exemplary non-ATP competitive inhibitor of the invention inhibits recombinant MEK1 or MEK2 with an IC_{50} of about 1 nM to about 1000 nM, about 1 μ M to about 50 μ M, about 1 μ M to about 25 μ M, about 1 μ M to about 10 μ M, about 500 nM to about 5 μ M, or about 10 nM to about 500 nM.

[0049] An “inhibitor pocket”, as used herein, refers to a structure formed at the interface of the interaction between MEK and KSR or BRAF or CRAF with which an inhibitor of the invention is engaged.

[0050] As used herein, a compound of the invention “allosterically binds an inhibitor pocket” when a compound binds outside the active site, including, for example, outside or adjacent to the ATP-binding site of a kinase.

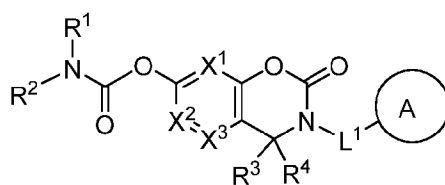
[0051] As used herein, an “inhibitor-inhibitor pocket complex” describes a species in which an inhibitor of the invention allosterically binds an inhibitor pocket formed at an interaction interface between human MEK (MEK1 or MEK2) and human Kinase Suppressor of Ras (KSR1, KSR2, or the KSR homolog BRAF or CRAF) adjacent to ATP in a physiological complex between MEK and KSR.

[0052] As used herein, when a moiety on an inhibitor “engages” an amino acid residue of MEK and/or KSR and/or BRAF or CRAF in an inhibitor pocket, this interaction is detectable by X-ray crystallography, or similar structural methods, such as cryo-electron microscopy, NMR, or in silico docking, including fragment binding and computational simulations, which demonstrates that the interaction defining the engagement is a separation between the inhibitor moiety and the amino acid residue of not more than about 8 Å, including, for example, from about 2 Å to about 5

Å, or from 5 Å to about 8 Å. The distances provided herein allow for the implicit inclusion of hydrogen atoms; however, hydrogen atoms were not included in the present crystallographic models, which is appropriate unless crystals diffract to very high resolutions (*i.e.*, better than 1.5 Angstroms). Literature surveys of drug-receptor atom pairs across all structures in the protein data bank have used 4-5 Angstrom distance cutoffs (PMID 29308120, 26517868, 19221587) to evaluate reasonable small molecule hydrophobic bonding interactions and have found that intermolecular carbon-carbon interactions similar to the trametinib-KSR contacts are among the most highly represented drug-receptor atom pairs within the protein data bank. With respect to the interactions between the inhibitors of the invention and the MEK-KSR and/or BRAF or CRAF complex, a 4 Angstrom contact is reasonable based on the nature of the trametinib-KSR interaction and precedence of known drug-receptor complexes. This contact is within the range of known contacts as defined by several independent groups (PMID 29308120, 26517868, 19221587).

2. Description of Exemplary Embodiments:

[0053] In one aspect, the present disclosure provides a compound of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently H, optionally substituted C_1 - C_6 aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, or R^1 and R^2 , taken together with the atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^1 and R^2 attach;

X^1 is $C(R^{21})$ or N;

X^2 is $C(R^{22})$ or N;

X^3 is $C(R^{23})$ or N;

R^3 and R^4 are independently halogen, R, -OR, -N(R)₂, -N(R)-C(O)-R, or -C(O)-N(R)₂; or R^3 and R^4 , taken together with the atom to which they attach, form C(=O), or an optionally substituted 3-8 membered carbocyclic ring, or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S;

each of R^{21} , R^{22} , and R^{23} is independently halogen, R, -OR, -N(R)₂, -N(R)-C(O)-R, or -C(O)-N(R)₂;

L^1 is -C(R^5)(R^6)-;

each of R^5 and R^6 is independently halogen, R, -OR, or -N(R)₂; or R^5 and R^6 , together with the atom to which they attach, form an optionally substituted 3-8 membered carbocyclic ring or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S;

Ring A is an optionally substituted ring selected from a phenyl ring, a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from N, O, or S, or a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S; and

each R is independently H, optionally substituted C₁-C₆ aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

[0054] As defined generally above, R^1 and R^2 are independently H, optionally substituted C₁-C₆ aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, or R^1 and R^2 , taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^1 and R^2 attach.

[0055] In some embodiments, R^1 and R^2 are independently H, optionally substituted C₁-C₆ aliphatic, or R^1 and R^2 , taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^1 and R^2 attach.

[0056] In some embodiments, R^1 and R^2 are independently hydrogen or optionally substituted C₁-C₆ alkyl. In some embodiments, R^1 and R^2 are independently hydrogen or C₁-C₆ alkyl. In some

embodiments, R^1 and R^2 are independently hydrogen, methyl, ethyl, propyl, butyl, or hexyl. In some embodiments, R^1 and R^2 are methyl.

[0057] In some embodiments, R^1 and R^2 taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^1 and R^2 attach. In some embodiments, R^1 and R^2 taken together with the N atom to which they attach, form optionally substituted 3, 4, 5, 6, 7, or 8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^1 and R^2 attach. In some embodiments, R^1 and R^2 taken together with the N atom to which they attach, form optionally substituted 3, 4, 5, 6, 7, or 8 membered heterocyclyl having 1, 2, or 3 N atoms. In some embodiments, R^1 and R^2 , taken together with the N atom to which they attach, form an optionally substituted azetidine ring.

[0058] As defined generally above, X^1 is $C(R^{21})$ or N. In some embodiments, X^1 is $C(R^{21})$. In some embodiments, X^1 is N. In some embodiments, X^1 is C(H).

[0059] As defined generally above, X^2 is $C(R^{22})$ or N. In some embodiments, X^2 is $C(R^{22})$. In some embodiments, X^2 is N. In some embodiments, X^2 is C(H). In some embodiments, X^2 is $C(R^{22})$, wherein R^{22} is halogen.

[0060] As defined generally above, X^3 is $C(R^{23})$ or N. In some embodiments, X^3 is $C(R^{23})$. In some embodiments, X^3 is N. In some embodiments, X^3 is C(H). In some embodiments, X^3 is $C(R^{23})$, wherein R^{23} is halogen.

[0061] As defined generally above, each of R^{21} , R^{22} , and R^{23} is independently halogen, R, -OR, $-N(R)_2$, $-N(R)-C(O)-R$, or $-C(O)-N(R)_2$.

[0062] In some embodiments, R^{21} is halogen. In some embodiments, R^{21} is R. In some embodiments, R^{21} is H. In some embodiments, R^{21} is optionally substituted C_1-C_6 aliphatic. In some embodiments, R^{21} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^{21} is -OR. In some embodiments, R^{21} is optionally substituted C_1-C_6 alkoxy. In some embodiments, R^{21} is $-N(R)_2$. In some embodiments, R^{21} is $-N(R)-C(O)-R$. In some embodiments, R^{21} is $-C(O)-N(R)_2$.

[0063] In some embodiments, R^{22} is halogen. In some embodiments, R^{22} is -Cl. In some embodiments, R^{22} is -F. In some embodiments, R^{22} is R. In some embodiments, R^{22} is H. In some embodiments, R^{22} is optionally substituted C_1-C_6 aliphatic. In some embodiments, R^{22} is optionally substituted C_1-C_6 alkyl. In some embodiments, R^{22} is -OR. In some embodiments, R^{22} is optionally

substituted C₁-C₆ alkoxy. In some embodiments, R²² is -N(R)₂. In some embodiments, R²² is -N(R)-C(O)-R. In some embodiments, R²² is -C(O)-N(R)₂.

[0064] In some embodiments, R²³ is halogen. In some embodiments, R²³ is -Cl. In some embodiments, R²³ is -F. In some embodiments, R²³ is R. In some embodiments, R²³ is H. In some embodiments, R²³ is optionally substituted C₁-C₆ aliphatic. In some embodiments, R²³ is optionally substituted C₁-C₆ alkyl. In some embodiments, R²³ is -OR. In some embodiments, R²³ is optionally substituted C₁-C₆ alkoxy. In some embodiments, R²³ is -N(R)₂. In some embodiments, R²³ is -N(R)-C(O)-R. In some embodiments, R²³ is -C(O)-N(R)₂.

[0065] As defined generally above, R³ and R⁴ are independently halogen, R, -OR, -N(R)₂, -N(R)-C(O)-R, or -C(O)-N(R)₂; or R³ and R⁴, taken together with the atom to which they attach, form C(=O), or an optionally substituted 3-8 membered carbocyclic ring, or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S. In some embodiments, R³ and R⁴ are independently hydrogen or R, or R³ and R⁴, taken together with the atom to which they attach, form C(=O), each of R is independently optionally substituted C₁-C₆ aliphatic. In some embodiments, R³ and R⁴ are independently hydrogen or R, or R³ and R⁴, taken together with the atom to which they attach, form C(=O), each of R is independently C₁-C₆ aliphatic. In some embodiments, R³ is unsubstituted C₁-C₆ alkoxy, or optionally substituted C₁-C₆ alkoxy. In some embodiments, R⁴ is unsubstituted C₁-C₆ alkoxy, or optionally substituted C₁-C₆ alkoxy. In some embodiments, R³ and R⁴ are independently hydrogen, -CH₃, -CH₂N(CH₃)₂, C(=O), or -(C₃H₅). In some embodiments, R³ and R⁴ are independently hydrogen, -CH₃, -CH₂N(CH₃)₂, or -(C₃H₅).

[0066] In some embodiments, R³ and R⁴ are independently R; or R³ and R⁴, taken together with the atom to which they attach, form C(=O), or an optionally substituted 3-8 membered carbocyclic ring, or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S. In some embodiments, R³ and R⁴ are independently R; or R³ and R⁴, taken together with the atom to which they attach, form C(=O), or an optionally substituted 3-8 membered carbocyclic ring. In some embodiments, R³ and R⁴ are independently R; and each R is independently H, optionally substituted C₁₋₆ aliphatic, or optionally substituted 3-8 membered carbocyclyl. In some embodiments, R³ and R⁴ are independently R; and each R is independently H, methyl, or cyclopropyl. In some embodiments, R³ and R⁴ are independently hydrogen, -CH₃, or -CH₂N(CH₃)₂. In some embodiments, R³ and R⁴ are

independently R; and each R is independently C₁-C₆ aliphatic. In some embodiments, R³ and R⁴ are independently hydrogen or CH₃.

[0067] In some embodiments, R³ is -T-N(R)₂, wherein T is a bivalent C₁-C₈ saturated or unsaturated, straight or branched, hydrocarbon chain wherein one, two or three methylene units of the chain are optionally and independently replaced by -Cy-, -C(R)₂-, -S-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂- or -N(R)CH₂C(O)-; and -Cy- is an optionally substituted 3-8 membered bivalent carbocyclic ring, or an optionally substituted 3-8 membered bivalent heterocyclic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

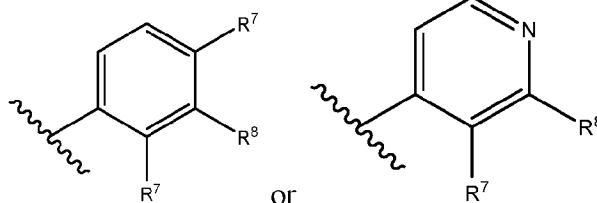
[0068] In some embodiments, R⁴ is -T-N(R)₂, wherein T is a bivalent C₁-C₈ saturated or unsaturated, straight or branched, hydrocarbon chain wherein one, two or three methylene units of the chain are optionally and independently replaced by -Cy-, -C(R)₂-, -S-, -N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -C(O)N(R)-, -N(R)C(O)-, -S(O)-, -S(O)₂- or -N(R)CH₂C(O)-; and -Cy- is an optionally substituted 3-8 membered bivalent carbocyclic ring, or an optionally substituted 3-8 membered bivalent heterocyclic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

[0069] As defined generally above, L¹ is -C(R⁵)(R⁶)-, wherein each of R⁵ and R⁶ is independently halogen, R, -OR, or -N(R)₂; or R⁵ and R⁶, together with the atom to which they attach, form an optionally substituted 3-8 membered carbocyclic ring or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S. In some embodiments, R⁵ is hydrogen, and R⁶ is R. In some embodiments, R⁶ is hydrogen. In some embodiments, R⁵ and R⁶ are independently optionally substituted C₁-C₆ aliphatic. In some embodiments, R⁵ is unsubstituted C₁-C₆ alkoxy, or optionally substituted C₁-C₆ alkoxy. In some embodiments, R⁶ is unsubstituted C₁-C₆ alkoxy, or optionally substituted C₁-C₆ alkoxy. In some embodiments, R⁵ and R⁶ are independently hydrogen, methyl, ethyl, propyl, butyl, or hexyl. In some embodiments, R⁵ is hydrogen, and R⁶ is methyl. In some embodiments, R⁵ and R⁶ are independently halogen or R. In some embodiments, R⁵ and R⁶ are independently hydrogen, halogen, or C₁-C₆ aliphatic.

[0070] In some embodiments, L¹ is -CH₂-. In some embodiments, L¹ is -C(H)(CH₃)-.

[0071] As defined generally above, Ring A is an optionally substituted ring selected from a phenyl ring, a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected

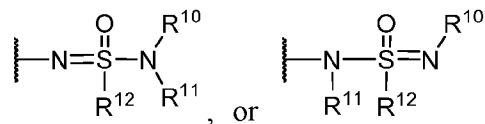
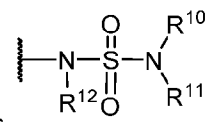
from N, O, or S, or a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S. In some embodiments, Ring A is an optionally substituted ring selected from a phenyl ring, a 5 or 6 membered heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from N, O, or S, or a 8, 9, 10, or 11 membered bicyclic heteroaromatic ring having 1, 2, 3, 4, or 5 heteroatoms independently selected from N, O, or S. In some embodiments, Ring A is an optionally substituted ring selected from a phenyl ring or a 6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from N. In some embodiments, Ring A is an optionally substituted ring selected from a phenyl ring or a 6 membered heteroaromatic ring having 1, 2, 3, or 4 heteroatoms independently selected from N. In some embodiments, Ring A is an optionally substituted ring selected form a phenyl ring or a 5 or 6 membered heteroaromatic having 1, 2, 3, or 4 heteroatoms independent selected from N. In some embodiments, Ring A is pyridinyl, pyrimidinyl, pyrazinyl, or pyrazolyl.



[0072] In some embodiments, Ring A is

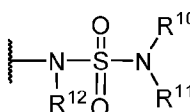
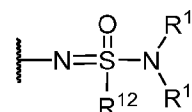
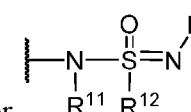
or ; R⁷

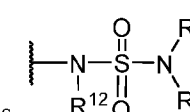
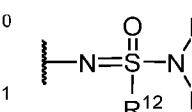
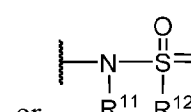
is independently halogen, R, -OR, or -N(R)₂; and R⁸ is halogen, R, -OR, -N(R)₂,



; each of R¹⁰ and R¹¹ is independently H, optionally substituted C₁₋₆ aliphatic, optionally substituted 3-8 membered carbocyclyl, optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from N, O, or S, or R¹⁰ and R¹¹ taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R¹⁰ and R¹¹ attach; and R¹² is H, optionally substituted C_{1-C6} aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

[0073] In some embodiments, each R^7 is independently halogen, R, or -OR. In some embodiments, R^7 is independently H, or optionally substituted C_1 - C_6 aliphatic. In some embodiments, R^7 is independently H, halogen, or C_1 - C_6 aliphatic. In some embodiments, R^7 is unsubstituted C_1 - C_6 alkoxy, or optionally substituted C_1 - C_6 alkoxy. In some embodiments, each R^7 is independently halogen. In some embodiments, R^7 is independently H or fluoro. In some embodiments, R^7 is fluoro. In some embodiments, R^7 is H.

[0074] In some embodiments, R^8 is , , or .

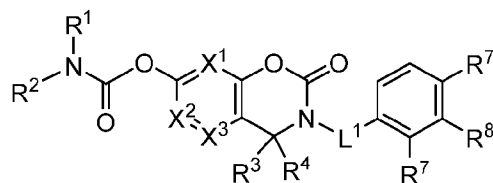
[0075] In some embodiments, R^8 is , , or ; each of R^{10} and R^{11} is independently H, C_1 - C_6 aliphatic, or 3-8 membered heterocyclyl having 1, 2, or 3 N atoms; and R^{12} is H, optionally substituted C_1 - C_6 aliphatic, or optionally substituted 3-8 membered carbocyclyl. In some embodiments, R^8 is unsubstituted C_1 - C_6 alkoxy, or optionally substituted C_1 - C_6 alkoxy.

