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(54) **MACROCYCLIC COMPOUNDS AS ROS1 KINASE INHIBITORS**

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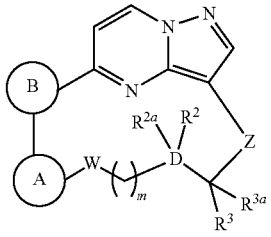
(57) **ABSTRACT**

Methods for inhibiting a ROS1 kinase with compounds of Formula I:

I



and pharmaceutically acceptable salts thereof, wherein ring A, ring B, W, m, D, R^2, R^{2a}, R^3, R^{3a}, and Z are as defined herein. The compounds and methods provided herein are useful in the treatment of cancer (e.g., ROS1-associated cancers as defined herein).

Specification includes a Sequence Listing.

MACROCYCLIC COMPOUNDS AS ROS1 KINASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of International Application No. PCT/US2018/022833, filed Mar. 16, 2018, which claims priority to U.S. Provisional Application No. 62/472,185, filed Mar. 16, 2017, the contents of which are incorporated by reference in their entirety herein.

TECHNICAL FIELD

[0002] Provided herein are compounds and pharmaceutical compositions comprising the compounds and the use of the compounds in therapy. More particularly, provided herein are certain macrocyclic compounds which exhibit ROS1 protein kinase inhibition, and which are useful in the treatment of cancer.

BACKGROUND

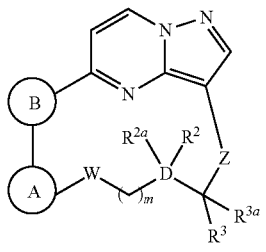
[0003] ROS1 is a receptor tyrosine kinase that is closely related to ALK, and, like ALK, it undergoes genomic rearrangement that creates fusion proteins in various cancers (Davies K D and Doebele R C (2013) *Clin Cancer Res* 19: 4040-4045). It is well established that these fusion proteins act as oncogenic drivers and that ROS1 inhibition is antiproliferative in cells that express ROS1 fusions (Davies K D, Le A T, Theodoro M F, Skokan M C, Aisner D L, et al. (2012) *Clin Cancer Res* 18: 4570-4579). Thus, it appears that ROS1 targeted therapy will likely soon be the standard of care for this patient population. However, based on the experiences with other kinase inhibitors in various cancers, it is fully expected that acquired resistance to ROS1 inhibition will occur, and this will ultimately limit the treatment options for patients.

SUMMARY

[0004] It has now been found that macrocyclic compounds are inhibitors of ROS1 kinase, and are useful for treating various cancers. Compounds which are inhibitors of ROS1 may be useful in the treatment of multiple types of cancer including cancers exhibiting resistance to ROS1 inhibition.

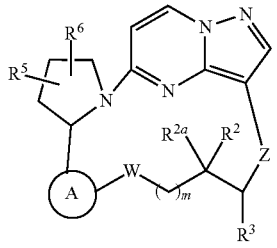
[0005] Accordingly, in one aspect of the present disclosure, the methods provided include administration of a ROS1 inhibitor, wherein the ROS1 inhibitor is a compound of Formula I

I



or a pharmaceutically acceptable salt or solvate thereof, wherein ring A, ring B, W, m, D, R^2, R^{2a}, R^3, R^{3a}, and Z are as defined herein.

[0006] In some embodiments, a compound of Formula I has the general formula:



or a pharmaceutically acceptable salt or solvate thereof, wherein ring A, W, m, R^2, R^{2a}, R^3, and Z are as defined herein.

[0007] In some embodiments, the compound of Formula I is selected from the compounds of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I is selected from the group consisting of Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof.

[0008] Provided herein is a method for treating a cancer in a patient in need thereof, the method comprising:

[0009] (a) determining if the cancer is associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same; and

[0010] (b) if the cancer is determined to be associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, administering to the patient a therapeutically effective amount of a ROS1 inhibitor, wherein the ROS1 inhibitor is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0011] Provided herein is a method for treating a cancer in a patient in need thereof, the method comprising:

[0012] (a) detecting that the cancer is associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same; and

[0013] (b) administering to the patient a therapeutically effective amount of a ROS1 inhibitor, wherein the ROS1 inhibitor is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0014] Also provided herein is a method for treating cancer in a patient in need thereof, the method comprising administering to a patient identified or diagnosed as having a ROS1-associated cancer a therapeutically effective amount of a ROS1 inhibitor, wherein the ROS1 inhibitor is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0015] In some embodiments of the present disclosure, a method of treating cancer in a patient in need thereof is provided. The method comprising:

[0016] (a) determining if the cancer in a patient is a ROS1-associated cancer; and

[0017] (b) administering to the patient determined to have a ROS1-associated cancer a therapeutically effective amount of a ROS1 inhibitor, wherein the ROS1 inhibitor is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0018] In some embodiments of the present disclosure, a method of treating cancer in a patient in need thereof is provided. The method comprising:

[0019] (a) detecting that a cancer in a patient is a ROS1-associated cancer; and

[0020] (b) administering to the patient a therapeutically effective amount of a ROS1 inhibitor, wherein the ROS1 inhibitor is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0021] Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

[0022] (a) administering a first ROS1 inhibitor to the subject;

[0023] (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and

[0024] (c) administering a second ROS1 inhibitor, wherein the second ROS1 inhibitor is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0025] (d) administering additional doses of the first ROS1 inhibitor of step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0026] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

[0027] (a) administering a first ALK inhibitor to the subject;

[0028] (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and

[0029] (c) administering a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0030] (d) administering additional doses of the first ALK inhibitor of step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0031] In some embodiments, a method of treating a subject having a cancer is provided herein, wherein the method comprises:

[0032] (a) administering a first TRK inhibitor to the subject;

[0033] (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and

[0034] (c) administering a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0035] (d) administering additional doses of the first TRK inhibitor of step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0036] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

[0037] (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ROS1 inhibitor has one or more ROS1 inhibitor resistance mutations that confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor that was previously administered to the subject; and

[0038] (b) administering a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations that confers increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor that was previously administered to the subject; or

[0039] (c) administering additional doses of the first ROS1 inhibitor to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations that confers increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor previously administered to the subject.

[0040] Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

[0041] (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ALK inhibitor has one or more ROS1 inhibitor resistance mutations; and

[0042] (b) administering a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0043] (c) administering additional doses of the first ALK inhibitor to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0044] In some embodiments, a method of treating a subject having a cancer is provided herein, wherein the method comprises:

[0045] (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first TRK inhibitor has one or more ROS1 inhibitor resistance mutations; and

[0046] (b) administering a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0047] (c) administering additional doses of the first TRK inhibitor to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0048] Also provided herein is a method of treating a subject having a cancer, wherein the method comprises:

[0049] (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ROS1 inhibitor has one or more ROS1 inhibitor resistance mutations that confer

increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor previously administered to the subject; and

[0050] (b) administering a second ROS1 inhibitor to the subject as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations that confers increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor that was previously administered to the subject; or

[0051] (c) administering additional doses of the first ROS1 inhibitor that was previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations that confers increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor that was previously administered to the subject.

[0052] Further provided herein is a method of treating a subject having a cancer, wherein the method comprises:

[0053] (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered an ALK inhibitor has one or more ROS1 inhibitor resistance mutations; and

[0054] (b) administering a ROS1 inhibitor to the subject as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0055] (c) administering additional doses of the ALK inhibitor that was previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0056] In some embodiments, a method of treating a subject having a cancer is provided, wherein the method comprises:

[0057] (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a TRK inhibitor has one or more ROS1 inhibitor resistance mutations; and

[0058] (b) administering a ROS1 inhibitor to the subject as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or

[0059] (c) administering additional doses of the TRK inhibitor that was previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0060] Also provided herein is a method of treating a patient, the method comprising administering a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, to a patient having a clinical record that indicates that the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same.

[0061] Further provided herein is a method of selecting a treatment for a patient, the method comprising selecting a treatment comprising administration of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, for a patient identified or diagnosed as having a ROS1-associated cancer.

[0062] In some embodiments, provided herein is a method of selecting a treatment for a patient having a cancer, the method comprising:

[0063] (a) determining if the cancer in the patient is a ROS1-associated cancer; and

[0064] (b) selecting a treatment including administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, for a patient determined to have a ROS1-associated cancer.

[0065] Also provided herein is a method of selecting a patient for treatment including administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, the method comprising:

[0066] (a) identifying a patient having a ROS1-associated cancer; and

[0067] (b) selecting the patient for treatment including administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof.

[0068] Further provided herein is a method of selecting a patient having cancer for treatment including administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, the method comprising:

[0069] (a) determining if the cancer in the patient is a ROS1-associated cancer; and

[0070] (b) selecting a patient determined to have a ROS1-associated cancer for treatment including administration of a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof.

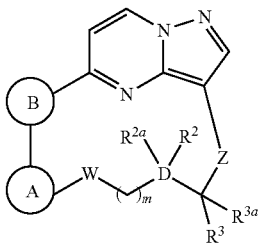
[0071] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials are described herein for use in the present invention; other, suitable methods and materials known in the art can also be used. The materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, sequences, database entries, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[0072] Other features and advantages of the invention will be apparent from the following detailed description and figures, and from the claims.