[0076] In some embodiments, each of R^{10} and R^{11} is independently hydrogen or C_1 - C_6 alkyl.

[0077] In some embodiments, R^{12} is hydrogen or C_1 - C_6 alkyl. In some embodiments, R^{12} is C_1 - C_6 alkyl. In some embodiments, R^{12} is hydrogen, methyl, ethyl, propyl, butyl, or hexyl.

[0078] As defined generally above, each R is independently H, optionally substituted C_1 - C_6 aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some embodiments, R is H. In some embodiments, R is unsubstituted, or optionally substituted C_1 - C_6 aliphatic. In some embodiments, R is unsubstituted, or optionally substituted C_1 - C_6 alkyl. In some embodiments, R is unsubstituted, or optionally substituted 3-8 membered carbocyclyl. In some embodiments, R is unsubstituted, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

[0079] In some embodiments, the present disclosure provides a compound of Formula (IA):



(IA)

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

[0080] In some embodiments, the present disclosure provides a compound of Formula (IA), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently H or optionally substituted C_1 - C_6 aliphatic, or R^1 and R^2 , taken together with the atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S;

X^1 is $C(R^{21})$ or N;

X^2 is $C(R^{22})$ or N;

X^3 is $C(R^{23})$ or N;

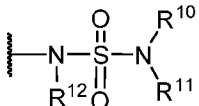
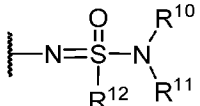
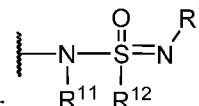
R^3 and R^4 are independently R or -OR; or R^3 and R^4 , taken together with the atom to which they attach, form $C(=O)$, or an optionally substituted 3-8 membered carbocyclic ring, or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S;

each of R^{21} , R^{22} , and R^{23} is independently halogen, R, $-N(R)_2$, -OR, $-N(R)-C(O)-R$, or $-C(O)-N(R)_2$;

L^1 is $-C(R^5)(R^6)-$;

each of R^5 and R^6 is independently H, halogen, R, or -OR;

each R^7 is independently halogen, R, or -OR;

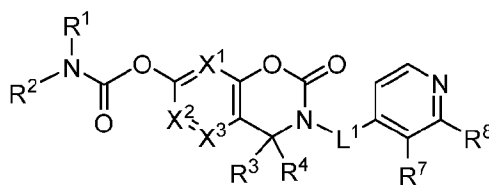
R^8 is halogen, R, -OR, $-N(R)_2$, , , or  ;

each of R^{10} and R^{11} is independently H, optionally substituted C_{1-6} aliphatic, optionally substituted 3-8 membered carbocyclyl, optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from N, O, or S, or R^{10} and R^{11} taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^{10} and R^{11} attach;

R^{12} is H, optionally substituted C_{1-6} aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S; and

each R is independently H, optionally substituted C_{1-6} aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

[0081] In some embodiments, the present disclosure provides a compound of Formula (IB):



(IB)

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

[0082] In some embodiments, the present disclosure provides a compound of Formula (IB), or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently H, optionally substituted C_{1-6} aliphatic, or R^1 and R^2 , taken together with the atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S;

X^1 is $C(R^{21})$ or N;

X^2 is $C(R^{22})$ or N;

X^3 is $C(R^{23})$ or N;

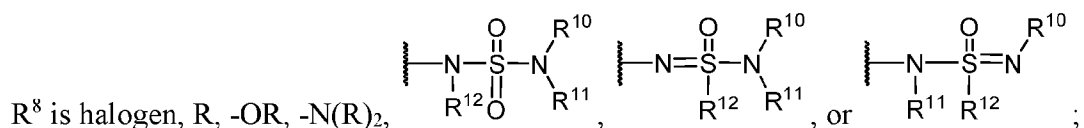
R^3 and R^4 are independently R or -OR; or R^3 and R^4 , taken together with the atom to which they attach, form $C(=O)$, or an optionally substituted 3-8 membered carbocyclic ring, or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S;

each of R^{21} , R^{22} , and R^{23} is independently halogen, R, -OR, $-N(R)_2$, $-N(R)-C(O)-R$, or $-C(O)-N(R)_2$;

L^1 is $-C(R^5)(R^6)-$;

each of R^5 and R^6 is independently H, halogen, R, or -OR;

R^7 is independently halogen, R, or -OR;



each of R^{10} and R^{11} is independently H, optionally substituted C_1 - C_6 aliphatic, optionally substituted 3-8 membered carbocyclyl, optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from N, O, or S, or R^{10} and R^{11} taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^{10} and R^{11} attach;

R^{12} is H, optionally substituted C_{1-6} aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S; and

each R is independently H, optionally substituted C_1 - C_6 aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

Table 1: Exemplary Compounds.	
Compound #	Structure
I-1	
I-2	
I-3	

I-4	
I-5	
I-6	
I-7	
I-8	
I-9	
I-10	
I-11	
I-12	

I-13	
I-14	
I-15	
I-16	
I-17	
I-18	
I-19	
I-20	
I-21	
I-22	

I-23	
I-24	
I-25	
I-26	
I-27	
I-28	
I-29	
I-30	
I-31	

I-32	
I-33	
I-34	
I-35	
I-36	
I-37	
I-38	
I-39	
I-40	
I-41	

I-42	
I-43	
I-44	
I-45	
I-46	
I-47	

[0083] In some embodiments, the present disclosure provides a compound set forth in **Table 1** above, or a pharmaceutically acceptable salt thereof.

3. Uses, Formulation, and Administration:

Pharmaceutically acceptable compositions

[0084] According to another embodiment, the disclosure provides a pharmaceutical composition comprising a compound of this disclosure or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this disclosure is such that is effective to measurably inhibit MEK, or a variant or mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this disclosure is such that is effective to measurably inhibit MEK, or a variant or mutant thereof, in a biological sample or in a patient. In certain embodiments, a

composition of this disclosure is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this disclosure is formulated for oral administration to a patient.

[0085] As used herein, the terms “subject” and “patient” are used interchangeably and refer to organisms to be treated by the methods of the present disclosure. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and, most preferably, includes humans.

[0086] The term “pharmaceutically acceptable carrier, adjuvant, or vehicle” refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this disclosure include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[0087] A “pharmaceutically acceptable derivative” means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this disclosure that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this disclosure or an active metabolite or residue thereof.

[0088] As used herein, the term "active metabolite or residue thereof" means that a metabolite or residue thereof also inhibits MEK, or a variant or mutant thereof.

[0089] Compositions of the present disclosure can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this disclosure may be aqueous or oleaginous suspension. These suspensions can be formulated according to techniques known in

the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[0090] For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[0091] Pharmaceutically acceptable compositions of this disclosure can be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents can also be added.

[0092] Alternatively, pharmaceutically acceptable compositions of this disclosure can be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[0093] Pharmaceutically acceptable compositions of this disclosure can also be administered topically, especially when the target of treatment includes areas or organs readily accessible by

topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[0094] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches can also be used.

[0095] For topical applications, provided pharmaceutically acceptable compositions can be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this disclosure include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0096] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions can be formulated in an ointment such as petrolatum.

[0097] Pharmaceutically acceptable compositions of this disclosure can also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[0098] Most preferably, pharmaceutically acceptable compositions of this disclosure are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this disclosure are administered without food. In other embodiments, pharmaceutically acceptable compositions of this disclosure are administered with food.

[0099] In some embodiments, the pharmaceutical compositions of this disclosure are brain-penetrant or CNS-penetrant or provide brain exposure. As used herein, the terms “brain-penetrant, “CNS-penetrant, “ or “brain exposure” refers that the compounds and pharmaceutical compositions of this disclosure are capable of crossing the blood brain barrier (BBB), and thus are useful for treating a brain or CNS disease, condition, injury or disorder. In some embodiments, a brain or CNS disease, condition, injury or disorder is a neurodegenerative diseases, neuronal injury, stroke, genetic disorders, psychiatric disorders, developmental disorders, inflammation, infection or damage, and brain cancers, spinal cord injury (SCI) and traumatic brain injury (TBI). In certain embodiments, a brain disorder is selected from epilepsy, meningitis, encephalitis including HIV Encephalitis, progressive multifocal leukoencephalopathy, neuromyelitis optica, multiple sclerosis, late-stage neurological trypanosomiasis, amyotrophic lateral sclerosis (ALS), progressive bulbar palsy (PBP), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA), Alzheimer's disease, Parkinson's disease, Huntington's disease, De Vivo disease, and any type of tumor, cancer or hyperproliferative disease in the brain or CNS.

[00100] In some embodiments, a brain or CNS disease, condition, injury or disorder is a neurological disorder which affects the CNS and/or which has an etiology in the CNS, which includes, but is not limited to, neuropathy, amyloidosis, cancer, an ocular disease or disorder, viral or microbial infection, inflammation, ischemia, neurodegenerative disease, seizure, behavioral disorders, and a lysosomal storage disease. For the purposes of this application, the CNS will be understood to include the eye, which is normally sequestered from the rest of the body by the blood-retina barrier. Specific examples of neurological disorders include, but are not limited to, neurodegenerative diseases (including, but not limited to, Lewy body disease, postpoliomyelitis syndrome, Shy-Draeger syndrome, olivopontocerebellar atrophy, Parkinson's disease, multiple system atrophy, striatonigral degeneration, tauopathies (including, but not limited to, Alzheimer disease and supranuclear palsy), prion diseases (including, but not limited to, bovine spongiform encephalopathy, scrapie, Creutzfeldt- Jakob syndrome, kuru, Gerstmann-Straussler-Scheinker disease, chronic wasting disease, and fatal familial insomnia), bulbar palsy, motor neuron disease, and nervous system hetero degenerative disorders (including, but not limited to, Canavan disease, Huntington's disease, neuronal ceroid- lipofuscinosis, Alexander's disease, Tourette's syndrome, Menkes kinky hair syndrome, Cockayne syndrome, Halervorden-Spatz syndrome, lafora disease, Rett syndrome, hepatolenticular degeneration, Lesch-Nyhan syndrome, and Unverricht- Lundborg

syndrome), dementia (including, but not limited to, Pick's disease, and spinocerebellar ataxia), cancer (e.g. of the CNS and/or brain, including brain metastases resulting from cancer elsewhere in the body).

[00101] The “central nervous system” or “CNS” refers to the complex of nerve tissues that control bodily function, and includes the brain and spinal cord.

[00102] The amount of compounds of the present disclosure that can be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00103] It should also be understood that a specific dosage and treatment regimen for any particular patient depends upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present disclosure in the composition also depends upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00104] In some embodiments, the present disclosure provides a method of using a compound as described herein for treating a disease or disorder associated with MEK. In some embodiments, a disease or disorder associated with MEK is a proliferative disorder. In some embodiments, a disease or disorder associated with MEK is a cancer. In some embodiments, a disease or disorder associated with MEK is a cancer as described herein.

[00105] In some aspects and embodiments, provided herein are methods of treating, reducing the severity of, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, of a disease or disorder characterized by or associated with increased MEK expression and/or increased MEK activity, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of the present disclosure, or pharmaceutically acceptable composition thereof. In some aspects and embodiments, provided herein are methods of treating, reducing the severity of, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof of a disease or disorder in

which inhibition or antagonizing of MEK activity is beneficial, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of the present disclosure, or pharmaceutically acceptable composition thereof.

[00106] Accordingly, in some aspects and embodiments, the present disclosure provides a method for treating one or more disorders, diseases, and/or conditions wherein the disorder, disease, or condition includes, but is not limited to, a cellular proliferative disorder, comprising administering to a patient in need thereof, a MEK inhibitor compound as described herein, or a pharmaceutical salt or composition thereof. In some embodiments, the cellular proliferative disorder is cancer. In some embodiments, the cancer is characterized by increased MEK expression and/or increased MEK activity, *i.e.*, “increased activated MEK.”

[00107] As used herein, the terms "increased," "elevated," or "enhanced," are used interchangeably and encompass any measurable increase in a biological function and/or biological activity and/or a concentration. For example, an increase can be by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to a control or baseline amount of a function, or activity, or concentration.

[00108] As used herein, the terms "increased expression" and/or "increased activity" of a substance, such as MEK, in a sample or cancer or patient, refers to an increase in the amount of the substance, such as MEK, of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to the amount of the substance, such as MEK, in a control sample or control samples, such as an individual or group of individuals who are not suffering from the disease or disorder (*e.g.*, cancer) or an internal control, as determined by techniques known in the art. A subject can also be determined to have an "increased expression" or "increased

activity" of MEK if the expression and/or activity of MEK is increased by one standard deviation, two standard deviations, three standard deviations, four standard deviations, five standard deviations, or more, relative to the mean (average) or median amount of MEK in a control group of samples or a baseline group of samples or a retrospective analysis of patient samples. As practiced in the art, such control or baseline expression levels can be previously determined, or measured prior to the measurement in the sample or cancer or subject, or can be obtained from a database of such control samples.

Cancer

[00109] In some embodiments, the present disclosure provides a method for treating or preventing or reducing the risk of a cancer in patient comprising administering to the patient a compound of the disclosure, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00110] A "cancer," as used herein, refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth divide and grow results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system or bloodstream.

[00111] The cancer or proliferative disorder or tumor to be treated using the compounds and methods and uses described herein include, but are not limited to, a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, skin cancer, breast cancer, a prostate cancer, a colorectal cancer, lung cancer, head and neck cancer, a gastrointestinal cancer, a liver cancer, a pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and a vascular cancer.

[00112] In some embodiments, the cancer is a K-Ras mutant cancer. In some embodiments, the K-Ras mutant cancer is an activated mutant K-Ras cancer. In some embodiments, the K-Ras mutant cancer is a cancer having a mutant or variant K-Ras G12. In some embodiments, the mutant or variant K-Ras G12 is K-Ras G12D, K-Ras G12V, K-Ras G12C, K-Ras G12R, K-Ras G12A, or any combination thereof. In some embodiments, the mutant or variant K-Ras G12 is K-Ras G12D. In some embodiments, the mutant or variant K-Ras G12 is K-Ras G12V. In some embodiments, the mutant or variant K-Ras G12 is K-Ras G12C. In some embodiments, the mutant or variant K-Ras G12 is K-Ras G12R. In some embodiments, the mutant or variant K-Ras G12 is K-Ras G12A. In some embodiments, the K-Ras mutant cancer is a cancer having a mutant or variant K-Ras G13.

In some embodiments, the mutant or variant K-Ras G13 is K-Ras G13D, K-Ras G13C, or any combination thereof. In some embodiments, the K-Ras mutant cancer is a cancer having a mutant or variant K-Ras Q61. In some embodiments, the mutant or variant K-Ras Q61 is K-Ras Q61H, K-Ras Q61R, or any combination thereof. In some embodiments, the K-Ras mutant cancer is a cancer having a mutant or variant K-Ras A146. In some embodiments, the mutant or variant K-Ras A146 is K-Ras A146T. In some embodiments, the K-Ras mutant cancer is a cancer having a mutant or variant K-Ras G12D, K-Ras G12V, K-Ras G12C, K-Ras G12R, K-Ras G12A, K-Ras G13D, K-Ras G13C, K-Ras Q61H, K-Ras Q61R, K-Ras A146T, or any combination thereof.

[00113] In some embodiments, the cancer is a mutant B-Raf cancer. In some embodiments, the mutant B-Raf cancer comprises a B-Raf amplification. As used herein, a “B-Raf amplification” refers to a cancer or cancer cell comprising at least three B-Raf copies, at least four B-Raf copies, at least five B-Raf copies, at least six B-Raf copies, at least seven B-Raf copies, at least eight B-Raf copies, at least nine B-Raf copies, at least ten B-Raf copies, or more. In some embodiments, the mutant B-Raf cancer is a cancer having a mutant or variant B-Raf V600, also referred to as a “Class I B-Raf mutation.” In some embodiments, the mutant or variant B-Raf V600 is B-Raf V600E, V600K, V600D, V600R, or any combination thereof. In some embodiments, the mutant B-Raf cancer is a cancer having a mutant or variant B-Raf K601, B-Raf P367, B-Raf G464, B-Raf L485, B-Raf E586, B-Raf T588, B-Raf T599, B-Raf L597, B-Raf G469, or any combination thereof, which are also collectively referred to as “Class II B-Raf mutations.” In some embodiments, the mutant B-Raf K601 is B-Raf K601E, K601N, K601T, or any combination thereof. In some embodiments, the mutant B-Raf P367 is B-Raf P367L, P367S, or any combination thereof. In some embodiments, the mutant B-Raf G464 is B-Raf G464V, G464E, or any combination thereof. In some embodiments, the mutant B-Raf L485 is L485W. In some embodiments, the mutant B-Raf E586 is E586K. In some embodiments, the mutant B-Raf T599 is T588TT, T588TS, T599I, T599K, or any combination thereof. In some embodiments, the mutant B-Raf L597 is B-Raf L597Q, L597R, L597S, L597V, or any combination thereof. In some embodiments, the mutant B-Raf G469 is B-Raf G469A, G469V, G469R, or any combination thereof. In some embodiments, the mutant B-Raf cancer is a cancer having a mutant or variant B-Raf D287, B-Raf V459, B-Raf G466, B-Raf S467, B-Raf G469, B-Raf N581, B-Raf D595, B-Raf F595, B-Raf G596, or any combination thereof, which are also collectively referred to as “Class III B-Raf mutations.” In some embodiments, the mutant B-Raf D287 is B-Raf D287N. In some

embodiments, the mutant B-Raf V459 is B-Raf B459L. In some embodiments, the mutant B-Raf G466 is B-Raf G466A, B-Raf G466E, B-Raf G466V, or any combination thereof. In some embodiments, the mutant B-Raf S467 is B-Raf S467L. In some embodiments, the mutant B-Raf G469 is B-Raf-G469E. In some embodiments, the mutant B-Raf N581 is B-Raf N581I, B-Raf N581S, B-Raf N581T, or any combination thereof. In some embodiments, the mutant B-Raf D595 is B-Raf D595A, B-Raf D595G, B-Raf D595H, B-Raf D595N, or any combination thereof. In some embodiments, the mutant B-Raf F595 is B-Raf F595L. In some embodiments, the mutant B-Raf G596 is B-Raf G596D, B-Raf G596R, or any combination thereof. In some embodiments, the mutant B-Raf cancer comprises a B-Raf amplification and at least one B-Raf mutant or variant B-Raf Class I, Class II, or Class III mutation.

[00114] In some embodiments, the cancer is an N-Ras mutant cancer. In some embodiments, the N-Ras mutant cancer is an activated mutant N-Ras cancer. In some embodiments, the N-Ras mutant cancer is a cancer having a mutant or variant N-Ras G12. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12D, N-Ras G12V, N-Ras G12C, N-Ras G12A, N-Ras G12R, N-Ras G12S, or any combination thereof. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12D. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12V. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12C. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12R. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12A. In some embodiments, the mutant or variant N-Ras G12 is N-Ras G12S. In some embodiments, the N-Ras mutant cancer is a cancer having a mutant or variant N-Ras Q61. In some embodiments, the N-Ras mutant cancer is a cancer having a mutant or variant N-Ras G12D, N-Ras G12V, N-Ras G12C, N-Ras G12R, N-Ras G12A, N-Ras G12S, N-Ras Q61, or any combination thereof.

[00115] In some embodiments, the cancer is a C-Raf mutant cancer. In some embodiments, the mutant C-Raf cancer comprises a C-Raf amplification. As used herein, a “C-Raf amplification” refers to a cancer cell comprising at least three C-Raf copies, at least four C-Raf copies, at least five C-Raf copies, at least six C-Raf copies, at least seven C-Raf copies, at least eight C-Raf copies, at least nine C-Raf copies, at least ten C-Raf copies, or more. In some embodiments, the mutant C-Raf cancer is a cancer having a mutant or variant C-Raf S427. In some embodiments, the mutant or variant C-Raf S427 is C-Raf S427G. In some embodiments, the mutant C-Raf cancer is a cancer having a mutant or variant C-Raf I448. In some embodiments, the mutant C-Raf I448 is C-Raf

I448V. In some embodiments, the mutant C-Raf cancer comprises a C-Raf amplification and/or at least one C-Raf mutant or variant C-Raf.

[00116] In some embodiments, the cancer is an NF1 and/or NF2 mutant cancer. As used herein, an “NF1 mutant cancer” refers to a cancer having a mutant or variant gene encoding the neurofibromin protein, and includes deletion mutations, loss-of-function mutations, microdeletion mutations, missense mutations, copy number loss mutations, and substitution mutations. As used herein, an “NF2 mutant cancer” refers to a cancer having a mutant or variant gene encoding the Merlin protein (also known as schwannomin protein), and includes deletion mutations, loss-of-function mutations, microdeletion mutations, missense mutations, copy number loss mutations, and substitution mutations.

[00117] In some embodiments of the methods and uses described herein, the cancer is selected from non-small cell lung cancer (NSCLC), pancreatic cancer, colorectal cancer (CRC), uterine carcinoma, endometrial carcinoma, bladder cancer, head and neck cancer, thyroid cancer, melanoma, multiple myeloma, acute myeloid leukemia (AML), low-grade serous ovarian cancer, neurofibroma, and glioma.

[00118] In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant non-small cell lung cancer (NSCLC). In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant pancreatic cancer. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant colorectal cancer. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant uterine carcinoma. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant endometrial carcinoma. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant bladder cancer. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant head and neck cancer. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant thyroid cancer. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant low-grade serous ovarian cancer. In some embodiments of the methods and uses described herein, the cancer is an N-Ras mutant melanoma. In some embodiments of the methods and uses described herein, the cancer is an N-Ras mutant multiple myeloma. In some embodiments of the methods and uses described herein, the cancer is an N-Ras mutant acute myeloid leukemia (AML). In some embodiments of the methods and uses described herein, the cancer is an N-Ras mutant Bladder

cancer. In some embodiments of the methods and uses described herein, the cancer is a K-Ras mutant low-grade serous ovarian cancer. In some embodiments of the methods and uses described herein, the cancer is a B-Raf mutant non-small cell lung cancer (NSCLC). In some embodiments of the methods and uses described herein, the cancer is a C-Raf mutant bladder cancer. In some embodiments of the methods and uses described herein, the cancer is an NF1 mutant glioma. In some embodiments of the methods and uses described herein, the cancer is an NF1 mutant non-small cell lung cancer (NSCLC). In some embodiments of the methods and uses described herein, the cancer is an NF2 mutant neurofibroma. In some embodiments of the methods and uses described herein, the cancer is lung cancer, thyroid cancer, ovarian cancer, colorectal cancer, prostate cancer, cancer of the pancreas, cancer of the esophagus, liver cancer, breast cancer, skin cancer, or mesothelioma. In some embodiments, the cancer is mesothelioma, such as malignant mesothelioma. In some embodiments, a cancer includes, without limitation, leukemias (*e.g.*, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (*e.g.*, Hodgkin's disease or non-Hodgkin's disease), Waldenstrom's macroglobulinemia, multiple myeloma, heavy chain disease, and solid tumors such as sarcomas and carcinomas (*e.g.*, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

[00119] In some embodiments, a cancer is glioma, astrocytoma, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

[00120] In some embodiments, a cancer is acoustic neuroma, astrocytoma (*e.g.* Grade I – Pilocytic Astrocytoma, Grade II – Low-grade Astrocytoma, Grade III – Anaplastic Astrocytoma, or Grade IV – Glioblastoma (GBM)), chordoma, CNS lymphoma, craniopharyngioma, brain stem glioma, ependymoma, mixed glioma, optic nerve glioma, subependymoma, medulloblastoma, meningioma, metastatic brain tumor, oligodendroglioma, pituitary tumors, primitive neuroectodermal (PNET) tumor, or schwannoma. In some embodiments, the cancer is a type found more commonly in children than adults, such as brain stem glioma, craniopharyngioma, ependymoma, juvenile pilocytic astrocytoma (JPA), medulloblastoma, optic nerve glioma, pineal tumor, primitive neuroectodermal tumors (PNET), or rhabdoid tumor. In some embodiments, the patient is an adult human. In some embodiments, the patient is a child or pediatric patient.

[00121] Cancer includes, in another embodiment, without limitation, mesothelioma, hepatobiliary (hepatic and biliary duct), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, non-Hodgkins's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

[00122] In some embodiments, a cancer is a solid tumor, such as a sarcoma, carcinoma, or lymphoma. Solid tumors generally comprise an abnormal mass of tissue that typically does not include cysts or liquid areas. In some embodiments, the cancer is selected from renal cell

carcinoma, or kidney cancer; hepatocellular carcinoma (HCC) or hepatoblastoma, or liver cancer; melanoma; breast cancer; colorectal carcinoma, or colorectal cancer; colon cancer; rectal cancer; anal cancer; lung cancer, such as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC); ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, or fallopian tube cancer; papillary serous cystadenocarcinoma or uterine papillary serous carcinoma (UPSC); prostate cancer; testicular cancer; gallbladder cancer; hepatocholangiocarcinoma; soft tissue and bone synovial sarcoma; rhabdomyosarcoma; osteosarcoma; chondrosarcoma; Ewing sarcoma; anaplastic thyroid cancer; adrenocortical carcinoma; pancreatic cancer; pancreatic ductal carcinoma or pancreatic adenocarcinoma; gastrointestinal/stomach (GIST) cancer; lymphoma; squamous cell carcinoma of the head and neck (SCCHN); salivary gland cancer; glioma, or brain cancer; neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST); Waldenstrom's macroglobulinemia; or medulloblastoma.

[00123] In some embodiments, a cancer is hepatocellular carcinoma (HCC). In some embodiments, the cancer is hepatoblastoma. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is rectal cancer. In some embodiments, the cancer is ovarian cancer, or ovarian carcinoma. In some embodiments, the cancer is ovarian epithelial cancer. In some embodiments, the cancer is fallopian tube cancer. In some embodiments, the cancer is papillary serous cystadenocarcinoma. In some embodiments, the cancer is uterine papillary serous carcinoma (UPSC). In some embodiments, the cancer is hepatocholangiocarcinoma. In some embodiments, the cancer is soft tissue and bone synovial sarcoma. In some embodiments, the cancer is rhabdomyosarcoma. In some embodiments, the cancer is osteosarcoma. In some embodiments, the cancer is anaplastic thyroid cancer. In some embodiments, the cancer is adrenocortical carcinoma. In some embodiments, the cancer is pancreatic cancer, or pancreatic ductal carcinoma. In some embodiments, the cancer is pancreatic adenocarcinoma. In some embodiments, the cancer is glioma. In some embodiments, the cancer is malignant peripheral nerve sheath tumors (MPNST). In some embodiments, the cancer is neurofibromatosis-1 associated MPNST. In some embodiments, the cancer is Waldenstrom's macroglobulinemia. In some embodiments, the cancer is medulloblastoma.

[00124] In some embodiments, a cancer is a viral-associated cancer, including human immunodeficiency virus (HIV) associated solid tumors, human papilloma virus (HPV)-16 positive incurable solid tumors, and adult T-cell leukemia, which is caused by human T-cell leukemia virus

type I (HTLV-I) and is a highly aggressive form of CD4+ T-cell leukemia characterized by clonal integration of HTLV-I in leukemic cells (See <https://clinicaltrials.gov/ct2/show/study/NCT02631746>); as well as virus-associated tumors in gastric cancer, nasopharyngeal carcinoma, cervical cancer, vaginal cancer, vulvar cancer, squamous cell carcinoma of the head and neck, and Merkel cell carcinoma. (See <https://clinicaltrials.gov/ct2/show/study/NCT02488759>; see also <https://clinicaltrials.gov/ct2/show/study/NCT0240886>; <https://clinicaltrials.gov/ct2/show/study/NCT02426892>)

[00125] In some embodiments, the methods or uses described herein inhibit or reduce or arrest or ameliorate the growth or spread of a cancer or tumor. In some embodiments, the tumor is treated by arresting, reducing, or inhibiting further growth of the cancer or tumor. In some embodiments, the methods or uses described herein increase or potentiate or activate one or more immune responses to inhibit or reduce or arrest or ameliorate the growth or spread of a cancer or tumor. In some embodiments, the cancer or tumor is treated by reducing the size (*e.g.*, volume or mass) of the cancer or tumor by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% relative to the size of the cancer or tumor prior to treatment. In some embodiments, cancers or tumors are treated by reducing the quantity of the cancers or tumors in the patient by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% relative to the quantity of cancers or tumors prior to treatment.

[00126] In some embodiments, a patient treated using the methods or uses described herein exhibits progression-free survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about one year, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after the treatment is initiated. In some embodiments, a patient treated using the methods or uses described herein exhibits an overall survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about one year, at least about 14 months, at least about 16 months, at least about 18 months, at least about 20 months, at least about 22 months, at least about two years, at least

about three years, at least about four years, or at least about five years after the treatment is initiated.

[00127] In some embodiments, a patient treated using the methods or uses described herein exhibits an objective response rate (ORR) of at least about 15%, at least about 20%, at least about 25%, at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[00128] The compounds and compositions, according to the method of the present disclosure, may be administered using any amount and any route of administration effective for inhibiting MEK and treating or lessening the severity of a disease, for example, as those described herein. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the disease or condition, the particular agent, its mode of administration, and the like. Compounds of the disclosure are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression “dosage unit form” as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “patient”, as used herein, means an animal, preferably a mammal, and most preferably a human.

[00129] Pharmaceutically acceptable compositions of this disclosure can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the disease or disorder being treated. In certain embodiments, the compounds of the disclosure may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about

25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00130] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00131] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00132] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00133] In order to prolong the effect of a compound of the present disclosure, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming

microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00134] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this disclosure with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00135] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00136] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples

of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00137] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00138] Dosage forms for topical or transdermal administration of a compound of this disclosure include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this disclosure. Additionally, the present disclosure contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Co-Administration with One or More Other Therapeutic Agent(s)

[00139] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition, can also be present in the compositions of this disclosure. As used herein, additional therapeutic agents that are normally

administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00140] In some embodiments, the present disclosure provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents. In some embodiments, the combination of the disclosed compound and the additional therapeutic agent or agents acts synergistically.

[00141] A compound of the current disclosure can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the disclosure and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds.

[00142] One or more other therapeutic agent(s) can be administered separately from a compound or composition of the disclosure, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agent(s) may be part of a single dosage form, mixed together with a compound of this disclosure in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent(s) and a compound or composition of the disclosure can be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours from one another. In some embodiments, one or more other therapeutic agent(s) and a compound or composition of the disclosure are administered as a multiple dosage regimen within greater than 24 hours apart.

[00143] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this disclosure. For example, a compound of the present disclosure can be administered with one or more other therapeutic agent(s) simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present disclosure provides a single unit dosage form

comprising a compound of the current disclosure, one or more other therapeutic agent(s), and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00144] The amount of a compound of the disclosure and one or more other therapeutic agent(s) (in those compositions which comprise an additional therapeutic agent as described above) that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Preferably, a composition of the disclosure should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of a compound of the disclosure can be administered.

[00145] In those compositions which comprise one or more other therapeutic agent(s), the one or more other therapeutic agent(s) and a compound of the disclosure can act synergistically. Therefore, the amount of the one or more other therapeutic agent(s) in such compositions may be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 1,000 g/kg body weight/day of the one or more other therapeutic agent(s) can be administered.

[00146] The amount of one or more other therapeutic agent(s) present in the compositions of this disclosure may be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of one or more other therapeutic agent(s) in the presently disclosed compositions ranges from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent. In some embodiments, one or more other therapeutic agent(s) is administered at a dosage of about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the amount normally administered for that agent. As used herein, the phrase "normally administered" means the amount an FDA approved therapeutic agent is approved for dosing per the FDA label insert.

[00147] The compounds of this disclosure, or pharmaceutical compositions thereof, can also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically

acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this disclosure are another embodiment of the present disclosure.

Exemplary Other Therapeutic Agents

[00148] In some embodiments, the one or more other therapeutic agent is a TEAD inhibitor. In certain embodiments, the TEAD inhibitor is selected from those described in WO 2020/243415, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the TEAD inhibitor is selected from those described in WO 2020/243423, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the TEAD inhibitor is selected from those described in U.S. Patent No. 11,274,082, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the TEAD inhibitor is selected from those described in WO 2022/120353, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the TEAD inhibitor is selected from those described in WO 2022/120354, the contents of which are herein incorporated by reference in their entirety.

[00149] In certain embodiments, the one or more other therapeutic agents is a TEAD degrader. In certain embodiments, the TEAD degrader is selected from those described in WO 2022/120355, the contents of which are herein incorporated by reference in their entirety.