DETAILED DESCRIPTION

[0073] Provided herein are methods for using compounds of the general Formula I containing a pyrazolo[1,5-a]pyrimidinyl ring and having the structure:

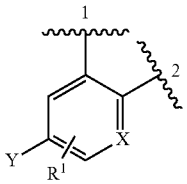
I



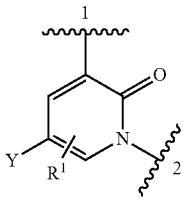
or pharmaceutically acceptable salts or solvates thereof, wherein:

[0074] ring A is selected from rings A-1, A-2 and A-3 having the structures:

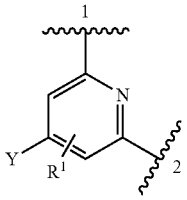
A-1



A-2



A-3



[0075] wherein the wavy line labeled 1 indicates the point of attachment of ring A to ring B and the wavy line labeled 2 indicates the point of attachment of ring A to W;

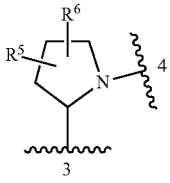
[0076] X is N or CH;

[0077] Y is H or F;

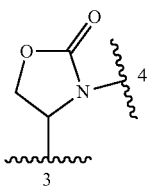
[0078] R^1 is H, (1-3C)alkoxy or halogen;

[0079] ring B is selected from rings B-1 and B-2 having the structures:

B-1



B-2



[0080] wherein the wavy line labeled 3 indicates the point of attachment to ring A and the wavy line labeled 4 indicates the point of attachment to the pyrazolo[1,5-a]pyrimidine ring of Formula I;

[0081] W is O, NH or CH_2, wherein when ring A is A-2, then W is CH_2;

[0082] m is 0, 1 or 2;

[0083] D is carbon;

[0084] R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH, provided that R^2 and R^{2a} are not both OH;

[0085] R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0086] or D is carbon or nitrogen, R^2 and R^3 are absent and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms;

[0087] Z is *—$NR^{4a}C(=O)$—, *—ONHC(=O)—, *—$NR^{4b}CH_2$— or *—OC(=O)—, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

[0088] R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

[0089] R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)—, (3-6C cycloalkyl)C(O)—, $Ar^1C(O)$—, $HOCH_2C(O)$—, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$—, HO_2CCH_2— or (1-6C alkyl)NH(CO)—;

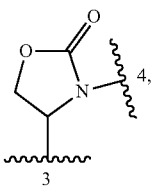
[0090] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy;

[0091] Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

[0092] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0093] In some embodiments of Formula I, ring B is ring B-2 having the structure:

B-2

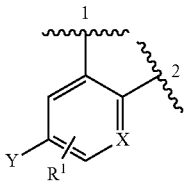


[0094] D is carbon, R^2 and R^{2a} are independently (1-3 C)alkyl, and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl, or

[0095] D is carbon or nitrogen, R^2 and R^3 are absent and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms.

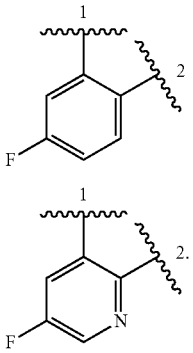
[0096] In some embodiments of Formula I, ring A is ring A-1 having the structure

A-1



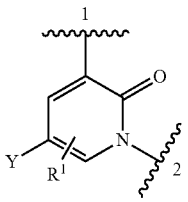
[0097] wherein X, Y and R^1 are as defined for Formula I. In some embodiments of Formula I, X is CH. In some embodiments, X is N. In some embodiments of Formula I, Y is F. In some embodiments, Y is H. In some embodiments of Formula I, R^1 is H. In some embodiments, R^1 is (1-3C)alkoxy. A particular example is methoxy. In some embodiments, R^1 is halogen. In some embodiments, R^1 is F.

[0098] Particular examples of ring A when represented by structure A-1 include the structures:



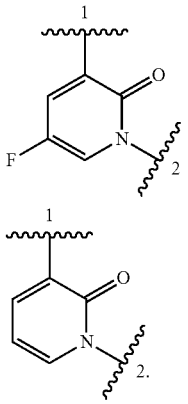
[0099] In some embodiments, ring A is ring A-2 having the structure

A-2



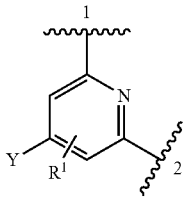
[0100] wherein Y is H or F. In some embodiments, Y is F. In some embodiments, Y is H. In some embodiments, R^1 is H. In some embodiments, R^1 is (1-3C)alkoxy. A particular example is methoxy. In some embodiments, R^1 is halogen. In some embodiments, R^1 is F.

[0101] Particular examples of ring A when represented by ring A-2 are the structures:



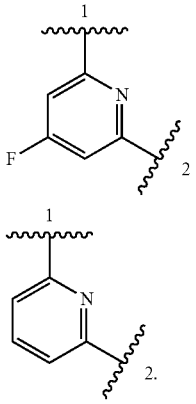
[0102] In some embodiments of Formula I, ring A is ring A-3 having the structure

A-3



[0103] wherein Y and R^1 is as defined for Formula I. In some embodiments, Y is F. In some embodiments, Y is H. In some embodiments, R^1 is H. In some embodiments, R^1 is (1-3C)alkoxy. A particular example is methoxy. In some embodiments, R^1 is halogen. In some embodiments, R^1 is F.

[0104] Particular examples of ring A when represented by ring A-3 are the structures:



[0105] In some embodiments of Formula I, W is O.

[0106] In some embodiments, W is NH.

[0107] In some embodiments, W is CH_2.

[0108] In some embodiments of Formula I, D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), and R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl.

[0109] In some embodiments, R^2 and R^{2a} are independently H, F, methyl or OH, provided that R^2 and R^{2a} are not both OH.

[0110] In some embodiments, R^2 and R^{2a} are both H.

[0111] In some embodiments, R^2 is H and R^{2a} is F.

[0112] In some embodiments, R^2 and R^{2a} are both F.

[0113] In some embodiments, R^2 is H and R^{2a} is OH.

[0114] In some embodiments, R^2 is H and R^{2a} is methyl.

[0115] In some embodiments, R^2 and R^{2a} are both methyl.

[0116] In some embodiments, R^3 and R^{3a} are independently H, (1-3C)alkyl or hydroxy(1-3 C)alkyl.

[0117] In some embodiments, R^{3a} is H. In some embodiments, R^3 is H. In some embodiments, both R^3 and R^{3a} are H.

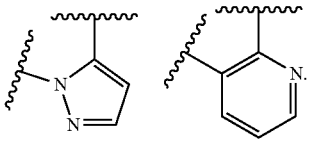
[0118] In some embodiments, R^{3a} is (1-3C)alkyl. Examples include methyl, ethyl, propyl and isopropyl. In some embodiments, R^3 is (1-3C)alkyl. Examples include methyl, ethyl, propyl and isopropyl.

[0119] In some embodiments, R^{3a} is (1-3C)alkyl and R^3 is H. In some embodiments, R^{3a} is methyl and R^3 is H.

[0120] In some embodiments, both R^{3a} and R^3 are (1-3C) alkyl. In some embodiments, R^{3a} and R^{3a} are both methyl.

[0121] In some embodiments, R^3 is hydroxy(1-3C)alkyl. Examples include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, and 3-hydroxypropyl. In some embodiments, R^3 is hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl, or 3-hydroxypropyl and R^{3a} is H.

[0122] In some embodiments of Formula I, D is carbon or nitrogen, R^2 and R^3 are absent, and R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring heteroatoms. In some embodiments, R^{2a} and R^{3a} together with the atoms to which they are attached form a 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms. Examples of heteroaryl rings include pyridyl and pyrazolyl rings. Specific examples of heteroaryl rings include the structures:



[0123] In some embodiments, Z is *—$NR^{4a}C(=O)$—.

[0124] In some embodiments, R^{4a} is H.

[0125] In some embodiments, R^{4a} is (1-6C)alkyl. Examples include methyl, ethyl, propyl, isopropyl, butyl, and isobutyl.

[0126] In some embodiments, R^{4a} is fluoro(1-6C)alkyl. Examples include fluoromethyl and 2-fluoroethyl.

[0127] In some embodiments, R^{4a} is difluoro(1-6C)alkyl. Example include difluoromethyl and 2,2-difluoroethyl.

[0128] In some embodiments, R^{4a} is trifluoro(1-6C)alkyl. Examples include trifluoromethyl and 2,2,2-trifluoroethyl.

[0129] In some embodiments, R^{4a} is hydroxy(1-6C alkyl). Examples include hydroxymethyl, 2-hydroxyethyl, 2-hydroxypropyl and 3-hydroxypropyl.

[0130] In some embodiments, R^{4a} is dihydroxy(2-6C alkyl). An example includes 2,3-dihydroxypropyl.

[0131] In some embodiments, R^{4a} is H or (1-6C)alkyl. In some embodiments, R^{4a} is H or Me.

[0132] An example of Z when represented by *—$NR^{4a}C(=O)$— is *—$ONHC(=O)$—.

[0133] In some embodiments, Z is *—$NR^{4b}CH_2$—.

[0134] In some embodiments, R^{4b} is H.

[0135] In some embodiments, R^{4b} is selected from (1-6C) alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, and trifluoro (1-6C)alkyl.

[0136] In some embodiments, R^{4b} is (1-6C)alkyl. Examples include methyl, ethyl, propyl, isopropyl, butyl and tert-butyl. In some embodiments, R^{4b} is methyl.

[0137] In some embodiments, R^{4b} is fluoro(1-6C)alkyl. Examples include fluoromethyl and 2-fluoroethyl.

[0138] In some embodiments, R^{4b} is difluoro(1-6C)alkyl. Example include difluoromethyl and 2,2-difluoroethyl.

[0139] In some embodiments, R^{4b} is trifluoro(1-6C)alkyl. Examples include trifluoromethyl and 2,2,2-trifluoroethyl.

[0140] In some embodiments, R^{4b} is selected from (1-6C alkyl)C(O)—, (3-6C cycloalkyl)C(O)—, $Ar^1C(O)$— and $HOCH_2C(O)$—.

[0141] In some embodiments, R^{4b} is (1-6C alkyl)C(O)—. Examples include $CH_3C(O)$—, $CH_3CH_2C(O)$—, $CH_3CH_2CH_2C(O)$—, and $(CH_3)_2CHC(O)$—. In some embodiments, R^4 is $CH_3C(O)$—.

[0142] In some embodiments, R^{4b} is (3-6C cycloalkyl)C (O)—. Examples include cyclopropylC(O)—, cyclobutylC (O)—, cyclopentylC(O)— and cyclohexylC(O)—.