[00150] TEAD inhibitors can be produced by organic synthesis methods known to one of ordinary skill in the art. Additionally, certain TEAD inhibitors can be prepared as described in Pobbati *et al.*, "Targeting the Central Pocket in Human Transcription Factor TEAD as a Potential Cancer Therapeutic Strategy," *Structure* 2015, 23, 2076-2086; Gibault *et al.*, "Targeting Transcriptional Enhanced Associate Domains (TEADs)," *J. Med. Chem.* 2018, 61, 5057-5072; Bum-Erdene *et al.*, "Small-Molecule Covalent Modification of Conserved Cysteine Leads to Allosteric Inhibition of the TEADoYap Protein-Protein Interaction," *Cell Chemical Biology* 2019, 26, 1-12; Holden *et al.*, "Small Molecule Dysregulation of TEAD Lipidation Induces a Dominant-Negative Inhibition of HippoPathway Signaling," *Cell Reports* 2020, 31, 107809; WO 2017/053706, WO 2017/111076, WO 2018/204532, WO 2018/235926, US 20190010136, WO 2019/040380, WO 2019/113236, WO 2019/222431, WO 2019/232216, WO 2020/051099, WO 2020/081572, WO 2020/097389, WO 2020/190774, WO 2020/214734, PCT/US2020/35098, and PCT/US2020/35111, the contents of each of which are herein incorporated by reference in its entirety.

[00151] In some embodiments, the one or more other therapeutic agent is an ERK5 inhibitor. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051567, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051565, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051569, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051568, the contents of which are herein incorporated by reference in their entirety.

[00152] In some embodiments, one or more other therapeutic agent is a Poly ADP ribose polymerase (PARP) inhibitor. In some embodiments, a PARP inhibitor is selected from olaparib (LYNPARZA®, AstraZeneca); rucaparib (RUBRACA®, Clovis Oncology); niraparib (ZEJULA®, Tesaro); talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin); veliparib (ABT-888, AbbVie); and BGB-290 (BeiGene, Inc.).

[00153] In some embodiments, one or more other therapeutic agent is a histone deacetylase (HDAC) inhibitor. In some embodiments, an HDAC inhibitor is selected from vorinostat (ZOLINZA®, Merck); romidepsin (ISTODAX®, Celgene); panobinostat (FARYDAK®, Novartis); belinostat (BELEODAQ®, Spectrum Pharmaceuticals); entinostat (SNDX-275, Syndax Pharmaceuticals) (NCT00866333); and chidamide (EPIDAZA®, HBI-8000, Chipscreen Biosciences, China).

[00154] In some embodiments, one or more other therapeutic agent is a CDK inhibitor, such as a CDK4/CDK6 inhibitor. In some embodiments, a CDK 4/6 inhibitor is selected from palbociclib (IBRANCE®, Pfizer); ribociclib (KISQALI®, Novartis); abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics).

[00155] In some embodiments, one or more other therapeutic agent is a phosphatidylinositol 3 kinase (PI3K) inhibitor. In some embodiments, a PI3K inhibitor is selected from idelalisib (ZYDELIG®, Gilead), alpelisib (BYL719, Novartis), taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity Pharmaceuticals); PQR309 (Piqur Therapeutics, Switzerland); and TGR1202 (formerly RP5230, TG Therapeutics).

[00156] In some embodiments, one or more other therapeutic agent is a platinum-based therapeutic, also referred to as platins. Platins cause cross-linking of DNA, such that they inhibit DNA repair and/or DNA synthesis, mostly in rapidly reproducing cells, such as cancer cells.

[00157] In some embodiments, a platinum-based therapeutic is selected from cisplatin (PLATINOL®, Bristol-Myers Squibb); carboplatin (PARAPLATIN®, Bristol-Myers Squibb; also, Teva; Pfizer); oxaliplatin (ELOXITIN® Sanofi-Aventis); nedaplatin (AQUPLA®, Shionogi), picoplatin (Poniard Pharmaceuticals); and satraplatin (JM-216, Agennix).

[00158] In some embodiments, one or more other therapeutic agent is a taxane compound, which causes disruption of microtubules, which are essential for cell division. In some embodiments, a taxane compound is selected from paclitaxel (TAXOL®, Bristol-Myers Squibb), docetaxel (TAXOTERE®, Sanofi-Aventis; DOCEFREZ®, Sun Pharmaceutical), albumin-bound paclitaxel (ABRAXANE®; Abraxis/Celgene), cabazitaxel (JEVTANA®, Sanofi-Aventis), and SID530 (SK Chemicals, Co.) (NCT00931008).

[00159] In some embodiments, one or more other therapeutic agent is a nucleoside inhibitor, or a therapeutic agent that interferes with normal DNA synthesis, protein synthesis, cell replication, or will otherwise inhibit rapidly proliferating cells.

[00160] In some embodiments, a nucleoside inhibitor is selected from trabectedin (guanidine alkylating agent, YONDELIS®, Janssen Oncology), mechlorethamine (alkylating agent, VALCHLOR®, Aktelion Pharmaceuticals); vincristine (ONCOVIN®, Eli Lilly; VINCASAR®, Teva Pharmaceuticals; MARQIBO®, Talon Therapeutics); temozolomide (prodrug to alkylating agent 5-(3-methyltriazene-1-yl)-imidazole-4-carboxamide (MTIC) TEMODAR®, Merck); cytarabine injection (ara-C, antimetabolic cytidine analog, Pfizer); lomustine (alkylating agent, CEENU®, Bristol-Myers Squibb; GLEOSTINE®, NextSource Biotechnology); azacitidine (pyrimidine nucleoside analog of cytidine, VIDAZA®, Celgene); omacetaxine mepesuccinate (cephalotaxine ester) (protein synthesis inhibitor, SYNRIPO®, Teva Pharmaceuticals); asparaginase *Erwinia chrysanthemi* (enzyme for depletion of asparagine, ELSPAR®, Lundbeck; ERWINAZE®, EUSA Pharma); eribulin mesylate (microtubule inhibitor, tubulin-based antimetabolic, HALAVEN®, Eisai); cabazitaxel (microtubule inhibitor, tubulin-based antimetabolic, JEVTANA®, Sanofi-Aventis); capecitabine (thymidylate synthase inhibitor, XELODA®, Genentech); bendamustine (bifunctional mechlorethamine derivative, believed to form interstrand DNA cross-links, TREANDA®, Cephalon/Teva); ixabepilone (semi-synthetic analog of

epothilone B, microtubule inhibitor, tubulin-based antimetabolic, IXEMPRA®, Bristol-Myers Squibb); nelarabine (prodrug of deoxyguanosine analog, nucleoside metabolic inhibitor, ARRANON®, Novartis); clorafabine (prodrug of ribonucleotide reductase inhibitor, competitive inhibitor of deoxycytidine, CLOLAR®, Sanofi-Aventis); and trifluridine and tipiracil (thymidine-based nucleoside analog and thymidine phosphorylase inhibitor, LONSURF®, Taiho Oncology).

[00161] In some embodiments, one or more other therapeutic agent is a kinase inhibitor or VEGF-R antagonist. Approved VEGF inhibitors and kinase inhibitors useful in the present disclosure include: bevacizumab (AVASTIN®, Genentech/Roche) an anti-VEGF monoclonal antibody; ramucirumab (CYRAMZA®, Eli Lilly), an anti-VEGFR-2 antibody and ziv-aflibercept, also known as VEGF Trap (ZALTRAP®, Regeneron/Sanofi). VEGFR inhibitors, such as regorafenib (STIVARGA®, Bayer); vandetanib (CAPRELSA®, AstraZeneca); axitinib (INLYTA®, Pfizer); and lenvatinib (LENVIMA®, Eisai); Raf inhibitors, such as sorafenib (NEXAVAR®, Bayer AG and Onyx); dabrafenib (TAFINLAR®, Novartis); and vemurafenib (ZELBORAF®, Genentech/Roche); MEK inhibitors, such as cobimetanib (COTELLIC®, Exelexis/Genentech/Roche); trametinib (MEKINIST®, Novartis); Bcr-Abl tyrosine kinase inhibitors, such as imatinib (GLEEVEC®, Novartis); nilotinib (TASIGNA®, Novartis); dasatinib (SPRYCEL®, BristolMyersSquibb); bosutinib (BOSULIF®, Pfizer); and ponatinib (INCLUSIG®, Ariad Pharmaceuticals); Her2 and EGFR inhibitors, such as gefitinib (IRESSA®, AstraZeneca); erlotinib (TARCEEVA®, Genentech/Roche/Astellas); lapatinib (TYKERB®, Novartis); afatinib (GILOTRIF®, Boehringer Ingelheim); osimertinib (targeting activated EGFR, TAGRISSO®, AstraZeneca); and brigatinib (ALUNBRIG®, Ariad Pharmaceuticals); c-Met and VEGFR2 inhibitors, such as cabozantinib (COMETRIQ®, Exelexis); and multikinase inhibitors, such as sunitinib (SUTENT®, Pfizer); pazopanib (VOTRIENT®, Novartis); ALK inhibitors, such as crizotinib (XALKORI®, Pfizer); ceritinib (ZYKADIA®, Novartis); and alectinib (ALECENZA®, Genentech/Roche); Bruton's tyrosine kinase inhibitors, such as ibrutinib (IMBRUVICA®, Pharmacyclics/Janssen); and Flt3 receptor inhibitors, such as midostaurin (RYDAPT®, Novartis).

[00162] Other kinase inhibitors and VEGF-R antagonists that are in development and may be used in the present disclosure include tivozanib (Aveo Pharmaceuticals); vatalanib (Bayer/Novartis); lucitanib (Clovis Oncology); dovitinib (TKI258, Novartis); Chiauanib (Chipscreen Biosciences); CEP-11981 (Cephalon); linifanib (Abbott Laboratories); neratinib

(HKI-272, Puma Biotechnology); radotinib (SUPECT®, IY5511, Il-Yang Pharmaceuticals, S. Korea); ruxolitinib (JAKAFI®, Incyte Corporation); PTC299 (PTC Therapeutics); CP-547,632 (Pfizer); foretinib (Exelexis, GlaxoSmithKline); quizartinib (Daiichi Sankyo) and motesanib (Amgen/Takeda).

[00163] In some embodiments, one or more other therapeutic agent is an mTOR inhibitor, which inhibits cell proliferation, angiogenesis and glucose uptake. In some embodiments, an mTOR inhibitor is everolimus (AFINITOR®, Novartis); temsirolimus (TORISEL®, Pfizer); and sirolimus (RAPAMUNE®, Pfizer).

[00164] In some embodiments, one or more other therapeutic agent is a proteasome inhibitor. Approved proteasome inhibitors useful in the present disclosure include bortezomib (VELCADE®, Takeda); carfilzomib (KYPROLIS®, Amgen); and ixazomib (NINLARO®, Takeda).

[00165] In some embodiments, one or more other therapeutic agent is a growth factor antagonist, such as an antagonist of platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) or its receptor (EGFR). Approved PDGF antagonists which may be used in the present disclosure include olaratumab (LARTRUVO®; Eli Lilly). Approved EGFR antagonists which may be used in the present disclosure include cetuximab (ERBITUX®, Eli Lilly); necitumumab (PORTRAZZA®, Eli Lilly), panitumumab (VECTIBIX®, Amgen); and osimertinib (targeting activated EGFR, TAGRISSO®, AstraZeneca).

[00166] In some embodiments, one or more other therapeutic agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from exemestane (AROMASIN®, Pfizer); anastazole (ARIMIDEX®, AstraZeneca) and letrozole (FEMARA®, Novartis).

[00167] In some embodiments, one or more other therapeutic agent is an antagonist of the hedgehog pathway. Approved hedgehog pathway inhibitors which may be used in the present disclosure include sonidegib (ODOMZO®, Sun Pharmaceuticals); and vismodegib (ERIVEDGE®, Genentech), both for treatment of basal cell carcinoma.

[00168] In some embodiments, one or more other therapeutic agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present disclosure include pemetrexed (ALIMTA®, Eli Lilly).

[00169] In some embodiments, one or more other therapeutic agent is a CC chemokine receptor 4 (CCR4) inhibitor. CCR4 inhibitors being studied that may be useful in the present disclosure include mogamulizumab (POTELIGEO®, Kyowa Hakko Kirin, Japan).

[00170] In some embodiments, one or more other therapeutic agent is an isocitrate dehydrogenase (IDH) inhibitor. IDH inhibitors being studied which may be used in the present disclosure include AG120 (Celgene; NCT02677922); AG221 (Celgene, NCT02677922; NCT02577406); BAY1436032 (Bayer, NCT02746081); IDH305 (Novartis, NCT02987010).

[00171] In some embodiments, one or more other therapeutic agent is an arginase inhibitor. Arginase inhibitors being studied which may be used in the present disclosure include AEB1102 (pegylated recombinant arginase, Aeglea Biotherapeutics), which is being studied in Phase 1 clinical trials for acute myeloid leukemia and myelodysplastic syndrome (NCT02732184) and solid tumors (NCT02561234); and CB-1158 (Calithera Biosciences).

[00172] In some embodiments, one or more other therapeutic agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present disclosure include CB-839 (Calithera Biosciences).

[00173] In some embodiments, one or more other therapeutic agent is an antibody that binds to tumor antigens, that is, proteins expressed on the cell surface of tumor cells. Approved antibodies that bind to tumor antigens which may be used in the present disclosure include rituximab (RITUXAN®, Genentech/BiogenIdec); ofatumumab (anti-CD20, ARZERRA®, GlaxoSmithKline); obinutuzumab (anti-CD20, GAZYVA®, Genentech), ibritumomab (anti-CD20 and Yttrium-90, ZEVALIN®, Spectrum Pharmaceuticals); daratumumab (anti-CD38, DARZALEX®, Janssen Biotech), dinutuximab (anti-glycolipid GD2, UNITUXIN®, United Therapeutics); trastuzumab (anti-HER2, HERCEPTIN®, Genentech); ado-trastuzumab emtansine (anti-HER2, fused to emtansine, KADCYLA®, Genentech); and pertuzumab (anti-HER2, PERJETA®, Genentech); and brentuximab vedotin (anti-CD30-drug conjugate, ADCETRIS®, Seattle Genetics).

[00174] In some embodiments, one or more other therapeutic agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present disclosure include irinotecan (ONIVYDE®, Merrimack Pharmaceuticals); topotecan (HYCAMTIN®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present disclosure include pixantrone (PIXUVRI®, CTI Biopharma).

[00175] In some embodiments, one or more other therapeutic agent is an inhibitor of anti-apoptotic proteins, such as BCL-2. Approved anti-apoptotics which may be used in the present disclosure include venetoclax (VENCLEXTA®, AbbVie/Genentech); and blinatumomab (BLINCYTO®, Amgen). Other therapeutic agents targeting apoptotic proteins which have undergone clinical testing and may be used in the present disclosure include navitoclax (ABT-263, Abbott), a BCL-2 inhibitor (NCT02079740).

[00176] In some embodiments, one or more other therapeutic agent is an androgen receptor inhibitor. Approved androgen receptor inhibitors useful in the present disclosure include enzalutamide (XTANDI®, Astellas/Medivation); approved inhibitors of androgen synthesis include abiraterone (ZYTIGA®, Centocor/Ortho); approved antagonist of gonadotropin-releasing hormone (GnRH) receptor (degaralix, FIRMAGON®, Ferring Pharmaceuticals).

[00177] In some embodiments, one or more other therapeutic agent is a selective estrogen receptor modulator (SERM), which interferes with the synthesis or activity of estrogens. Approved SERMs useful in the present disclosure include raloxifene (EVISTA®, Eli Lilly).

[00178] In some embodiments, one or more other therapeutic agent is an inhibitor of bone resorption. An approved therapeutic which inhibits bone resorption is Denosumab (XGEVA®, Amgen), an antibody that binds to RANKL, prevents binding to its receptor RANK, found on the surface of osteoclasts, their precursors, and osteoclast-like giant cells, which mediates bone pathology in solid tumors with osseous metastases. Other approved therapeutics that inhibit bone resorption include bisphosphonates, such as zoledronic acid (ZOMETA®, Novartis).

[00179] In some embodiments, one or more other therapeutic agent is an inhibitor of interaction between the two primary p53 suppressor proteins, MDMX and MDM2. Inhibitors of p53 suppression proteins being studied which may be used in the present disclosure include ALRN-6924 (Aileron), a stapled peptide that equipotently binds to and disrupts the interaction of MDMX and MDM2 with p53. ALRN-6924 is currently being evaluated in clinical trials for the treatment of AML, advanced myelodysplastic syndrome (MDS) and peripheral T-cell lymphoma (PTCL) (NCT02909972; NCT02264613).

[00180] In some embodiments, one or more other therapeutic agent is an inhibitor of transforming growth factor-beta (TGF-beta or TGF-β). Inhibitors of TGF-beta proteins being studied which may be used in the present disclosure include NIS793 (Novartis), an anti-TGF-beta antibody being tested in the clinic for treatment of various cancers, including breast, lung,

hepatocellular, colorectal, pancreatic, prostate and renal cancer (NCT 02947165). In some embodiments, the inhibitor of TGF-beta proteins is fresolimumab (GC1008; Sanofi-Genzyme), which is being studied for melanoma (NCT00923169); renal cell carcinoma (NCT00356460); and non-small cell lung cancer (NCT02581787). Additionally, in some embodiments, the additional therapeutic agent is a TGF-beta trap, such as described in Connolly et al. (2012) *Int'l J. Biological Sciences* 8:964-978. One therapeutic compound currently in clinical trials for treatment of solid tumors is M7824 (Merck KgaA - formerly MSB0011459X), which is a bispecific, anti-PD-L1/TGF- β trap compound (NCT02699515); and (NCT02517398). M7824 is comprised of a fully human IgG1 antibody against PD-L1 fused to the extracellular domain of human TGF-beta receptor II, which functions as a TGF- β "trap."

[00181] In some embodiments, one or more other therapeutic agent is selected from glembatumumab vedotin-monomethyl auristatin E (MMAE) (Celldex), an anti-glycoprotein NMB (gpNMB) antibody (CR011) linked to the cytotoxic MMAE. gpNMB is a protein overexpressed by multiple tumor types associated with cancer cells' ability to metastasize.

[00182] In some embodiments, one or more other therapeutic agents is an antiproliferative compound. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (TEMODAL[®]); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or

pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZd₆244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00183] The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name AROMASIN™. Formestane is marketed under the trade name LENTARON™. Fadrozole is marketed under the trade name AFEMA™. Anastrozole is marketed under the trade name ARIMIDEX™. Letrozole is marketed under the trade names FEMARA™ or FEMAr™. Aminoglutethimide is marketed under the trade name ORIMETEN™. A combination of the disclosure comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[00184] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name NOLVADEX™. Raloxifene hydrochloride is marketed under the trade name EVISTA™. Fulvestrant can be administered under the trade name FASLODEX™. Fulvestrant can be administered under the trade name Faslodex™. A combination of the disclosure comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, such as breast tumors.

[00185] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX™). The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin, and goserelin acetate. Goserelin can be administered under the trade name ZOLADEX™.

[00186] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, *e.g.*, in the

form as it is marketed, *e.g.*, under the trademark CAMPTOSAR™. Topotecan is marketed under the trade name Hycamptin™.

[00187] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as CAELYX™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophyllotoxines etoposide and teniposide. Etoposide is marketed under the trade name ETOPOPHOS™. Teniposide is marketed under the trade name VM 26-Bristol. Doxorubicin is marketed under the trade name Acriblastin™ or Adriamycin™. Epirubicin is marketed under the trade name Farmorubicin™. Idarubicin is marketed under the trade name Zavedos™. Mitoxantrone is marketed under the trade name Novantron™.

[00188] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; cochicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name Taxol™. Docetaxel is marketed under the trade name Taxotere™. Vinblastine sulfate is marketed under the trade name Vinblastin R.P™. Vincristine sulfate is marketed under the trade name Farmistin™.

[00189] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide is marketed under the trade name Cyclostin™. Ifosfamide is marketed under the trade name Holoxan™.

[00190] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[00191] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name Xeloda™. Gemcitabine is marketed under the trade name Gemzar™.

[00192] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.*, under the trademark CARBOPLAT™. Oxaliplatin can be administered, *e.g.*, in the form as it is marketed, *e.g.* under the trademark ELOXATIN™.

[00193] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-111; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the AxI receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting, decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (*e.g.*, BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1,

PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVECT[™]) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5- dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR₁ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (HERCEPTIN[™]), cetuximab (ERBITUX[™]), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothed

receptor (SMO) pathways, including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[00194] The term “PI3K inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3K α , PI3K γ , PI3K δ , PI3K β , PI3K-C2 α , PI3K-C2 β , PI3K-C2 γ , Vps34, p110- α , p110- β , p110- γ , p110- δ , p85- α , p85- β , p55- γ , p150, p101, and p87. Examples of PI3K inhibitors useful in this disclosure include but are not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib.

[00195] The term “Bcl-2 inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta’s pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; see WO2008118802), navitoclax (and analogs thereof, see US7390799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, see WO2004106328), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[00196] The term “BTK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against Bruton’s Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[00197] The term “SYK inhibitor” as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib.

[00198] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this disclosure can be found in WO2008039218 and WO2011090760, the entirety of which are incorporated herein by reference.

[00199] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this disclosure can be found in WO2003063794, WO2005007623, and WO2006078846, the entirety of which are incorporated herein by reference.

[00200] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this disclosure can be found in WO2004019973, WO2004089925, WO2007016176, US8138347, WO2002088112, WO2007084786, WO2007129161, WO2006122806, WO2005113554, and WO2007044729 the entirety of which are incorporated herein by reference.

[00201] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this disclosure can be found in WO2009114512, WO2008109943, WO2007053452, WO2000142246, and WO2007070514, the entirety of which are incorporated herein by reference.

[00202] Further anti-angiogenic compounds include compounds having another mechanism for their activity, *e.g.*, unrelated to protein or lipid kinase inhibition *e.g.*, thalidomide (THALOMID™) and TNP-470.

[00203] Examples of proteasome inhibitors useful for use in combination with compounds of the disclosure include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[00204] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are *e.g.*, inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00205] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α - γ - or δ - tocopherol or α - γ - or δ -tocotrienol.

[00206] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylaminoethylacetic acid and derivatives, such as celecoxib (

[00207] CELEBREX™), rofecoxib (VIOXX™), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminoethylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)ethyl acetic acid, lumiracoxib.

[00208] The term "bisphosphonates" as used herein includes, but is not limited to, etidronic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridronic acid is marketed under the trade name DIDRONEL™. Clodronic acid is marketed under the trade name BONEFOS™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name AREDIA™. Alendronic acid is marketed under the trade name FOSAMAX™. Ibandronic acid is marketed under the trade name BONDRANAT™. Risedronic

acid is marketed under the trade name ACTONEL™. Zoledronic acid is marketed under the trade name ZOMETA™. The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (RAPAMUNE®), everolimus (CERTICAN™), CCI-779 and ABT578.

[00209] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[00210] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R115777 (ZARNESTRA™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[00211] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[00212] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (VELCADE™) and MLN 341.

[00213] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, *e.g.*, hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

[00214] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R);

interferon, 1- β -D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[00215] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00216] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteasome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[00217] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (HERCEPTIN™), Trastuzumab-DM1, erbitux, bevacizumab (AVASTIN™), rituximab (RITUXAN®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[00218] For the treatment of acute myeloid leukemia (AML), compounds of the current disclosure can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current disclosure can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[00219] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including,

but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]- amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

[00220] Also included are EDG binders and ribonucleotide reductase inhibitors. The term "EDG binders" as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1,3-dione derivatives.

[00221] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; ANGIOSTATIN[™]; ENDOSTATIN[™]; anthranilic acid amides; ZD4190; ZD₆474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMAb and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (AVASTIN[™]).

[00222] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as VISUDYNET[™] and porfimer sodium.

[00223] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11- α -epihydrocortisol,

cortisolone, 17 α -hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[00224] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00225] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[00226] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, *e.g.*, Patents International (*e.g.*, IMS World Publications).

Exemplary Immuno-Oncology agents

[00227] In some embodiments, one or more other therapeutic agent is an immuno-oncology agent. As used herein, the term "an immuno-oncology agent" refers to an agent which is effective to enhance, stimulate, and/or up-regulate immune responses in a subject. In some embodiments, the administration of an immuno-oncology agent with a compound of the disclosure has a synergic effect in treating a cancer.

[00228] An immuno-oncology agent can be, for example, a small molecule drug, an antibody, or a biologic or small molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In some embodiments, an antibody is a monoclonal antibody. In some embodiments, a monoclonal antibody is humanized or human.

[00229] In some embodiments, an immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses.

[00230] Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes

CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LT β R, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α /TNF β , TNFR2, TNF α , LT β R, Lymphotoxin α 1 β 2, FAS, FASL, RELT, DR6, TROY, NGFR.

[00231] In some embodiments, an immuno-oncology agent is a cytokine that inhibits T cell activation (*e.g.*, IL-6, IL-10, TGF- β , VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

[00232] In some embodiments, a combination of a compound of the disclosure and an immuno-oncology agent can stimulate T cell responses. In some embodiments, an immuno-oncology agent is: (i) an antagonist of a protein that inhibits T cell activation (*e.g.*, immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4; or (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

[00233] In some embodiments, an immuno-oncology agent is an antagonist of inhibitory receptors on NK cells or an agonist of activating receptors on NK cells. In some embodiments, an immuno-oncology agent is an antagonist of KIR, such as lirilumab.

[00234] In some embodiments, an immuno-oncology agent is an agent that inhibits or depletes macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

[00235] In some embodiments, an immuno-oncology agent is selected from agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (*e.g.*, block inhibitory receptor engagement (*e.g.*, PD-L1/PD-1 interactions), deplete or inhibit Tregs (*e.g.*, using an anti-CD25 monoclonal antibody (*e.g.*,

daclizumab) or by *ex vivo* anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell energy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

[00236] In some embodiments, an immuno-oncology agent is a CTLA-4 antagonist. In some embodiments, a CTLA-4 antagonist is an antagonistic CTLA-4 antibody. In some embodiments, an antagonistic CTLA-4 antibody is YERVOY (ipilimumab) or tremelimumab.

[00237] In some embodiments, an immuno-oncology agent is a PD-1 antagonist. In some embodiments, a PD-1 antagonist is administered by infusion. In some embodiments, an immuno-oncology agent is an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity. In some embodiments, a PD-1 antagonist is an antagonistic PD-1 antibody. In some embodiments, an antagonistic PD-1 antibody is OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). In some embodiments, an immuno-oncology agent may be pidilizumab (CT-011). In some embodiments, an immuno-oncology agent is a recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224.

[00238] In some embodiments, an immuno-oncology agent is a PD-L1 antagonist. In some embodiments, a PD-L1 antagonist is an antagonistic PD-L1 antibody. In some embodiments, a PD-L1 antibody is MPDL3280A (RG7446; WO2010/077634), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), and MSB0010718C (WO2013/79174).

[00239] In some embodiments, an immuno-oncology agent is a LAG-3 antagonist. In some embodiments, a LAG-3 antagonist is an antagonistic LAG-3 antibody. In some embodiments, a LAG3 antibody is BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO009/44273).

[00240] In some embodiments, an immuno-oncology agent is a CD137 (4-1BB) agonist. In some embodiments, a CD137 (4-1BB) agonist is an agonistic CD137 antibody. In some embodiments, a CD137 antibody is urelumab or PF-05082566 (WO12/32433).

[00241] In some embodiments, an immuno-oncology agent is a GITR agonist. In some embodiments, a GITR agonist is an agonistic GITR antibody. In some embodiments, a GITR antibody is BMS-986153, BMS-986156, TRX-518 (WO006/105021, WO009/009116), or MK-4166 (WO11/028683).

[00242] In some embodiments, an immuno-oncology agent is an indoleamine (2,3)-dioxygenase (IDO) antagonist. In some embodiments, an IDO antagonist is selected from epacadostat (INCB024360, Incyte); indoximod (NLG-8189, NewLink Genetics Corporation); capmanitib (INC280, Novartis); GDC-0919 (Genentech/Roche); PF-06840003 (Pfizer); BMS:F001287 (Bristol-Myers Squibb); Phy906/KD108 (Phytoceutica); an enzyme that breaks down kynurenine (Kynase, Ikena Oncology, formerly known as Kyn Therapeutics); and NLG-919 (WO09/73620, WO009/1156652, WO11/56652, WO12/142237).

[00243] In some embodiments, an immuno-oncology agent is an OX40 agonist. In some embodiments, an OX40 agonist is an agonistic OX40 antibody. In some embodiments, an OX40 antibody is MEDI-6383 or MEDI-6469.

[00244] In some embodiments, an immuno-oncology agent is an OX40L antagonist. In some embodiments, an OX40L antagonist is an antagonistic OX40 antibody. In some embodiments, an OX40L antagonist is RG-7888 (WO06/029879).

[00245] In some embodiments, an immuno-oncology agent is a CD40 agonist. In some embodiments, a CD40 agonist is an agonistic CD40 antibody. In some embodiments, an immuno-oncology agent is a CD40 antagonist. In some embodiments, a CD40 antagonist is an antagonistic CD40 antibody. In some embodiments, a CD40 antibody is lucatumumab or dacetuzumab.

[00246] In some embodiments, an immuno-oncology agent is a CD27 agonist. In some embodiments, a CD27 agonist is an agonistic CD27 antibody. In some embodiments, a CD27 antibody is varlilumab.

[00247] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[00248] In some embodiments, an immuno-oncology agent is abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, atezolimab, avelumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, or tremelimumab.

[00249] In some embodiments, an immuno-oncology agent is an immunostimulatory agent. For example, antibodies blocking the PD-1 and PD-L1 inhibitory axis can unleash activated tumor-reactive T cells and have been shown in clinical trials to induce durable anti-tumor responses in

increasing numbers of tumor histologies, including some tumor types that conventionally have not been considered immunotherapy sensitive. See, e.g., Okazaki, T. *et al.* (2013) *Nat. Immunol.* 14, 1212–1218; Zou *et al.* (2016) *Sci. Transl. Med.* 8. The anti-PD-1 antibody nivolumab (OPDIVO[®], Bristol-Myers Squibb, also known as ONO-4538, MDX1106 and BMS-936558), has shown potential to improve the overall survival in patients with RCC who had experienced disease progression during or after prior anti-angiogenic therapy.

[00250] In some embodiments, the immunomodulatory therapeutic specifically induces apoptosis of tumor cells. Approved immunomodulatory therapeutics which may be used in the present disclosure include pomalidomide (POMALYST[®], Celgene); lenalidomide (REVLIMID[®], Celgene); ingenol mebutate (PICATO[®], LEO Pharma).

[00251] In some embodiments, an immuno-oncology agent is a cancer vaccine. In some embodiments, the cancer vaccine is selected from sipuleucel-T (PROVENGE[®], Dendreon/Valeant Pharmaceuticals), which has been approved for treatment of asymptomatic, or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer; and talimogene laherparepvec (IMLYGIC[®], BioVex/Amgen, previously known as T-VEC), a genetically modified oncolytic viral therapy approved for treatment of unresectable cutaneous, subcutaneous and nodal lesions in melanoma. In some embodiments, an immuno-oncology agent is selected from an oncolytic viral therapy such as pexastimogene devacirepvec (PexaVec/JX-594, SillaJen/formerly Jennerex Biotherapeutics), a thymidine kinase- (TK-) deficient vaccinia virus engineered to express GM-CSF, for hepatocellular carcinoma (NCT02562755) and melanoma (NCT00429312); pelareorep (REOLYSIN[®], Oncolytics Biotech), a variant of respiratory enteric orphan virus (reovirus) which does not replicate in cells that are not RAS-activated, in numerous cancers, including colorectal cancer (NCT01622543); prostate cancer (NCT01619813); head and neck squamous cell cancer (NCT01166542); pancreatic adenocarcinoma (NCT00998322); and non-small cell lung cancer (NSCLC) (NCT 00861627); enadenotucirev (NG-348, PsiOxus, formerly known as ColoAd1), an adenovirus engineered to express a full length CD80 and an antibody fragment specific for the T-cell receptor CD3 protein, in ovarian cancer (NCT02028117); metastatic or advanced epithelial tumors such as in colorectal cancer, bladder cancer, head and neck squamous cell carcinoma and salivary gland cancer (NCT02636036); ONCOS-102 (Targovax/formerly Oncos), an adenovirus engineered to express GM-CSF, in melanoma (NCT03003676); and peritoneal disease, colorectal cancer or ovarian cancer (NCT02963831); GL-

ONC1 (GLV-1h68/GLV-1h153, Genelux GmbH), vaccinia viruses engineered to express beta-galactosidase (beta-gal)/beta-glucuronidase or beta-gal/human sodium iodide symporter (hNIS), respectively, were studied in peritoneal carcinomatosis (NCT01443260); fallopian tube cancer, ovarian cancer (NCT 02759588); or CG0070 (Cold Genesys), an adenovirus engineered to express GM-CSF, in bladder cancer (NCT02365818).