[0143] In some embodiments, R^{4b} is $Ar^1C(O)$—. An example is phenylC(O)—.

[0144] In some embodiments, R^{4b} is $HOCH_2C(O)$—.

[0145] In some embodiments, R^{4b} is selected from (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, and $Ar^2(SO_2)$—.

[0146] In some embodiments, R^{4b} is (1-6C alkyl)sulfonyl. Examples include methylsulfonyl, ethylsulfonyl and propylsulfonyl.

[0147] In some embodiments, R^{4b} is (3-6C cycloalkyl) sulfonyl. Examples include cyclopropylsulfonyl, cyclobutylsulfonyl, cyclopentylsulfonyl and cyclohexylsulfonyl. In some embodiments, R^4 is methylsulfonyl.

[0148] In some embodiments, R^{4b} is $Ar^2(SO_2)$—. An example is phenylsulfonyl.

[0149] In some embodiments, R^{4b} is HO_2CCH_2—.

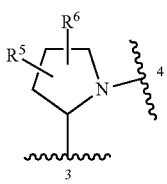
[0150] In some embodiments, R^{4b} is (1-6C alkyl)NH (CO)—. Examples include $CH_3NHC(O)$—, $CH_3CH_2NHC(O)$—, $CH_3CH_2CH_2NHC(O)$—, and $(CH_3)_2CHNHC(O)$—. In some embodiments, R^4 is $CH_3NHC(O)$—.

[0151] In some embodiments, R^{4b} is selected from H, methyl, —$C(O)CH_3$, methylsulfonyl, —$C(O)CH_2OH$, —CH_2COOH and —$C(O)NHCH_2CH_3$.

[0152] In some embodiments, Z is *—$OC(=O)$—.

[0153] In some embodiments of Formula I, ring B is ring B-1:

B-1



[0154] where R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0155] In some embodiments, R^5 and R^6 are independently H, F, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl. In some embodiments, R^5 is H and R^6 is H, F, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0156] In some embodiments, R^5 and R^6 are independently H, F, OH, (1-3C)alkyl or hydroxy(1-3C)alkyl. In some embodiments, R^5 is hydrogen and R^6 is H, F, OH, (1-3C) alkyl or hydroxy(1-3C)alkyl.

[0157] In some embodiments, R^5 and R^6 are independently H, F, OH, methyl, ethyl, $HOCH_2$— or $HOCH_2CH_2$—. In some embodiments, R^5 is hydrogen and R^6 is H, F, OH, methyl, ethyl, $HOCH_2$— or $HOCH_2CH_2$—.

[0158] In some embodiments, R^5 and R^6 are independently H, F, or methyl. In some embodiments, R^5 is H and R^6 is H, F, or methyl.

[0159] In some embodiments, R^5 is H and R^6 is F.

[0160] In some embodiments, R^5 is H and R^6 is methyl.

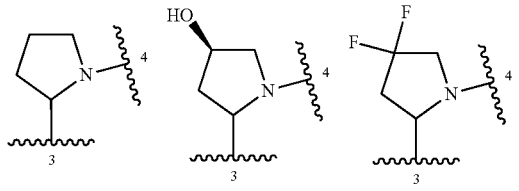
[0161] In some embodiments, R^5 and R^6 are both H.

[0162] In some embodiments, R^5 and R^6 are both F.

[0163] In some embodiments, R^5 and R^6 are both methyl.

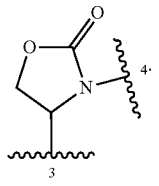
[0164] In some embodiments, ring B is ring B-1 which is optionally substituted with one or two substituents independently selected from OH and F, provided that two OH substituents are not on the same ring carbon atom.

[0165] Particular examples of ring B when represented by ring B-1 include the structures:



[0166] In some embodiments of Formula I, ring B is ring B-2 having the formula:

B-2



[0167] In some embodiments, m is 0.

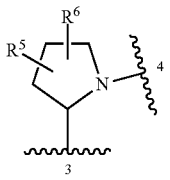
[0168] In some embodiments, m is 1.

[0169] In some embodiments, m is 2.

[0170] Provided herein are compounds of the general Formula I or pharmaceutically acceptable salts or solvates thereof, wherein:

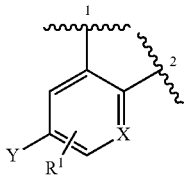
[0171] ring B is ring B-1:

B-1

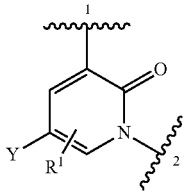


[0172] ring A is selected from rings A-1, A-2 and A-3 having the structures:

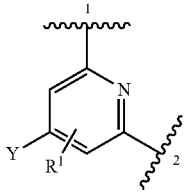
A-1



A-2



A-3



[0173] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0174] X is N or CH;

[0175] Y is H or F;

[0176] R^1 is H, (1-3C)alkoxy or halogen;

[0177] W is O, NH or CH_2, wherein when ring A is A-2, then W is CH_2;

[0178] m is 0, 1 or 2;

[0179] D is carbon;

[0180] R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH, provided that R^2 and R^{2a} are not both OH;

[0181] R^3 and R^{3a} are independently H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0182] or R^2 and R^3 are absent and R^{2a} and R^{3a} together with the atoms to which they are attached form a bivalent 5-6 membered heteroaryl ring having 1-2 ring nitrogen atoms;

[0183] Z is *—$NR^{4a}C(=O)$—, *—$ONHC(=O)$—, *—$NR^{4b}CH_2$— or *—$OC(=O)$—, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

[0184] R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

[0185] R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)—, (3-6C cycloalkyl)C(O)—, $Ar^1C(O)$—, $HOCH_2C(O)$—, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$—, HO_2CCH_2— or (1-6C alkyl)NH(CO)—;

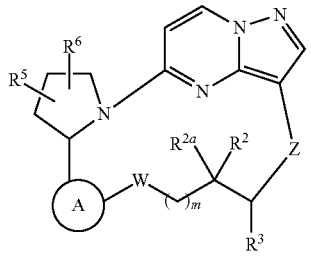
[0186] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy;

[0187] Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

[0188] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0189] Also provided herein are compounds of the general Formula IA

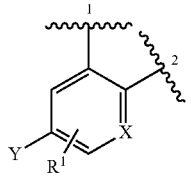
IA



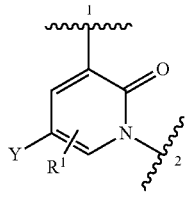
[0190] or pharmaceutically acceptable salts or solvates thereof, wherein:

[0191] ring A is selected from rings A-1, A-2 and A-3 having the structures:

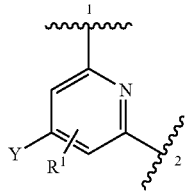
A-1



A-2



A-3



[0192] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0193] X is N or CH;

[0194] Y is H or F;

[0195] R^1 is H, (1-3C)alkoxy or halogen;

[0196] W is O, NH or CH_2, wherein when ring A is A-2, then W is CH_2;

[0197] m is 0, 1 or 2;

[0198] R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

[0199] R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0200] Z is *—$NR^{4a}C(=O)$—, *—ONHC(=O)—, *—$NR^{4b}CH_2$— or *—OC(=O)—, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

[0201] R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl);

[0202] R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl), dihydroxy(2-6C alkyl), (1-6C alkyl)C(O)—, (3-6C cycloalkyl)C(O)—, $Ar^1C(O)$—, $HOCH_2C(O)$—, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$—, HO_2CCH_2— or (1-6C alkyl)NH(CO)—;

[0203] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy;

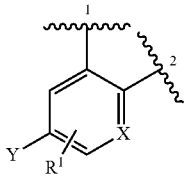
[0204] Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

[0205] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0206] In some embodiments, Formula IA includes compounds wherein:

[0207] ring A is ring A-1 represented by the structure

A-1



[0208] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0209] X is N or CH;

[0210] Y is H or F;

[0211] R^1 is H, (1-3C)alkyl, (1-3C)alkoxy or halogen;

[0212] W is O or NH;

[0213] m is 0, 1 or 2;

[0214] R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

[0215] R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0216] Z is *—$NR^{4a}C(=O)$—, *—ONHC(=O)—, or *—OC(=O)—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

[0217] R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl); and

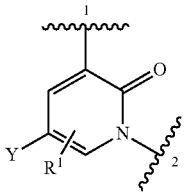
[0218] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0219] In some embodiments of Formula IA, X is N. In some embodiments, X is CH.

[0220] In some embodiments, Formula IA includes compounds wherein:

[0221] ring A is ring A-2 represented by the structure

A-2



[0222] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0223] Y is H or F;

[0224] R^1 is H, (1-3C)alkyl, (1-3C)alkoxy or halogen;

[0225] m is 0, 1 or 2;

[0226] W is CH_2;

[0227] m is 0, 1 or 2;

[0228] R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

[0229] R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0230] Z is *—$NR^{4a}C(=O)$—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

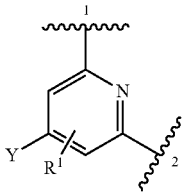
[0231] R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl); and

[0232] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0233] In some embodiments, Formula IA includes compounds wherein:

[0234] ring A is ring A-3 represented by the structure

A-3



[0235] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0236] Y is H or F;

[0237] R^1 is H, (1-3C)alkyl, (1-3C)alkoxy or halogen;

[0238] W is O;

[0239] m is 0, 1 or 2;

[0240] R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

[0241] R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0242] Z is *—OC(=O)— or *—$NR^{4a}C(=O)$—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

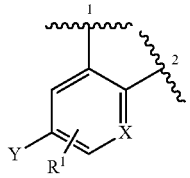
[0243] R^{4a} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl, hydroxy(1-6C alkyl) or dihydroxy(2-6C alkyl); and

[0244] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

[0245] In some embodiments, Formula IA includes compounds wherein:

[0246] ring A is ring A-1 represented by the structure

A-1



[0247] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0248] X is N or CH;

[0249] Y is H or F;

[0250] R^1 is H, (1-3C)alkyl, (1-3C)alkoxy or halogen;

[0251] W is O;

[0252] m is 0, 1 or 2;

[0253] R^2 and R^{2a} are independently H, F, or OH, provided that R^2 and R^{2a} are not both OH;

[0254] R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl;

[0255] Z is *—$NR^{4b}CH_2$—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

[0256] R^{4b} is H, (1-6C)alkyl, fluoro(1-6C)alkyl, difluoro(1-6C)alkyl, trifluoro(1-6C)alkyl (1-6C alkyl)C(O)—, (3-6C cycloalkyl)C(O)—, $Ar^1C(O)$—, $HOCH_2C(O)$—, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, $Ar^2(SO_2)$—, HO_2CCH_2— or (1-6C alkyl)NH(CO)—;

[0257] Ar^1 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy;

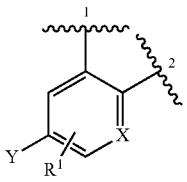
[0258] Ar^2 is phenyl optionally substituted with one or more substituents independently selected from halogen, (1-6C)alkyl, and (1-6C)alkoxy; and

[0259] R^5 and R^6 are independently H, halogen, OH, (1-6C)alkyl or hydroxy(1-6C)alkyl.