[00252] In some embodiments, an immuno-oncology agent is selected from JX-929 (SillaJen/formerly Jennerex Biotherapeutics), a TK- and vaccinia growth factor-deficient vaccinia virus engineered to express cytosine deaminase, which is able to convert the prodrug 5-fluorocytosine to the cytotoxic drug 5-fluorouracil; TG01 and TG02 (Targovax/formerly Oncos), peptide-based immunotherapy agents targeted for difficult-to-treat RAS mutations; and TILT-123 (TILT Biotherapeutics), an engineered adenovirus designated: Ad5/3-E2F-delta24-hTNF α -IRES-hIL20; and VSV-GP (ViraTherapeutics) a vesicular stomatitis virus (VSV) engineered to express the glycoprotein (GP) of lymphocytic choriomeningitis virus (LCMV), which can be further engineered to express antigens designed to raise an antigen-specific CD8⁺ T cell response.

[00253] In some embodiments, an immuno-oncology agent is a T-cell engineered to express a chimeric antigen receptor, or CAR. The T-cells engineered to express such chimeric antigen receptor are referred to as a CAR-T cells.

[00254] CARs have been constructed that consist of binding domains, which may be derived from natural ligands, single chain variable fragments (scFv) derived from monoclonal antibodies specific for cell-surface antigens, fused to endodomains that are the functional end of the T-cell receptor (TCR), such as the CD3-zeta signaling domain from TCRs, which is capable of generating an activation signal in T lymphocytes. Upon antigen binding, such CARs link to endogenous signaling pathways in the effector cell and generate activating signals similar to those initiated by the TCR complex.

[00255] For example, in some embodiments the CAR-T cell is one of those described in U.S. Patent 8,906,682 (June *et al.*; hereby incorporated by reference in its entirety), which discloses CAR-T cells engineered to comprise an extracellular domain having an antigen binding domain (such as a domain that binds to CD19), fused to an intracellular signaling domain of the T cell antigen receptor complex zeta chain (such as CD3 zeta). When expressed in the T cell, the CAR is able to redirect antigen recognition based on the antigen binding specificity. In the case of CD19, the antigen is expressed on malignant B cells. Over 200 clinical trials are currently in

progress employing CAR-T in a wide range of indications. [<https://clinicaltrials.gov/ct2/results?term=chimeric+antigen+receptors&pg=1>].

[00256] In some embodiments, an immunostimulatory agent is an activator of retinoic acid receptor-related orphan receptor γ (ROR γ t). ROR γ t is a transcription factor with key roles in the differentiation and maintenance of Type 17 effector subsets of CD4⁺ (Th17) and CD8⁺ (Tc17) T cells, as well as the differentiation of IL-17 expressing innate immune cell subpopulations such as NK cells. In some embodiments, an activator of ROR γ t is LYC-55716 (Lycera), which is currently being evaluated in clinical trials for the treatment of solid tumors (NCT02929862).

[00257] In some embodiments, an immunostimulatory agent is an agonist or activator of a toll-like receptor (TLR). Suitable activators of TLRs include an agonist or activator of TLR9 such as SD-101 (Dynavax). SD-101 is an immunostimulatory CpG which is being studied for B-cell, follicular and other lymphomas (NCT02254772). Agonists or activators of TLR8 which may be used in the present disclosure include motolimod (VTX-2337, VentiRx Pharmaceuticals) which is being studied for squamous cell cancer of the head and neck (NCT02124850) and ovarian cancer (NCT02431559).

[00258] Other immuno-oncology agents that can be used in the present disclosure include urelumab (BMS-663513, Bristol-Myers Squibb), an anti-CD137 monoclonal antibody; varlilumab (CDX-1127, Celldex Therapeutics), an anti-CD27 monoclonal antibody; BMS-986178 (Bristol-Myers Squibb), an anti-OX40 monoclonal antibody; lirilumab (IPH2102/BMS-986015, Innate Pharma, Bristol-Myers Squibb), an anti-KIR monoclonal antibody; monalizumab (IPH2201, Innate Pharma, AstraZeneca) an anti-NKG2A monoclonal antibody; andecaliximab (GS-5745, Gilead Sciences), an anti-MMP9 antibody; MK-4166 (Merck & Co.), an anti-GITR monoclonal antibody.

[00259] In some embodiments, an immunostimulatory agent is selected from elotuzumab, mifamurtide, an agonist or activator of a toll-like receptor, and an activator of ROR γ t.

[00260] In some embodiments, an immunostimulatory therapeutic is recombinant human interleukin 15 (rhIL-15). rhIL-15 has been tested in the clinic as a therapy for melanoma and renal cell carcinoma (NCT01021059 and NCT01369888) and leukemias (NCT02689453). In some embodiments, an immunostimulatory agent is recombinant human interleukin 12 (rhIL-12). In some embodiments, an IL-15 based immunotherapeutic is heterodimeric IL-15 (hetIL-15, Novartis/Admune), a fusion complex composed of a synthetic form of endogenous IL-15

complexed to the soluble IL-15 binding protein IL-15 receptor alpha chain (IL15:sIL-15RA), which has been tested in Phase 1 clinical trials for melanoma, renal cell carcinoma, non-small cell lung cancer and head and neck squamous cell carcinoma (NCT02452268). In some embodiments, a recombinant human interleukin 12 (rhIL-12) is NM-IL-12 (Neumedicines, Inc.), NCT02544724, or NCT02542124.

[00261] In some embodiments, an immuno-oncology agent is selected from those described in Jerry L. Adams *et al.*, “Big opportunities for small molecules in immuno-oncology,” *Cancer Therapy* **2015**, Vol. 14, pages 603-622, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is selected from the examples described in Table 1 of Jerry L. Adams *et al.* In some embodiments, an immuno-oncology agent is a small molecule targeting an immuno-oncology target selected from those listed in Table 2 of Jerry L. Adams *et al.* In some embodiments, an immuno-oncology agent is a small molecule agent selected from those listed in Table 2 of Jerry L. Adams *et al.*

[00262] In some embodiments, an immuno-oncology agent is selected from the small molecule immuno-oncology agents described in Peter L. Toogood, “Small molecule immuno-oncology therapeutic agents,” *Bioorganic & Medicinal Chemistry Letters* **2018**, Vol. 28, pages 319-329, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is an agent targeting the pathways as described in Peter L. Toogood.

[00263] In some embodiments, an immuno-oncology agent is selected from those described in Sandra L. Ross *et al.*, “Bispecific T cell engager (BITE®) antibody constructs can mediate bystander tumor cell killing”, *PLoS ONE* 12(8): e0183390, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is a bispecific T cell engager (BITE®) antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct is a CD19/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct is an EGFR/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells, which release cytokines inducing upregulation of intercellular adhesion molecule 1 (ICAM-1) and FAS on bystander cells. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells which result in induced bystander cell lysis. In some embodiments, the bystander cells are in solid tumors. In some embodiments, the bystander cells

being lysed are in proximity to the BITE®-activated T cells. In some embodiment, the bystander cells comprises tumor-associated antigen (TAA) negative cancer cells. In some embodiment, the bystander cells comprise EGFR-negative cancer cells. In some embodiments, an immuno-oncology agent is an antibody which blocks the PD-L1/PD1 axis and/or CTLA4. In some embodiments, an immuno-oncology agent is an *ex vivo* expanded tumor-infiltrating T cell. In some embodiments, an immuno-oncology agent is a bispecific antibody construct or chimeric antigen receptors (CARs) that directly connect T cells with tumor-associated surface antigens (TAAs).

Exemplary Immune Checkpoint Inhibitors

[00264] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[00265] The term “checkpoint inhibitor” as used herein relates to agents useful in preventing cancer cells from avoiding the immune system of the patient. One of the major mechanisms of anti-tumor immunity subversion is known as “T-cell exhaustion,” which results from chronic exposure to antigens that has led to up-regulation of inhibitory receptors. These inhibitory receptors serve as immune checkpoints in order to prevent uncontrolled immune reactions.

[00266] PD-1 and co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4, B and T Lymphocyte Attenuator (BTLA; CD272), T cell Immunoglobulin and Mucin domain-3 (Tim-3), Lymphocyte Activation Gene-3 (Lag-3; CD223), and others are often referred to as a checkpoint regulators. They act as molecular “gatekeepers” that allow extracellular information to dictate whether cell cycle progression and other intracellular signaling processes should proceed.

[00267] In some embodiments, an immune checkpoint inhibitor is an antibody to PD-1. PD-1 binds to the programmed cell death 1 receptor (PD-1) to prevent the receptor from binding to the inhibitory ligand PDL-1, thus overriding the ability of tumors to suppress the host anti-tumor immune response.

[00268] In one aspect, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In another aspect, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a fusion protein or a combination thereof. In a further aspect, the checkpoint inhibitor inhibits a checkpoint protein selected from CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4,

BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an additional aspect, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from CTLA-4, PDL1, PDL2, PDI, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an aspect, the checkpoint inhibitor is an immunostimulatory agent, a T cell growth factor, an interleukin, an antibody, a vaccine or a combination thereof. In a further aspect, the interleukin is IL-7 or IL-15. In a specific aspect, the interleukin is glycosylated IL-7. In an additional aspect, the vaccine is a dendritic cell (DC) vaccine.

[00269] Checkpoint inhibitors include any agent that blocks or inhibits in a statistically significant manner, the inhibitory pathways of the immune system. Such inhibitors may include small molecule inhibitors or may include antibodies, or antigen binding fragments thereof, that bind to and block or inhibit immune checkpoint receptors or antibodies that bind to and block or inhibit immune checkpoint receptor ligands. Illustrative checkpoint molecules that can be targeted for blocking or inhibition include, but are not limited to, CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, GAL9, LAG3, TIM3, VISTA, KIR, 2B4 (belongs to the CD2 family of molecules and is expressed on all NK, $\gamma\delta$, and memory CD8⁺ ($\alpha\beta$) T cells), CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, and various B-7 family ligands. B7 family ligands include, but are not limited to, B7- 1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7. Checkpoint inhibitors include antibodies, or antigen binding fragments thereof, other binding proteins, biologic therapeutics, or small molecules, that bind to and block or inhibit the activity of one or more of CTLA-4, PDL1, PDL2, PD1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160 and CGEN-15049. Illustrative immune checkpoint inhibitors include, but are not limited to, Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-L1 monoclonal Antibody (Anti-B7-H1; MEDI4736), MK-3475 (PD-1 blocker), Nivolumab (anti-PD1 antibody), CT-011 (anti-PD1 antibody), BY55 monoclonal antibody, AMP224 (anti-PDL1 antibody), BMS- 936559 (anti-PDL1 antibody), MPLDL3280A (anti-PDL1 antibody), MSB0010718C (anti-PDL1 antibody), and ipilimumab (anti-CTLA-4 checkpoint inhibitor). Checkpoint protein ligands include, but are not limited to PD-L1, PD-L2, B7-H3, B7-H4, CD28, CD86 and TIM-3.

[00270] In certain embodiments, the immune checkpoint inhibitor is selected from a PD-1 antagonist, a PD-L1 antagonist, and a CTLA-4 antagonist. In some embodiments, the checkpoint inhibitor is selected from the group consisting of nivolumab (OPDIVO®), ipilimumab (YERVOY®), and pembrolizumab (KEYTRUDA®). In some embodiments, the checkpoint inhibitor is selected from nivolumab (anti-PD-1 antibody, OPDIVO®, Bristol-Myers Squibb); pembrolizumab (anti-PD-1 antibody, KEYTRUDA®, Merck); ipilimumab (anti-CTLA-4 antibody, YERVOY®, Bristol-Myers Squibb); durvalumab (anti-PD-L1 antibody, IMFINZI®, AstraZeneca); and atezolizumab (anti-PD-L1 antibody, TECENTRIQ®, Genentech).

[00271] In some embodiments, the checkpoint inhibitor is selected from the group consisting of lambrolizumab (MK-3475), nivolumab (BMS-936558), pidilizumab (CT-011), AMP-224, MDX-1105, MEDI4736, MPDL3280A, BMS-936559, ipilimumab, lirlumab, IPH2101, pembrolizumab (KEYTRUDA®), and tremelimumab.

[00272] In some embodiments, an immune checkpoint inhibitor is REGN2810 (Regeneron), an anti-PD-1 antibody tested in patients with basal cell carcinoma (NCT03132636); NSCLC (NCT03088540); cutaneous squamous cell carcinoma (NCT02760498); lymphoma (NCT02651662); and melanoma (NCT03002376); pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (BAVENCIO®, Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; or PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors. Tremelimumab (CP-675,206; Astrazeneca) is a fully human monoclonal antibody against CTLA-4 that has been in studied in clinical trials for a number of indications, including: mesothelioma, colorectal cancer, kidney cancer, breast cancer, lung cancer and non-small cell lung cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, germ cell cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, prostate cancer, endometrial cancer, metastatic cancer in the liver, liver cancer, large B-cell lymphoma, ovarian cancer, cervical cancer, metastatic anaplastic thyroid cancer, urothelial cancer, fallopian tube cancer, multiple myeloma, bladder cancer, soft tissue sarcoma, and melanoma. AGEN-1884

(Agenus) is an anti-CTLA4 antibody that is being studied in Phase 1 clinical trials for advanced solid tumors (NCT02694822).

[00273] In some embodiments, a checkpoint inhibitor is an inhibitor of T-cell immunoglobulin mucin containing protein-3 (TIM-3). TIM-3 inhibitors that may be used in the present disclosure include TSR-022, LY3321367 and MBG453. TSR-022 (Tesar) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT02817633). LY3321367 (Eli Lilly) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT03099109). MBG453 (Novartis) is an anti-TIM-3 antibody which is being studied in advanced malignancies (NCT02608268).

[00274] In some embodiments, a checkpoint inhibitor is an inhibitor of T cell immunoreceptor with Ig and ITIM domains, or TIGIT, an immune receptor on certain T cells and NK cells. TIGIT inhibitors that may be used in the present disclosure include BMS-986207 (Bristol-Myers Squibb), an anti-TIGIT monoclonal antibody (NCT02913313); OMP-313M32 (Oncomed); and anti-TIGIT monoclonal antibody (NCT03119428).

[00275] In some embodiments, a checkpoint inhibitor is an inhibitor of Lymphocyte Activation Gene-3 (LAG-3). LAG-3 inhibitors that may be used in the present disclosure include BMS-986016 and REGN3767 and IMP321. BMS-986016 (Bristol-Myers Squibb), an anti-LAG-3 antibody, is being studied in glioblastoma and gliosarcoma (NCT02658981). REGN3767 (Regeneron), is also an anti-LAG-3 antibody, and is being studied in malignancies (NCT03005782). IMP321 (Immutep S.A.) is an LAG-3-Ig fusion protein, being studied in melanoma (NCT02676869); adenocarcinoma (NCT02614833); and metastatic breast cancer (NCT00349934).

[00276] Checkpoint inhibitors that may be used in the present disclosure include OX40 agonists. OX40 agonists that are being studied in clinical trials include PF-04518600/PF-8600 (Pfizer), an agonistic anti-OX40 antibody, in metastatic kidney cancer (NCT03092856) and advanced cancers and neoplasms (NCT02554812; NCT05082566); GSK3174998 (Merck), an agonistic anti-OX40 antibody, in Phase 1 cancer trials (NCT02528357); MEDI0562 (Medimmune/AstraZeneca), an agonistic anti-OX40 antibody, in advanced solid tumors (NCT02318394 and NCT02705482); MEDI6469, an agonistic anti-OX40 antibody (Medimmune/AstraZeneca), in patients with colorectal cancer (NCT02559024), breast cancer (NCT01862900), head and neck cancer (NCT02274155) and metastatic prostate cancer

(NCT01303705); and BMS-986178 (Bristol-Myers Squibb) an agonistic anti-OX40 antibody, in advanced cancers (NCT02737475).

[00277] Checkpoint inhibitors that may be used in the present disclosure include CD137 (also called 4-1BB) agonists. CD137 agonists that are being studied in clinical trials include utomilumab (PF-05082566, Pfizer) an agonistic anti-CD137 antibody, in diffuse large B-cell lymphoma (NCT02951156) and in advanced cancers and neoplasms (NCT02554812 and NCT05082566); urelumab (BMS-663513, Bristol-Myers Squibb), an agonistic anti-CD137 antibody, in melanoma and skin cancer (NCT02652455) and glioblastoma and gliosarcoma (NCT02658981); and CTX-471 (Compass Therapeutics), an agonistic anti-CD137 antibody in metastatic or locally advanced malignancies (NCT03881488).

[00278] Checkpoint inhibitors that may be used in the present disclosure include CD27 agonists. CD27 agonists that are being studied in clinical trials include varlilumab (CDX-1127, Celldex Therapeutics) an agonistic anti-CD27 antibody, in squamous cell head and neck cancer, ovarian carcinoma, colorectal cancer, renal cell cancer, and glioblastoma (NCT02335918); lymphomas (NCT01460134); and glioma and astrocytoma (NCT02924038).

[00279] Checkpoint inhibitors that may be used in the present disclosure include glucocorticoid-induced tumor necrosis factor receptor (GITR) agonists. GITR agonists that are being studied in clinical trials include TRX518 (Leap Therapeutics), an agonistic anti-GITR antibody, in malignant melanoma and other malignant solid tumors (NCT01239134 and NCT02628574); GWN323 (Novartis), an agonistic anti-GITR antibody, in solid tumors and lymphoma (NCT02740270); INCAGN01876 (Incyte/Agenus), an agonistic anti-GITR antibody, in advanced cancers (NCT02697591 and NCT03126110); MK-4166 (Merck), an agonistic anti-GITR antibody, in solid tumors (NCT02132754) and MEDI1873 (Medimmune/AstraZeneca), an agonistic hexameric GITR-ligand molecule with a human IgG1 Fc domain, in advanced solid tumors (NCT02583165).

[00280] Checkpoint inhibitors that may be used in the present disclosure include inducible T-cell co-stimulator (ICOS, also known as CD278) agonists. ICOS agonists that are being studied in clinical trials include MEDI-570 (Medimmune), an agonistic anti-ICOS antibody, in lymphomas (NCT02520791); GSK3359609 (Merck), an agonistic anti-ICOS antibody, in Phase 1 (NCT02723955); JTX-2011 (Jounce Therapeutics), an agonistic anti-ICOS antibody, in Phase 1 (NCT02904226).

[00281] Checkpoint inhibitors that may be used in the present disclosure include killer IgG-like receptor (KIR) inhibitors. KIR inhibitors that are being studied in clinical trials include lirilumab (IPH2102/BMS-986015, Innate Pharma/Bristol-Myers Squibb), an anti-KIR antibody, in leukemias (NCT01687387, NCT02399917, NCT02481297, NCT02599649), multiple myeloma (NCT02252263), and lymphoma (NCT01592370); IPH2101 (1-7F9, Innate Pharma) in myeloma (NCT01222286 and NCT01217203); and IPH4102 (Innate Pharma), an anti-KIR antibody that binds to three domains of the long cytoplasmic tail (KIR3DL2), in lymphoma (NCT02593045).

[00282] Checkpoint inhibitors that may be used in the present disclosure include CD47 inhibitors of interaction between CD47 and signal regulatory protein alpha (SIRPa). CD47/SIRPa inhibitors that are being studied in clinical trials include ALX-148 (Alexo Therapeutics), an antagonistic variant of (SIRPa) that binds to CD47 and prevents CD47/SIRPa-mediated signaling, in phase 1 (NCT03013218); TTI-621 (SIRPa-Fc, Trillium Therapeutics), a soluble recombinant fusion protein created by linking the N-terminal CD47-binding domain of SIRPa with the Fc domain of human IgG1, acts by binding human CD47, and preventing it from delivering its “do not eat” signal to macrophages, is in clinical trials in Phase 1 (NCT02890368 and NCT02663518); CC-90002 (Celgene), an anti-CD47 antibody, in leukemias (NCT02641002); and Hu5F9-G4 (Forty Seven, Inc.), in colorectal neoplasms and solid tumors (NCT02953782), acute myeloid leukemia (NCT02678338) and lymphoma (NCT02953509).

[00283] Checkpoint inhibitors that may be used in the present disclosure include CD73 inhibitors. CD73 inhibitors that are being studied in clinical trials include MEDI9447 (Medimmune), an anti-CD73 antibody, in solid tumors (NCT02503774); and BMS-986179 (Bristol-Myers Squibb), an anti-CD73 antibody, in solid tumors (NCT02754141).

[00284] Checkpoint inhibitors that may be used in the present disclosure include agonists of stimulator of interferon genes protein (STING, also known as transmembrane protein 173, or TMEM173). Agonists of STING that are being studied in clinical trials include MK-1454 (Merck), an agonistic synthetic cyclic dinucleotide, in lymphoma (NCT03010176); and ADU-S100 (MIW815, Aduro Biotech/Novartis), an agonistic synthetic cyclic dinucleotide, in Phase 1 (NCT02675439 and NCT03172936).

[00285] Checkpoint inhibitors that may be used in the present disclosure include CSF1R inhibitors. CSF1R inhibitors that are being studied in clinical trials include pexidartinib (PLX3397, Plexxikon), a CSF1R small molecule inhibitor, in colorectal cancer, pancreatic cancer,

metastatic and advanced cancers (NCT02777710) and melanoma, non-small cell lung cancer, squamous cell head and neck cancer, gastrointestinal stromal tumor (GIST) and ovarian cancer (NCT02452424); and IMC-CS4 (LY3022855, Lilly), an anti-CSF-1R antibody, in pancreatic cancer (NCT03153410), melanoma (NCT03101254), and solid tumors (NCT02718911); and BLZ945 (4-[2((1R,2R)-2-hydroxycyclohexylamino)-benzothiazol-6-yloxy]-pyridine-2-carboxylic acid methylamide, Novartis), an orally available inhibitor of CSF1R, in advanced solid tumors (NCT02829723).

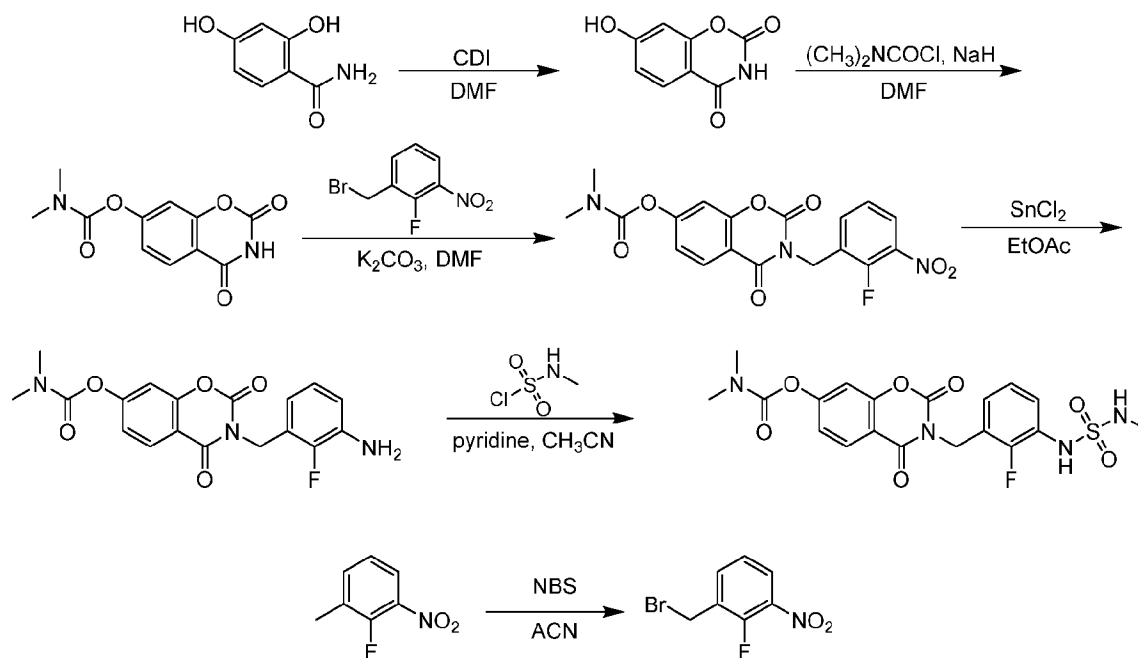
[00286] Checkpoint inhibitors that can be used in the present disclosure include NKG2A receptor inhibitors. NKG2A receptor inhibitors that are being studied in clinical trials include monalizumab (IPH2201, Innate Pharma), an anti-NKG2A antibody, in head and neck neoplasms (NCT02643550) and chronic lymphocytic leukemia (NCT02557516).

[00287] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

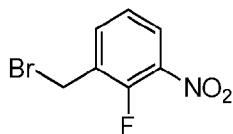
EXAMPLES

[00288] The following examples are included to demonstrate various aspects of the present disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent techniques discovered by the inventors to function well in the practice of the disclosure, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific examples which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

EXAMPLE 1: Synthesis of [3-[[2-Fluoro-3-(methylsulfamoylamino)phenyl]methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate (I-1)

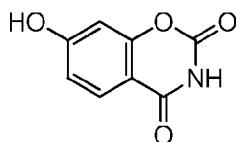


Step 1: 1-(Bromomethyl)-2-fluoro-3-nitro-benzene



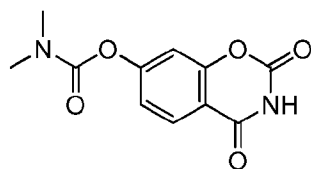
[00289] To a stirred solution of 2-fluoro-1-methyl-3-nitro-benzene (10 g, 64.46 mmol, 1 *eq*) in CH_3CN (100 mL) was added NBS (17.21 g, 96.70 mmol, 1.5 *eq*) and AIBN (1.27 g, 7.74 mmol, 0.12 *eq*). The reaction mixture was stirred at 80 °C for 16 h under N_2 . The reaction mixture was quenched by addition NaHCO_3 (aq) (200 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to yield a residue which was purified by column chromatography (SiO_2 , PE/EtOAc = 100/1 to 10/1, R_f = 0.50) to yield 1-(bromomethyl)-2-fluoro-3-nitro-benzene (10 g, 38.46 mmol, 59.7% yield, 90.0% purity) as a yellow solid. $^1\text{H NMR}$ (400 MHz, $\text{DMSO-}d_6$) δ ppm 8.12 (t, J = 7.7 Hz, 1H), 7.96 (t, J = 7.1 Hz, 1H), 7.45 (t, J = 7.9 Hz, 1H), 4.79 (s, 2H).

Step 2: 7-Hydroxy-1,3-benzoxazine-2,4-dione



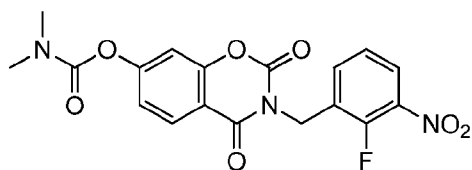
[00290] To a stirred solution of 2, 4-dihydroxybenzamide (1 g, 6.53 mmol, 1 *eq*) in DMF (10 mL) was added CDI (3.18 g, 19.59 mmol, 3 *eq*). The reaction mixture was stirred at 45 °C for 12 h under N₂. The reaction mixture was diluted with H₂O (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield 7-hydroxy-1,3-benzoxazine-2,4-dione (1.3 g, 6.46 mmol, 98.9% yield, 89.0% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 7.76 (d, *J* = 8.6 Hz, 1H), 6.80 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.64 (d, *J* = 2.3 Hz, 1H). ES-LCMS *m/z* 180.2 [M+H]⁺.

Step 3: (2,4-Dioxo-1,3-benzoxazin-7-yl) *N,N*-dimethylcarbamate



[00291] To a stirred solution of 7-hydroxy-1,3-benzoxazine-2,4-dione (1.1 g, 5.47 mmol, 89.0% purity, 1 *eq*) in DMF (10 mL) was added NaH (437.18 mg, 10.93 mmol, 60.0%, 2 *eq*) at 0 °C. After stirring for 30 min, *N,N*-dimethylcarbamoyl chloride (1.18 g, 10.93 mmol, 1.00 mL, 2 *eq*) was added to the mixture dropwise. The reaction mixture was stirred at 25 °C for 2.5 h under N₂. The reaction mixture was quenched by addition H₂O (50 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield (2,4-dioxo-1,3-benzoxazin-7-yl) *N,N*-dimethylcarbamate (820 mg, 2.79 mmol, 51.0% yield, 85.0% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 12.04 (s, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 2.1, 8.5 Hz, 1H), 3.06 (s, 3H), 2.93 (s, 3H); ES-LCMS *m/z* 251.0 [M+H]⁺.

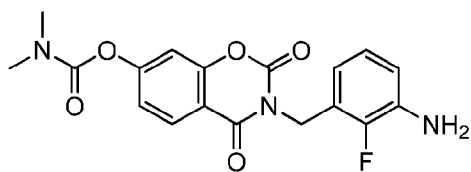
Step 4: [3-[(2-Fluoro-3-nitro-phenyl)methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate



[00292] To a stirred solution of (2,4-dioxo-1,3-benzoxazin-7-yl) *N,N*-dimethylcarbamate (820 mg, 2.79 mmol, 85.0% purity, 1 *eq*) and 1-(bromomethyl)-2-fluoro-3-nitro-benzene (796.78 mg, 3.06 mmol, 90.0% purity, 1.1 *eq*) in DMF (8 mL) was added K₂CO₃ (770.00 mg, 5.57 mmol, 2

eq). The reaction mixture was stirred at 25 °C for 5 h under N₂. The reaction mixture was diluted with H₂O (30 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield [3-[(2-fluoro-3-nitro-phenyl)methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate (760 mg, 1.70 mmol, 60.8% yield, 90.0% purity) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.09-8.03 (m, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.90-7.85 (m, 1H), 7.39-7.37 (m, 1H), 7.36-7.33 (m, 1H), 7.24 (dd, *J* = 2.1, 8.6 Hz, 1H), 5.17 (s, 2H), 3.06 (s, 3H), 2.94 (s, 3H).

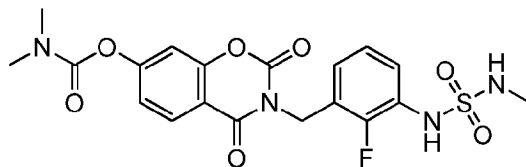
Step 5: [3-[(3-Amino-2-fluoro-phenyl)methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate



[00293] To a stirred solution of [3-[(2-fluoro-3-nitro-phenyl)methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate (710 mg, 1.58 mmol, 90.0% purity, 1 *eq*) in EtOAc (15 mL) was added dichlorotin;dihydrate (1.79 g, 7.92 mmol, 5 *eq*). The reaction mixture was stirred at 80 °C for 2 h under N₂. The reaction mixture was quenched by addition NaHCO₃ (aq) (50 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield [3-[(3-amino-2-fluoro-phenyl)methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate (400 mg, 964.28 μmol, 60.9% yield, 90.0% purity) as a white solid.

¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.00 (d, *J* = 8.6 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.24 (dd, *J* = 2.1, 8.6 Hz, 1H), 6.78-6.74 (m, 1H), 6.68-6.62 (m, 1H), 6.43 (t, *J* = 7.1 Hz, 1H), 5.15-5.09 (m, 2H), 5.05 (s, 2H), 3.06 (s, 3H), 2.94 (s, 3H); ES-LCMS *m/z* 374.0 [M+H]⁺.

Step 6: [3-[[2-Fluoro-3-(methylsulfamoylamino)phenyl]methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate



[00294] To a stirred solution of [3-[(3-amino-2-fluoro-phenyl)methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate (230 mg, 554.46 μ mol, 90.0% purity, 1 *eq*) in CH₃CN (5 mL) was added pyridine (131.57 mg, 1.66 mmol, 134.26 μ L, 3 *eq*) and *N*-methylsulfamoyl chloride (64.66 mg, 499.02 μ mol, 0.9 *eq*) at 0 °C. The reaction mixture was stirred at 25 °C for 2 h under N₂. The reaction mixture was diluted with H₂O (20 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Phenomenex luna C18 150*25 mm* 10 μ m; mobile phase: [water (HCl)-ACN]; B%: 51%-81%, 10 min) to yield [3-[[2-fluoro-3-(methylsulfamoylamino)phenyl]methyl]-2,4-dioxo-1,3-benzoxazin-7-yl] *N,N*-dimethylcarbamate as a white solid. ¹H NMR (400 MHz, CD₃OD) δ ppm 8.07 (d, *J* = 9.3 Hz, 1H), 7.49-7.44 (m, 1H), 7.24-7.20 (m, 2H), 7.09-7.06 (m, 2H), 5.26 (s, 2H), 3.13 (s, 3H), 3.02 (s, 3H), 2.63 (s, 3H); ES-LCMS *m/z* 466.9 [M+H]⁺.

EXAMPLE 2: SPR Assays

MEK-RAF binding assay

[00295] Compound effects on binding affinity of MEK to BRAF or CRAF were followed by surface plasmon resonance (SPR) with single-cycle kinetic analysis. GST-BRAF or GST-CRAF was immobilized onto a chip and increasing concentrations of His-tagged MEK1 were flowed over the sensor chip. 500 mM ATP was added to the running buffer. The dissociation constant for MEK1 binding to either BRAF or CRAF was calculated in the absence and presence of compound. Instruments were carried out on a Biacore 8K instrument. Sensorgrams were double-reference and DMSO corrected. Data was fit to a single-cycle kinetic model.