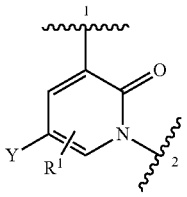
[0260] In some embodiments of general Formula IA,

[0261] ring A is selected from rings A-1, A-2 and A-3 having the structures:

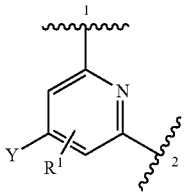
A-1



A-2



A-3



[0262] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0263] X is N or CH;

[0264] Y is H or F;

[0265] R^1 is H;

[0266] W is O or CH_2, wherein when ring A is A-2, then W is CH_2;

[0267] m is 0 or 1;

[0268] R^2 and R^{2a} are independently H, F, (1-3 C)alkyl, or OH, provided that R^2 and R^{2a} are not both OH;

[0269] R^3 is H or (1-3 C)alkyl;

[0270] Z is *—$NR^{4a}C(=O)$—, *—$NR^{4b}CH_2$— or *—$OC(=O)$—, wherein the asterisk indicates the point of attachment of Z to the carbon bearing R^3;

[0271] R^{4a} is H;

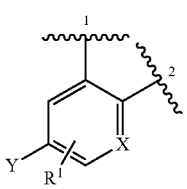
[0272] R^{4b} is (1-6C alkyl)C(O)—; and

[0273] R^5 and R^6 are independently H or halogen.

[0274] In some embodiments, Formula IA includes compounds wherein:

[0275] ring A is ring A-1 represented by the structure

A-1



[0276] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0277] X is N or CH;

[0278] Y is H or F;

[0279] R^1 is H;

[0280] W is O or CH_2;

[0281] m is 0 or 1;

[0282] R^2 and R^{2a} are independently H, F, (1-3 C)alkyl, or OH, provided that R^2 and R^{2a} are not both OH;

[0283] R^3 is H or (1-3 C)alkyl;

[0284] Z is *—$NR^{4a}C(=O)$—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

[0285] R^{4a} is H; and

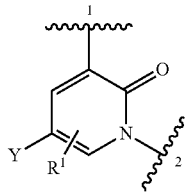
[0286] R^5 and R^6 are independently H or halogen.

[0287] In some embodiments of Formula IA where ring A is ring A-1, X is N. In some such embodiments of Formula IA where ring A is ring A-1, W is O. In some embodiments of Formula IA where ring A is ring A-1, W is CH_2. In some embodiments of Formula IA where ring A is ring A-1, R^2 and R^{2a} are H. In some embodiments of Formula IA where ring A is ring A-1, R^2 and R^{2a} are independently F, (1-3 C)alkyl, or OH. In some embodiments of Formula IA where ring A is ring A-1, R^3 is (1-3 C)alkyl. In some embodiments of Formula IA where ring A is ring A-1, R^3 is H. In some embodiments of Formula IA where ring A is ring A-1, Z is *—$NR^{4a}C(=O)$—. In some embodiments of Formula IA where ring A is ring A-1, R^5 and R^6 are H.

[0288] In some embodiments, Formula IA includes compounds wherein:

[0289] ring A is ring A-2 represented by the structure

A-2



[0290] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0291] Y is H or F;

[0292] R^1 is H;

[0293] W is CH_2;

[0294] m is 0 or 1;

[0295] R^2 and R^{2a} are independently H, F, (1-3 C)alkyl, or OH, provided that R^2 and R^{2a} are not both OH;

[0296] R^3 is H or (1-3 C)alkyl;

[0297] Z is *—$NR^{4a}C(=O)$—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

[0298] R^{4a} is H; and

[0299] R^5 and R^6 are independently H or halogen.

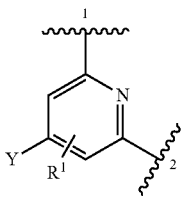
[0300] In some embodiments of Formula IA where ring A is ring A-2, Y is F. In some embodiments of Formula IA where ring A is ring A-2, R^2 and R^{2a} are H. In some

embodiments of Formula IA where ring A is ring A-2, R^2 and R^{2a} are independently H or (1-3 C)alkyl. In some embodiments of Formula IA where ring A is ring A-2, R^3 is (1-3 C)alkyl. In some embodiments of Formula IA where ring A is ring A-2, R^3 is H. In some embodiments of Formula IA where ring A is ring A-2, R^5 and R^6 are H.

[0301] In some embodiments, Formula IA includes compounds wherein:

[0302] ring A is ring A-3 represented by the structure

A-3



[0303] wherein the wavy line labeled 1 indicates the point of attachment of ring A to the pyrrolidine ring of Formula I and the wavy line labeled 2 indicates the point of attachment of ring A to W;

[0304] Y is H or F;

[0305] R^1 is H;

[0306] W is O;

[0307] m is 0 or 1;

[0308] R^2 and R^{2a} are independently H, F, (1-3 C)alkyl, or OH, provided that R^2 and R^{2a} are not both OH;

[0309] R^3 is H or (1-3 C)alkyl;

[0310] Z is *—$NR^{4a}C(=O)$—, wherein the asterisk indicates the point of attachment to the carbon bearing R^3;

[0311] R^{4a} is H; and

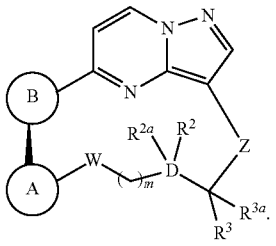
[0312] R^5 and R^6 are independently H or halogen.

[0313] In some embodiments of Formula IA where ring A is ring A-3, Y is F. In some embodiments of Formula IA where ring A is ring A-3, Y is H. In some embodiments of Formula IA where ring A is ring A-3, R^2 and R^{2a} are H. In some embodiments of Formula IA where ring A is ring A-3, R^2 and R^{2a} are independently H or (1-3 C)alkyl. In some embodiments of Formula IA where ring A is ring A-3, R^3 is (1-3 C)alkyl. In some embodiments of Formula IA where ring A is ring A-3, R^3 is H. In some embodiments of Formula IA where ring A is ring A-3, R^5 and R^6 are H.

[0314] It will be appreciated that certain compounds as provided herein may contain one or more centers of asymmetry and may therefore be prepared and isolated as a mixture of isomers such as a racemic or diastereomeric mixture, or in an enantiomerically or diastereomerically pure form. It is intended that all stereoisomeric forms of the compounds provided herein, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present disclosure.

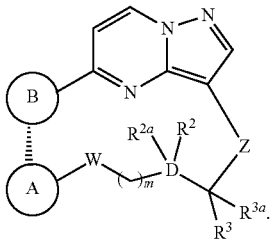
[0315] In some embodiments, compounds of the general Formula I wherein Ring B is ring B-1 have the absolute configuration of Formula 1-a:

1-a



[0316] In some embodiments, compounds of the general Formula I wherein Ring B is ring B-1 have the absolute configuration of Formula 1-b:

1-b



[0317] In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the disclosure. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

[0318] The terms "(1-3C)alkyl" and "(1-6C)alkyl" as used herein refer to saturated linear or branched-chain monovalent hydrocarbon radicals of one to three carbon atoms and one to six carbon atoms, respectively. Examples include, but are not limited to, methyl, ethyl, 1-propyl, isopropyl, 1-butyl, isobutyl, sec-butyl, tert-butyl, 2-methyl-2-propyl, pentyl, and hexyl.

[0319] The term "fluoro(1-6C)alkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms as defined herein, wherein one of the hydrogens is replaced by a fluorine atom.

[0320] The term "difluoro(1-6C)alkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms as defined herein, wherein two of the hydrogens are replaced by fluorine atoms.

[0321] The term "trifluoro(1-6C)alkyl" as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms as defined herein, wherein three of the hydrogens are replaced by fluorine atoms.

[0322] The term "hydroxy(1-6Calkyl) as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of one to six carbon atoms, wherein one of the hydrogens is replaced by a hydroxy (OH) group.

[0323] The term "dihydroxy(2-6C alkyl) as used herein refers to saturated linear or branched-chain monovalent hydrocarbon radicals of two to six carbon atoms as defined

herein, wherein two of the hydrogens are replaced by hydroxy (OH) groups, provided the hydroxy groups are not on the same carbon atom.

[0324] The term "(1-6C alkyl)sulfonyl" as used herein refers to a (1-6C alkyl)SO_2— group, wherein the radical is on the sulfur atom and the (1-6C alkyl) portion is as defined above. Examples include methylsulfonyl (CH_3SO_2—) and ethylsulfonyl ($CH_3CH_2SO_2$—).

[0325] The term "(3-6C cycloalkyl)sulfonyl" as used herein refers to a (3-6C cycloalkyl)SO_2— group, wherein the radical is on the sulfur atom. An example is cyclopropylsulfonyl.

[0326] The terms "(1-3C)alkoxy" and "(1-6C)alkoxy", as used herein refer to saturated linear or branched-chain monovalent alkoxy radicals of one to three carbon atoms or one to six carbon atoms, respectively, wherein the radical is on the oxygen atom. Examples include methoxy, ethoxy, propoxy, isopropoxy, and butoxy.

[0327] The term "halogen" includes fluoro, chloro, bromo and iodo.

[0328] Non-limiting examples of the compounds of Formula I include those in Table 1.

TABLE 1

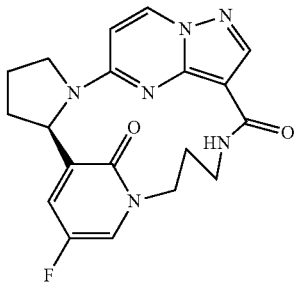
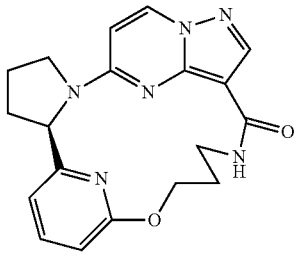
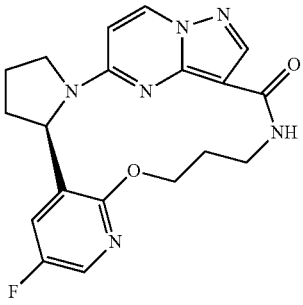
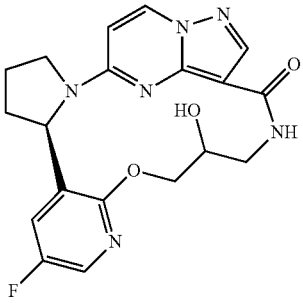
Compound No.	Compound Structure	Compound Name
1		(6R)-9-fluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
2		(6R)-12-oxa-2,16,20,21,24,26-hexaazapentacyclo[16.5.2.1^{7,11}.0^{2,6}.0^{21,25}]hexacosa-1(24),7(26),8,10,18(25),19,22-heptaen-17-one
3		(6R)-9-fluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
4		(6R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

TABLE 1-continued

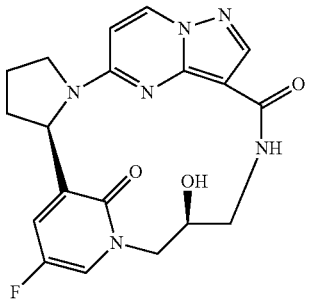
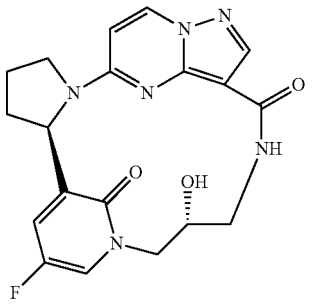
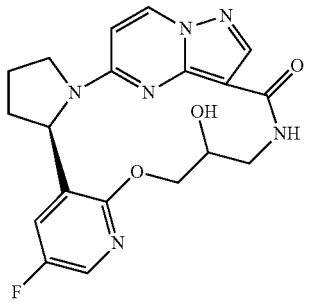
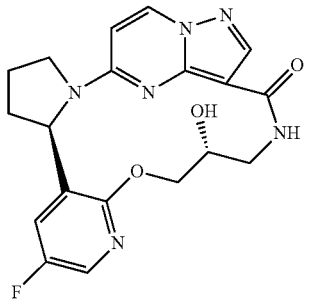
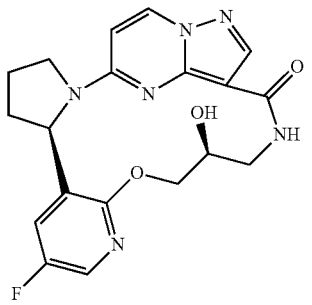
Compound No.	Compound Structure	Compound Name
5		(6R,13S)-9-fluoro-13-hydroxy-2,11,15,19,20,23-hexaazapentacyclo-[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
5-B		(6R,13R)-9-fluoro-13-hydroxy-2,11,15,19,20,23-hexaazapentacyclo-[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-heaene-16,25-dione
6		(6R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
7		(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
7-B		(6R,15S)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

TABLE 1-continued

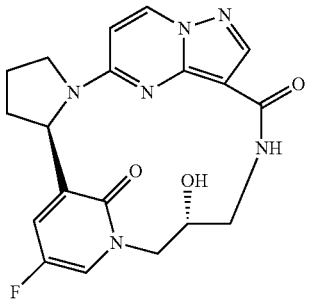
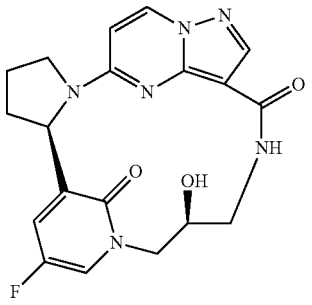
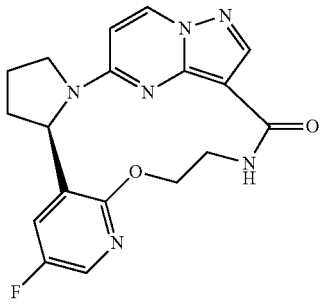
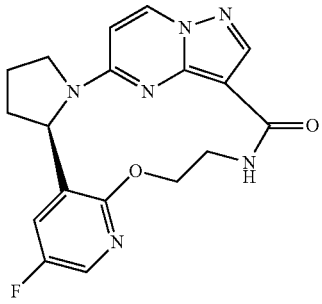
Compound No.	Compound Structure	Compound Name
8		(6R,13R)-9-fluoro-13-hydroxy-2,11,15,19,20,23-hexaazapentacyclo-[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
8-B		(6R,13S)-9-fluoro-13-hydroxy-2,11,15,19,20,23-hexaazapentacyclo-[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
9		(6R)-9-fluoro-13-oxa-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
10		(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.0^{2,6}.0^{7,12}.0^{23,27}]heptacosa-1(26),7,9,11,20(27),21,24-heptaen-19-one

TABLE 1-continued

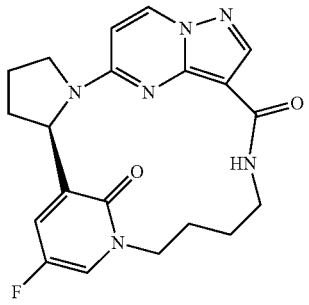
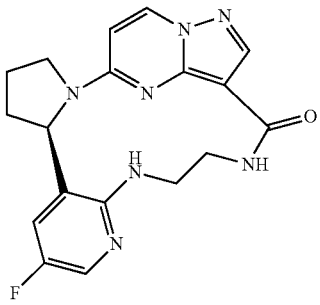
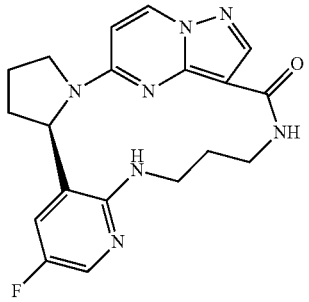
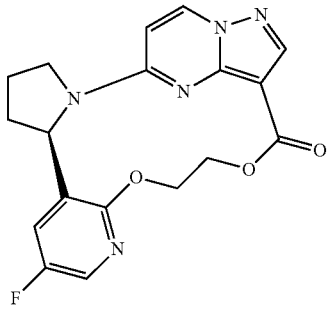
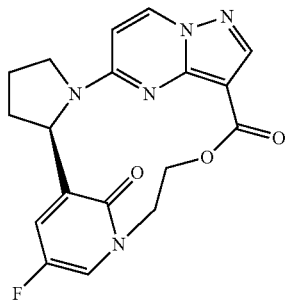
Compound No.	Compound Structure	Compound Name
11		(6R)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.1^{7,11}.0^{2,6}.0^{21,25}]hexacosa-1(24),7,9,18(25),19,22-hexaene-17,26-dione
12		(6R)-9-fluoro-2,11,13,16,20,21,24-heptaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
13		(6R)-9-fluoro-2,11,13,17,21,22,25-heptaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
14		(6R)-9-fluoro-13,16-dioxa-22,11,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]-pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
15		(6R)-9-fluoro-14-oxa-2,11,18,19,22-pentaazapentacyclo[14.5.2.1^{7,11}.0^{2,6}.0^{19,23}]tetracosa-1(22),7,9,16(23),17,20-hexaene-15,24-dione

TABLE 1-continued

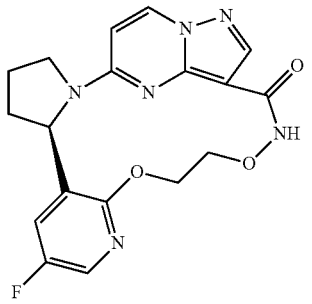
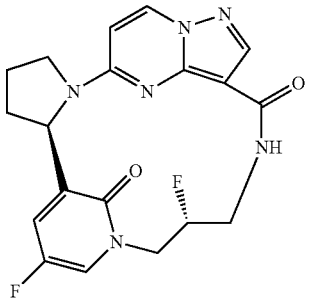
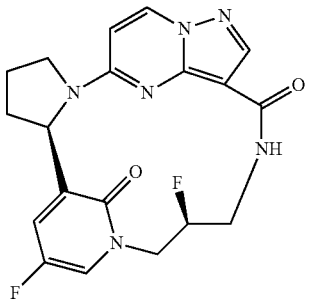
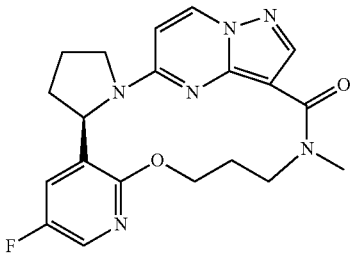
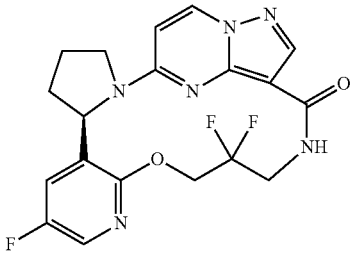
Compound No.	Compound Structure	Compound Name
16		(6R)-9-fluoro-13,16-dioxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
17		(6R,13R)-9,13-difluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
17-B		(6R,13S)-9,13-difluoro-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
18		(6R)-9-fluoro-17-methyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
19		(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