[00296] Experimental results are provided in Table 2, below. The compound numbers correspond to the compound numbers in **Table 1**. The activity is classified as A-D, wherein A represents IC₅₀ < 100 nM; B represents 100 nM \leq IC₅₀ < 1 μ M; C represents 1 \leq IC₅₀ < 10 μ M; and D represents IC₅₀ \geq 10 μ M.

TABLE 2.

Compound #	μMEK/BRAF HTRF: Average IC₅₀ (nM)
I-1	B
I-7	A
I-8	A

I-43	A
I-44	A
I-45	B
I-46	B

MEK-KSR binding assay

[00297] Compound effects on binding affinity of MEK to KSR1 or KSR2 are followed by surface plasmon resonance (SPR) with single-cycle kinetic analysis. GST-KSR1 or GST-KSR2 is immobilized onto a chip and increasing concentrations of His-tagged MEK1 are flowed over the sensor chip. 500 mM ATP is added to the running buffer. The dissociation constant for MEK1 binding to either BRAF or CRAF is calculated in the absence and presence of compound. Instruments are carried out on a Biacore 8K instrument. Sensorgrams are double-reference and DMSO corrected. Data is fit to a single-cycle kinetic model.

EXAMPLE 3: Immunoprecipitation Assay

[00298] Immunoprecipitation experiments were performed by plating about 450,000 HCT116 cells per well in 6-well plates. Cells were plated for 48 h so as to reach approximately 70% confluency before transfection. Then, 24 h after transfection, cells were treated with vehicle (0.1% DMSO) or a compound (about 200 nM) for 1 h. Cells were washed twice in cold PBS and then transferred to a pre-chilled tube in 0.6 ml of PBS solution. Cells were spun at 1,800g in a cold centrifuge for 10 min, and supernatant was aspirated. To lyse cells, pellets were resuspended in NP-40 buffer (50 mM Tris pH 7.8, 100 mM NaCl, 0.5% (v/v) NP-40, 10% (v/v) glycerol, 1 mM EDTA) supplemented with protease and phosphatase inhibitor cocktail (Thermo Fisher, 78440) and incubated on ice for 30 min. Lysates were centrifuged for 20 min at 2,100g, and supernatants are collected. Cleared lysates were quantified using BCA reagent (Pierce, 23225), with BSA as a standard. Five micrograms of rabbit anti-MEK1 antibody (Millipore-Sigma, 07-641), or rabbit IgG (Millipore Sigma, 12-370), was immobilized on 50 μ l of Sepharose Protein A Resin (Thermo Fisher, 53139) and washed three times in 300 μ l NP-40 buffer before initiating immunoprecipitations.

[00299] Next, for MEK1 immunoprecipitation, 250 μ g of total cell lysate in a total volume of 0.6 ml was mixed with the pre-immobilized anti-MEK1 antibody pre-conjugated to Protein A

resin. Samples were incubated at 4 °C on an end-over-end rotator for 4 h, followed by three washes in 0.6 ml volume of NP-40 buffer. Next, proteins were denatured and released from resin by the addition of 80 µl volume of 1× SDS sample buffer. Samples were boiled at 90 °C for 2 min, spun, and then applied to a 4–12% bis-tris glycine gel (Bio-Rad, 3450125) ran in MOPS-SDS buffer (Thermo Fisher, NP0001) for 60 min at 150 V. Gels were then transferred onto nitrocellulose in 20% methanol in Tris-glycine buffer (95 V, 250 A). Transfers were confirmed using Ponceau red and then analyzed by western blot. Signals for MEK, Flag-tagged proteins, BRAF, and GAPDH were detected by enhanced chemiluminescence on a ChemDoc XRS+ imaging system (Biorad).

[00300] Experimental results are provided in Table 3, below. The compound numbers correspond to the compound numbers in **Table 1**. The activity is classified as A-D, wherein A represents $IC_{50} < 100$ nM; B represents $100 \text{ nM} \leq IC_{50} < 1$ µM; C represents $1 \leq IC_{50} < 10$ µM; and D represents $IC_{50} \geq 10$ µM.

TABLE 3.

Compound #	pERK HCT-116 (G13D) ICW (4 hour): Average IC50 (nM)
I-1	A

4 hour – pERK1/2 HTRF Assay

[00301] AsPC1 cells were seeded at 20,000 cells/well overnight in 96-well plates, then treated with a 12-point dose response of compounds (Starting dose of 3000 nM and 3-fold dilution) for 4 hours. Phosphorylation of ERK1/2 on residues Thr202 and Tyr204 were detected using a Homogenous Time-Resolved Fluorescence (HTRF) assay (Cisbio Cat# 64ERKPEG). Briefly, ERK phosphorylation was detected using a sandwich assay format using two phospho-ERK specific antibodies, one labelled with Eu^{3+} - Cryptate (donor) and the second with d2 (acceptor). The Fluorescence Resonance Energy Transfer (FRET) towards the d2 acceptor was detected at a wavelength of 665 nm. ERK1/2 phosphorylation levels were normalized to total ERK1/2 protein levels in each well. IC_{50} values were determined by fitting a variable slope, four parameters curve to the compound concentration to normalized Phospho-ERK1/2 relationship. The activity is classified as A-D, wherein A represents $IC_{50} < 100$ nM; B represents $100 \text{ nM} \leq IC_{50} < 1$ µM; C represents $1 \leq IC_{50} < 10$ µM; and D represents $IC_{50} \geq 10$ µM.

TABLE 4.

Compound #	pERK AsPC-1 HTRF (4 hour): Average IC50 (nM)
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I-7	A
I-43	A
I-44	A

EXAMPLE 4: Biological Assay for Inhibiting Mouse Xenograft Tumor Growth

[00302] Exemplary compounds having MEK inhibitory activity can be tested, alone or in combination with a second anti-cancer agent, such as a TEAD inhibitor or an ERK5 inhibitor, for ability to inhibit tumor growth in patient-derived mouse xenograft models of pancreatic cancer and lung cancer. Assay procedures are described below.

Procedures for Patient-Derived Mouse Xenograft (PDX) Tumor Growth Assay

[00303] Balb/c mice (6-8 weeks old) are inoculated subcutaneously in the right flank with a primary human tumor xenograft model tumor fragment (2-3 mm³ in diameter) for tumor development. In one study, mice are inoculated with a human lung adenocarcinoma tumor model (MSCLC, ADC model LU6424) that harbors a BRAF mutation (LU6424); in a second study, mice are inoculated with a human pancreatic tumor model (adenosquamous carcinoma model PA6258) with a K-Ras G12D mutation (PA6258). When mean tumor volume reaches approximately 150-200 mm³, animals are randomly allocated to appropriate treatment groups. Mice are treated with one of the following: (1) Vehicle control, (2) Exemplary MEK inhibitor alone, (3) Second anti-cancer agent alone, or (4) Combination of MEK inhibitor and second anti-cancer agent. Tumors are measured twice per week using calipers.

[00304] While a number of embodiments of this disclosure are described, it is apparent that the basic examples may be altered to provide other embodiments that utilize the compounds and methods of this disclosure. Therefore, it will be appreciated that the scope of this disclosure is to be defined by the application and appended claims rather than by the specific embodiments that have been represented by way of example.

INCORPORATION BY REFERENCE

[00305] The entire disclosure of each of the patent documents and scientific articles referred to herein is incorporated by reference for all purposes.

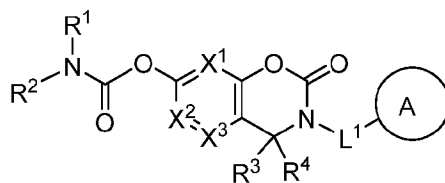
EQUIVALENTS

[00306] The disclosure may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting the disclosure described herein. Scope of the disclosure is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are independently H, optionally substituted C_1 - C_6 aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, or R^1 and R^2 , taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^1 and R^2 attach;

X^1 is $C(R^{21})$ or N;

X^2 is $C(R^{22})$ or N;

X^3 is $C(R^{23})$ or N;

R^3 and R^4 are independently halogen, R, or $-C(O)-N(R)_2$; or R^3 and R^4 , taken together with the atom to which they attach, form $C=O$, or an optionally substituted 3-8 membered carbocyclic ring, or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S;

each of R^{21} , R^{22} , and R^{23} is independently halogen, R, $-OR$, $-N(R)_2$, $-N(R)-C(O)-R$, or $-C(O)-N(R)_2$;

L^1 is $-C(R^5)(R^6)-$;

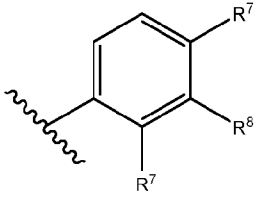
each of R^5 and R^6 is independently halogen, R, or R^5 and R^6 , together with the atom to which they attach, form an optionally substituted 3-8 membered carbocyclic ring or an optionally substituted 3-8 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S;

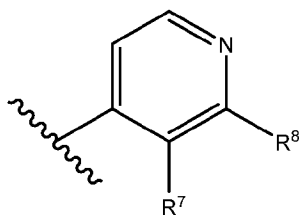
Ring A is an optionally substituted ring selected from a phenyl ring, a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from N, O, or S, or a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S; and

each R is independently H, optionally substituted C₁-C₆ aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

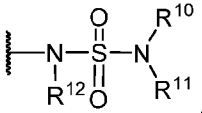
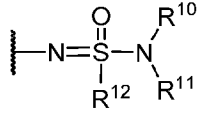
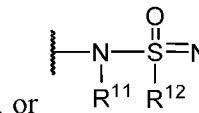
2. The compound of claim 1, wherein R¹ and R² are independently hydrogen or optionally substituted C₁-C₆ alkyl.
3. The compound of claim 1 or 2, wherein R¹ and R² are independently hydrogen or C₁-C₆ alkyl.
4. The compound of any one of claims 1 to 3, wherein R¹ and R² are methyl.
5. The compound of claim 1, wherein R¹ and R² taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R¹ and R² attach.
6. The compound of claim 1 or 5, wherein R¹ and R², taken together with the atom to which they attach, form an optionally substituted azetidine ring.
7. The compound of any one of claims 1 to 6, wherein R²¹ is hydrogen.
8. The compound of any one of claims 1 to 7, wherein R²² is hydrogen or halogen.
9. The compound of any one of claims 1 to 8, wherein R²³ is hydrogen or halogen.

10. The compound of any one of claims 1 to 9, wherein R^3 and R^4 are independently hydrogen, optionally substituted C_1 - C_6 aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, or R^3 and R^4 , taken together with the atom to which they attach, form $C=O$.
11. The compound of claim 10, wherein R^3 and R^4 are independently C_1 - C_6 aliphatic, 3-8 membered carbocyclyl, or 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, each of which is substituted by $-N(R)_2$, and each R is independently C_1 - C_6 aliphatic.
12. The compound of claim 10 or 11, wherein R^3 and R^4 are independently hydrogen, $-CH_3$, $-CH_2N(CH_3)_2$, or cyclopropyl, or R^3 and R^4 , taken together with the atom to which they attach, form $C=O$.
13. The compound of any one of claims 1 to 12, wherein L^1 is $-CH(R^6)-$.
14. The compound of claim 13, wherein R^6 is R.
15. The compound of claim 14, wherein R^6 is optionally substituted C_1 - C_6 aliphatic.
16. The compound of claim 15, wherein R^6 is methyl.
17. The compound of any one of claims 1 to 16, wherein Ring A is an optionally substituted ring selected from a phenyl ring or a 6 membered heteroaromatic ring having 1-4 N atoms.

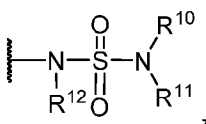
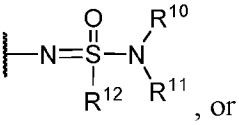
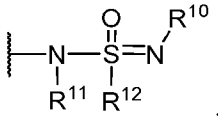
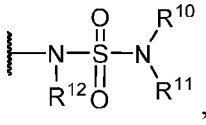
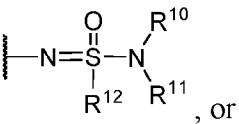
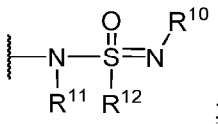
18. The compound of any one of claims 1 to 17, wherein Ring A is  or



; R^7 is independently halogen, R, -OR, or -N(R)₂; and R^8 is

halogen, R, -OR, -N(R)₂, , , or ; each of R^{10} and R^{11} is independently H, optionally substituted C₁-C₆ aliphatic, optionally substituted 3-8 membered carbocyclyl, optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S, optionally substituted phenyl, or optionally substituted 5-6 membered heteroaryl having 1-4 heteroatoms independently selected from N, O, or S, or R^{10} and R^{11} taken together with the N atom to which they attach, form optionally substituted 3-8 membered heterocyclyl having 0, 1, or 2 heteroatoms independently selected from N, O, or S in addition to the N atom to which R^{10} and R^{11} attach; and R^{12} is H, optionally substituted C₁-C₆ aliphatic, optionally substituted 3-8 membered carbocyclyl, or optionally substituted 3-8 membered heterocyclyl having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

19. The compound of claim 18, wherein each R is independently H, or optionally substituted C₁-C₆ aliphatic.
20. The compound of claim 18, wherein R^7 is independently H, halogen, or C₁-C₆ aliphatic.
21. The compound of claim 20, wherein R^7 is independently H or fluoro.

22. The compound of any one of claims 18 to 21, wherein R⁸ is , , or .
23. The compound of any one of claims 18 to 22, wherein R⁸ is , , or ; each of R¹⁰ and R¹¹ is independently H, C₁-C₆ aliphatic, or 3-8 membered heterocyclyl having 1, 2, or 3 N atoms; and R¹² is H, optionally substituted C₁-C₆ aliphatic, or optionally substituted 3-8 membered carbocyclyl.
24. The compound of claim 22 or 23, wherein each of R¹⁰ and R¹¹ is independently hydrogen or C₁-C₆ alkyl.
25. The compound of any one of claims 22 to 24, wherein R¹² is hydrogen or C₁-C₆ alkyl.
26. The compound of any one of claims 1 to 25, wherein the compound is a compound selected from those listed in Table 1, or a pharmaceutically acceptable salt thereof.
27. A pharmaceutical composition comprising the compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.
28. A method of treating a disorder mediated by MEK, comprising administering a therapeutically effective amount of a compound of any one of claims 1-26, or the

pharmaceutical composition of claim 27, to the subject in need thereof to treat the disorder.

29. The method of claim 28, wherein the disorder is cancer.
30. A method for treating a cancer in a patient, comprising administering the compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 27, to the patient in need thereof to treat the cancer.
31. A method of inhibiting MEK activity, comprising contacting MEK or a KSR-MEK complex or a RAF-MEK complex with an effective amount of a compound of any one of claims 1-26, or the pharmaceutical composition of claim 27, to inhibit MEK activity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2023/064086

A. CLASSIFICATION OF SUBJECT MATTER		
INV. C07D265/18 C07D265/26 C07D413/06 C07D498/04 A61P35/00 A61K31/5365		
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) C07D A61P A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 107 200 716 A (UNIV BEIJING) 26 September 2017 (2017-09-26) Abstract; claims; pages 8-10, paragraphs 49-52; page 13, paragraph 87: compounds 4a, 6-14, 26; page 14, paragraph 95: e.g. compounds 29-38, wherein compound 31 = present compound I-1. ----- -/--	1-31
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
Date of the actual completion of the international search 3 May 2023		Date of mailing of the international search report 11/05/2023
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		Authorized officer Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SUN JING ET AL.: "Discovery of 3-benzyl-1,3-benzoxazine-2,4-dione analogues as allosteric mitogen-activated kinase kinase (MEK) inhibitors and anti-enterovirus 71 (EV71) agents", BIOORG. MED. CHEM., vol. 24, no. 16, 30 May 2016 (2016-05-30), pages 3472-3482, XP029642285, ISSN: 0968-0896, DOI: 10.1016/J.BMC.2016.05.055 Abstract; page 3474, scheme 1 and table 1: compounds 5a-g, 7c-g, 9c-h; page 3475, scheme 2 and table 2: compounds 5f, 7f, 9i-p, wherein compound 9k = present compound I-1.</p> <p style="text-align: center;">-----</p>	1-4, 7-10, 12-14, 17-26, 28, 31

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 107200716	A	26-09-2017	NONE