TABLE 1-continued

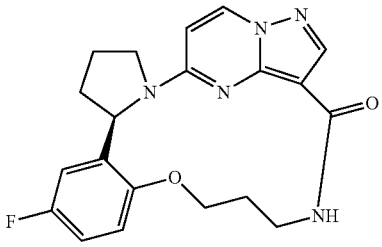
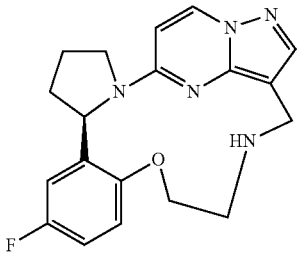
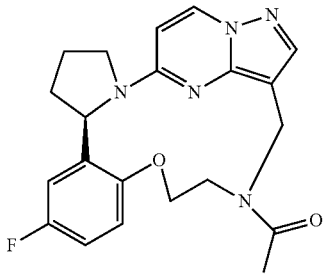
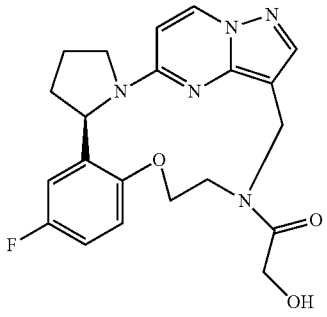
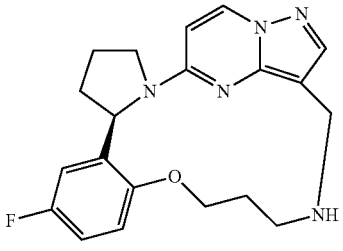
Compound No.	Compound Structure	Compound Name
20		(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one
21		(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaene
22		1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]ethan-1-one
23		1-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]-2-hydroxyethan-1-one
24		(6R)-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,11,19(26),20,23-heptaene

TABLE 1-continued

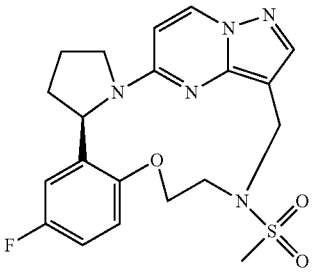
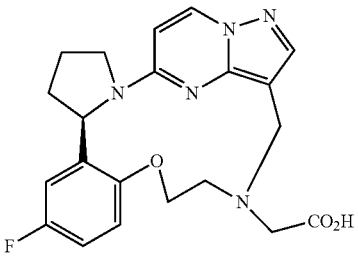
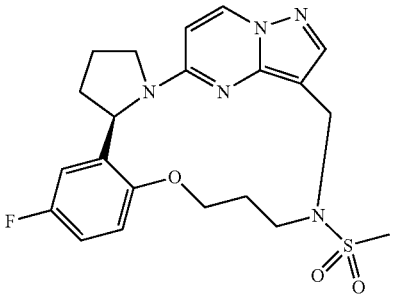
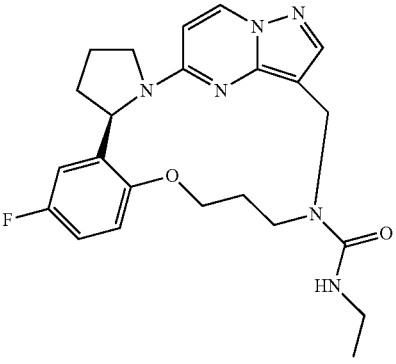
Compound No.	Compound Structure	Compound Name
25		(6R)-9-fluoro-16-methanesulfonyl-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaene
26		2-[(6R)-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-16-yl]acetic acid
27		(6R)-9-fluoro-17-methanesulfonyl-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaene
28		(6R)-N-ethyl-9-fluoro-13-oxa-2,17,21,22,25-pentaazapentacyclo 17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaene-17-carboxamide

TABLE 1-continued

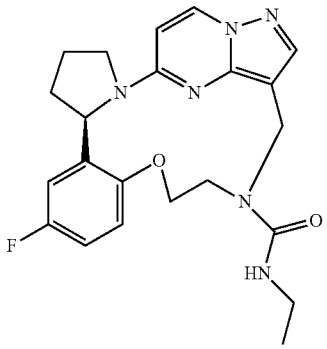
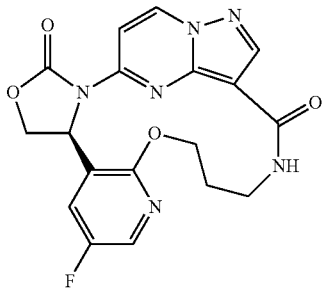
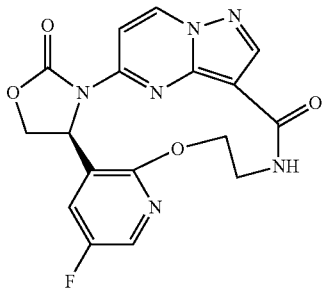
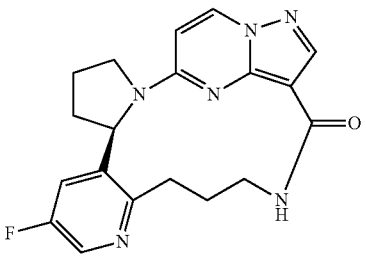
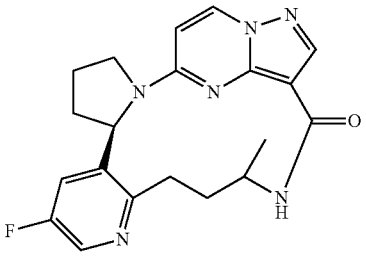
Compound No.	Compound Structure	Compound Name
29		(6R)-N-ethyl-9-fluoro-13-oxa-2,16,20,21,24-pentaazapentacyclo-[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaene-16-carboxamide
30		(6S)-9-fluoro-4,13-dioxa-2,11,17,21,22,25-hexaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaene-3,18-dione
31		(6S)-9-fluoro-4,13-dioxa-2,11,16,20,21,24-hexaazapentacyclo [16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7(12),8,10,18(25),19,22-heptaene-3,17-dione
32		(6R)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}] pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
33		(6R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}] pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one

TABLE 1-continued

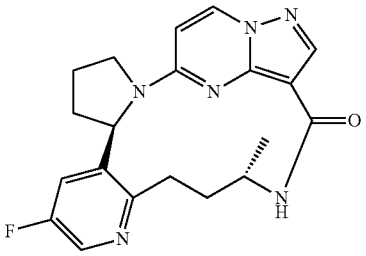
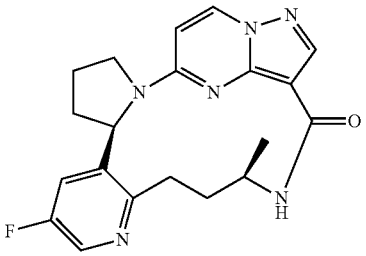
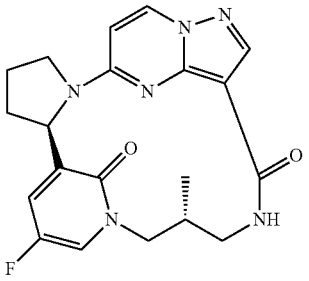
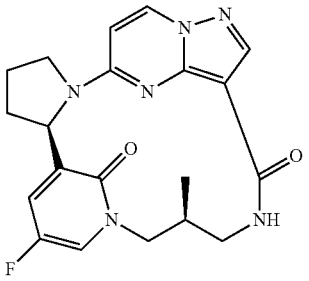
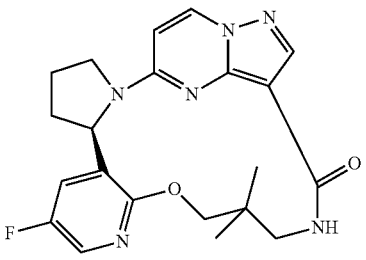
Compound No.	Compound Structure	Compound Name
33-A		(6R,15S)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
33-B		(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
34		(6R,13R)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
35		(6R,13S)-9-fluoro-13-methyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
36		(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one

TABLE 1-continued

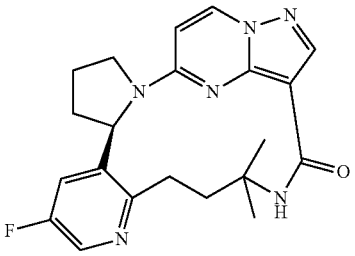
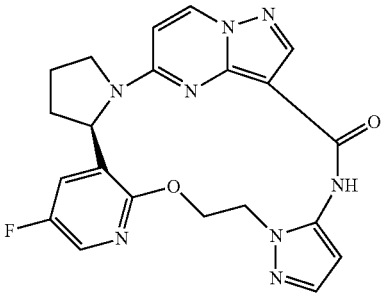
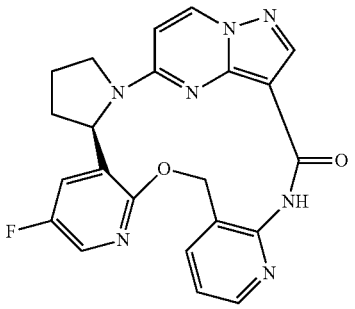
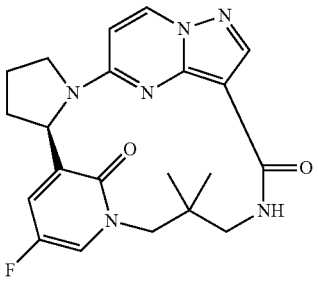
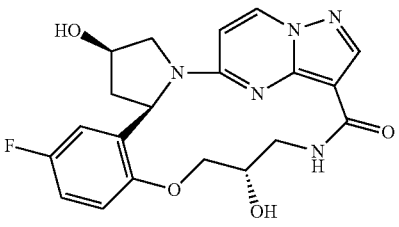
Compound No.	Compound Structure	Compound Name
37		(6R)-9-fluoro-15,15-dimethyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
38		(6R)-9-fluoro-13-oxa-2,11,16,17,21,25,26,29-octaazahexacyclo[21.5.2.0^{2,6}.0^{7,12}.0^{16,20}.0^{26,30}]triaconta-1(29),7,9,11,17,19,23(30),24,27-nonaen-22-one
39		(6R)-9-fluoro-13-oxa-2,11,19,21,25,26,29-heptaazahexacyclo[21.5.2.0^{2,6}.0^{7,12}.0^{15,20}.0^{26,30}]triaconta-1(29),7,9,11,15(20),16,18,23(30),24,27-decaen-22-one
40		(6R)-9-fluoro-13,13-dimethyl-2,11,15,19,20,23-hexaazapentacyclo[15.5.2.1^{7,11}.0^{2,6}.0^{20,24}]pentacosa-1(23),7,9,17(24),18,21-hexaene-16,25-dione
41		(4R,6R,15S)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one

TABLE 1-continued

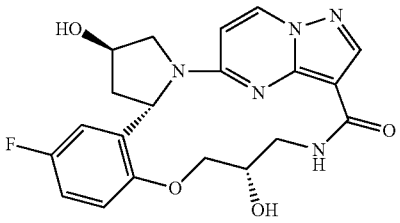
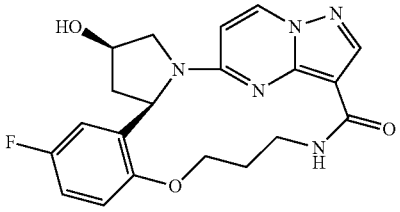
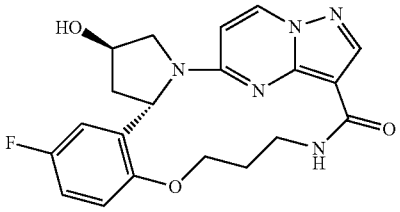
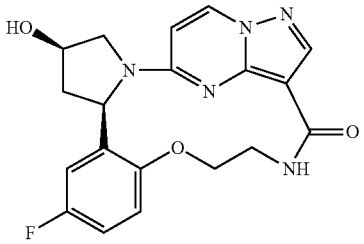
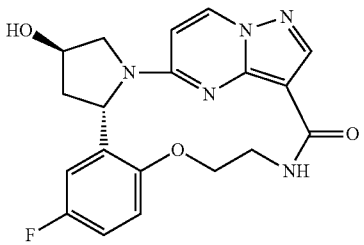
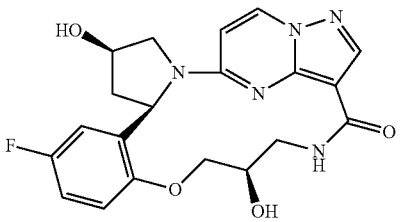
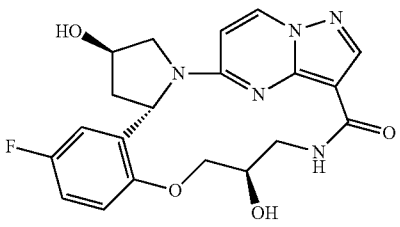
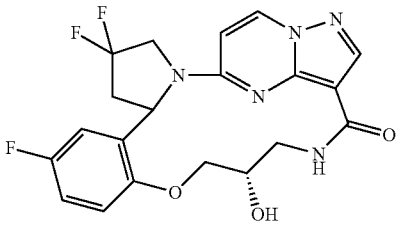
Compound No.	Compound Structure	Compound Name
41-B		(4R,6S,15S)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one
42		(4R,6R)-9-fluoro-4-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one
42-B		(4R,6S)-9-fluoro-4-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one
43		(4R,6R)-9-fluoro-4-hydroxy-13-oxa-2,16,20,21,24-pentaazapentacyclo [16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
43-B		(4R,6S)-9-fluoro-4-hydroxy-13-oxa-2,16,20,21,24-pentaazapentacyclo [16.5.2.0^{2,6}.0^{7,12}.0^{21,25}]pentacosa-1(24),7,9,11,18(25),19,22-heptaen-17-one
44		(4R,6R,15R)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one

TABLE 1-continued

Compound No.	Compound Structure	Compound Name
44-B		(4R,6S,15R)-9-fluoro-4,15-dihydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo [17.5.2.0^{2,6}.0^{7,12}.0^{22,26}]hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one
45		Diastereomer 1 and Diastereomer 2 of (15S)-4,4,9-trifluoro-15-hydroxy-13-oxa-2,17,21,22,25-pentaazapentacyclo[17.5.2.0^{2,6}.0^{7,12}.0^{22,26}] hexacosa-1(25),7(12),8,10,19(26),20,23-heptaen-18-one

[0329] It will also be appreciated that certain compounds of Formula I may be used as intermediates for the preparation of further compounds of Formula I.

[0330] The compounds of Formula I include salts thereof. In certain embodiments, the salts are pharmaceutically acceptable salts. In addition, the compounds of Formula I include other salts of such compounds which are not necessarily pharmaceutically acceptable salts, and which may be useful as intermediates for preparing and/or purifying compounds of Formula I and/or for separating enantiomers of compounds of Formula I.

[0331] The term "pharmaceutically acceptable" indicates that the substance or composition is compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

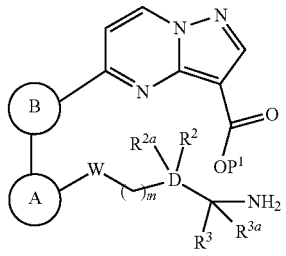
[0332] It will further be appreciated that the compounds of Formula I and their salts may be isolated in the form of solvates, and accordingly that any such solvate is included within the scope of the present disclosure.

[0333] The compounds provided herein may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. That is, an atom, in particular when mentioned in relation to a compound according to Formula I, comprises all isotopes and isotopic mixtures of that atom, either naturally occurring or synthetically produced, either with natural abundance or in an isotopically enriched form. For example, when hydrogen is mentioned, it is understood to refer to ^{1}H, ^{2}H, ^{3}H or mixtures thereof; when carbon is mentioned, it is understood to refer to ^{11}C, ^{12}C, ^{13}C, ^{14}C or mixtures thereof; when nitrogen is mentioned, it is understood to refer to ^{13}N, ^{14}N, ^{15}N or mixtures thereof; when oxygen is mentioned, it is understood to refer to ^{14}O, ^{15}O, ^{16}O, ^{17}O, ^{18}O or mixtures thereof; and when fluoro is mentioned, it is understood to refer to ^{18}F, ^{19}F or mixtures thereof. The compounds provided herein therefore also comprise compounds with one or more isotopes of one or more atom, and mixtures thereof, including radioactive compounds, wherein one or more non-radioactive atoms has been replaced by one of its radioactive enriched isotopes. Radiolabeled compounds are useful as therapeutic agents, e.g., cancer therapeutic agents, research reagents, e.g., assay reagents, and diagnostic agents, e.g., in vivo imaging agents. All isotopic variations of the compounds of the present disclosure, whether radioactive or not, are intended to be encompassed within the scope of the present disclosure.

[0334] The compounds of Formula I or a salt thereof as defined herein can be prepared as described in U.S. Pat. No. 8,933,084, which is incorporated by reference in its entirety herein. For example, a process for preparing a compound of Formula I or a salt thereof as defined herein can include:

[0335] (a) for a compound of Formula I wherein Z is *—NHC(═O)—, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, cyclizing a corresponding compound having the formula II

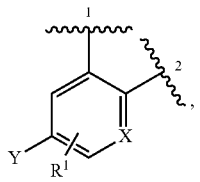
II



[0336] where P^1 is H or a carboxyl protecting group, in the presence of a coupling reagent and a base; or

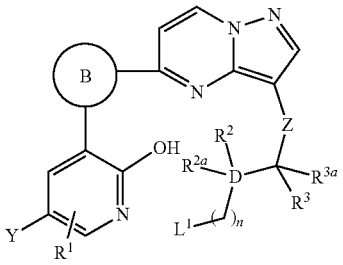
[0337] (b) for a compound of Formula I wherein W is O, ring A is formula A-1:

A-1



[0338] X is N, and ring B, D, Z, Y, R^1, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, cyclizing a corresponding compound having the formula III

III

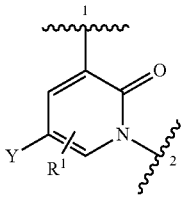


[0339] where n is 1, 2, 3 or 4 and L^1 is a leaving group or atom, in the presence of a base;

or

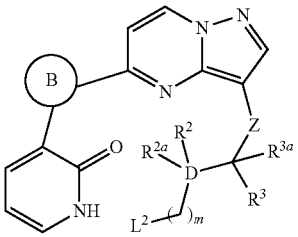
[0340] (c) for a compound of Formula I wherein W is CH_2, ring A is formula A-2:

A-2



[0341] and ring B, Z, D, Y, R^1, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, cyclizing a corresponding compound having the formula IV

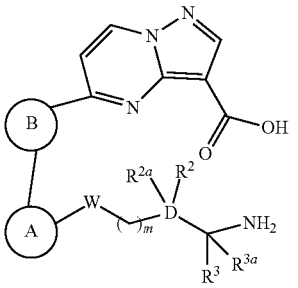
IV



[0342] where L^2 is a leaving group or atom, in the presence of a base; or

[0343] (d) for a compound of Formula I wherein Z is *—NHC(═O)—, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, cyclizing a corresponding compound having the formula V

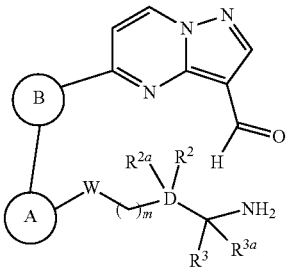
V



[0344] in the presence of a base and a coupling reagent; or

[0345] (e) for a compound of Formula I wherein Z is *—$NHCH_2$—, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, cyclizing a corresponding compound having the formula VI

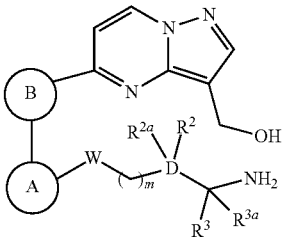
VI



[0346] in the presence of a reducing agent; or

[0347] (f) for a compound of Formula I wherein Z is *—$NHCH_2$—, and ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, cyclizing a corresponding compound having the formula VII

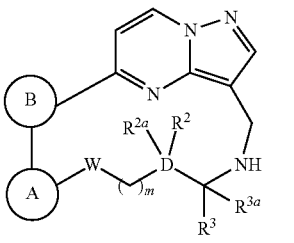
VII



[0348] in the presence of triphenylphosphine; or

[0349] (g) for a compound of Formula I wherein ring A, ring B, W, D, m, R^2, R^{2a}, R^3, and R^{3a} are as defined for Formula I, Z is *—$NR^{4b}CH_2$—, and R^{4b} is (1-6C alkyl)C(O)—, (3-6C cycloalkyl)C(O)—, $Ar^1C(O)$—, $HOCH_2C(O)$—, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, (1-6C alkyl)sulfonyl, (3-6C cycloalkyl)sulfonyl, or $Ar^2(SO_2)$—, coupling a corresponding compound having the formula VIII

VIII

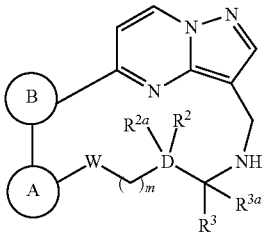


[0350] with a reagent having the formula (1-6C alkyl) C(O)-L^3, (3-6C cycloalkyl)C(O)-L^3, $Ar^1C(O)$-L^3, $HOCH_2C(O)$-L^3, (1-6C alkyl)(SO_2)-L^3, (3-6C

cycloalkyl)(SO_2)-L^3, or Ar^2(SO_2)-L^3, respectively, where L^3 is a leaving atom, in the presence of a base; or

[0351] (h) for a compound of Formula I wherein ring A, ring B, W, D, R^2, R^{2a}, R^3, R^{3a} and m are as defined for Formula I, Z is *—$NR^{4b}CH_2$—, and R^{4b} is (1-6C alkyl)NH(CO)—, reacting a compound having the formula VIII

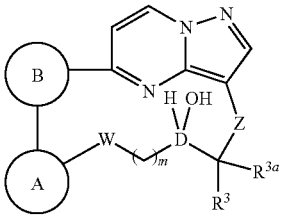
VIII



[0352] with a reagent having the formula (1-6C alkyl) N═C═O in the presence of a base; or

[0353] (i) for a compound of Formula I wherein R^2 is F, R^{2a} is H, and ring A, ring B, Z, W, D, R^3, R^{3a}, and m are as defined for Formula I, reacting a corresponding compound having the formula IX

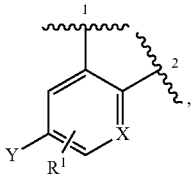
IX



[0354] with a fluorination reagent;

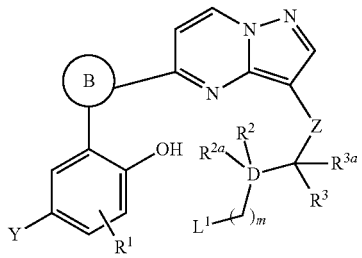
[0355] (j) for a compound of Formula I wherein W is O, ring A is formula A-1,

A-1



[0356] X is CH, and Y, R^1, D, ring B, Z, R^2, R^{2a}, R^3 and m are as defined for Formula I, cyclizing a corresponding compound having the formula X

X

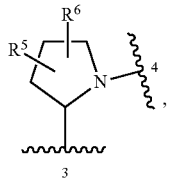


[0357] where n is 1, 2, 3 or 4 and L^1 is a leaving group or atom, in the presence of a base; and

[0358] optionally removing any protecting groups and optionally preparing a salt thereof.

[0359] In some embodiments of the above-described methods (a)-(j), ring B is ring B-1 having the structure:

B-1



D is carbon, R^2 and R^{2a} are independently H, F, (1-3 C)alkyl or OH (provided that R^2 and R^{2a} are not both OH), R^3 is H, (1-3 C)alkyl or hydroxy(1-3 C)alkyl, and ring A, W, m, Z, Y, R^{3a}, R^5 and R^6 are as defined for Formula I.

[0360] Referring to method (a), the cyclization may be performed using conventional amide bond formation conditions, for example by treating the carboxylic acid with an activating agent, followed by addition of the amine in the presence of a base. Suitable activating agents include EDCI, oxalyl chloride, thionyl chloride, HATU, and HOBt. Suitable bases include amine bases, for example triethylamine, diisopropylethylamine, pyridine, or excess ammonia. Suitable solvents include DCM, DCE, THF and DMF.

[0361] Referring to methods (b) and (c), the leaving atoms L^1 and L^2 may be, for example a halogen atom such as Br, Cl or I. Alternatively, L^1 and L^2 can be a leaving group, for example an arylsulfonyloxy group or an alkylsulfonyloxy group, such as a mesylate or a tosylate group. Suitable bases include alkali metal carbonates, such as sodium carbonate, potassium carbonate or cesium carbonate. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane), DMF, or acetone. The reaction can be conveniently performed at elevated temperatures, for example 50-150° C., for example at 85° C.

[0362] Referring to method (d), suitable coupling reagents include HATU, HBTU, TBTU, DCC, DIEC, and any other amide coupling reagents well known to persons skilled in the art. Suitable bases include tertiary amine bases such as DIEA and triethylamine. Convenient solvents include DMF, THF, DCM and DCE.

[0363] Referring to method (e), suitable reducing agents include $Me_4N(OAc)_3BH$, $Na(OAc)_3BH$ and $NaCNBH_3$. Suitable solvents include neutral solvents such as acetoni-

trile, THF and DCE. The reaction can be conveniently performed at ambient temperature.

[0364] Referring to method (f), in certain embodiments the triphenylphosphine reagent is used in the form of a polystyrene-bound PPh_3 resin (sold as PS-PPh_3 by Biotage Systems). The reaction is conveniently performed at ambient temperature. Suitable solvents include neutral solvents, for example DCM.

[0365] Referring to method (g), the leaving atom L^3 may be a halogen, for example Cl or Br. Suitable bases include tertiary amine bases such as diisopropylethylamine and triethylamine. The reaction is conveniently performed at ambient temperature.

[0366] Referring to method (h), suitable bases include tertiary amine bases such as DIEA and triethylamine. The reaction is conveniently performed at ambient temperature.

[0367] Referring to method (i), the fluorination reagent may be, for example, bis(2-methoxyethyl)amino-sulfur trifluoride (Deoxo-Fluor™) or diethylaminosulfur trifluoride (DAST). Suitable solvents include dichloromethane, chloroform, dichloroethane, and toluene. The reaction is conveniently performed at ambient temperature.

[0368] Referring to method (j), base may be, for example, an alkali metal carbonate, such as for example sodium carbonate, potassium carbonate or cesium carbonate. Convenient solvents include aprotic solvents such as ethers (for example tetrahydrofuran or p-dioxane) or toluene. The reaction can be conveniently performed at a temperature between ambient temperature and reflux, for example at 85° C.

[0369] Amine groups in compounds described in any of the above methods may be protected with any convenient amine protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2^{nd} ed. New York; John Wiley & Sons, Inc., 1991. Examples of amine protecting groups include acyl and alkoxycarbonyl groups, such as t-butoxycarbonyl (BOC), and [2-(trimethylsilyl)ethoxy]methyl (SEM). Likewise, carboxyl groups may be protected with any convenient carboxyl protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2^{nd} ed. New York; John Wiley & Sons, Inc., 1991. Examples of carboxyl protecting groups include (1-6C)alkyl groups, such as methyl, ethyl and t-butyl. Alcohol groups may be protected with any convenient alcohol protecting group, for example as described in Greene & Wuts, eds., "Protecting Groups in Organic Synthesis", 2^{nd} ed. New York; John Wiley & Sons, Inc., 1991. Examples of alcohol protecting groups include benzyl, trityl, silyl ethers, and the like.

[0370] The ability of test compounds to act as ROS1 inhibitors may be demonstrated by the assay described in Example A. IC_{50} values are shown in Table 17.

[0371] In some embodiments, inhibition of L2026M is similar to, or better than, that observed for wild-type ROS1. For example, inhibition of L2026M is within about 2-fold (e.g., about 5-fold, about 7-fold, about 10-fold) of inhibition of wild-type ROS1 (i.e. the compounds are similarly potent against wild-type ROS1 and L2026M). In some embodiments, inhibition of L2026M is about the same as inhibition of wild-type ROS1. In some embodiments, inhibition of L2026M is about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, or greater than inhibition of wild-type ROS1. In some embodiments, selectivity for a wildtype or L2026M ROS1 kinase over another kinase is measured in an enzyme assay (e.g., an enzyme assay as provided herein). In some embodiments, the compounds provided herein exhibit selective cytotoxicity to ROS1-mutant cells.

[0372] In some embodiments, inhibition of D2033N is similar to, or better than, that observed for wild-type ROS1. In some embodiments, inhibition of D2033N is within about 2-fold (e.g., about 5-fold, about 7-fold, about 10-fold) of inhibition of wild-type ROS1 (i.e. the compounds are similarly potent against wild-type ROS1 and D2033N). In some embodiments, inhibition of D2033N is about the same as inhibition of wild-type ROS1. In some embodiments, inhibition of D2033N is about 2-fold, 3-fold, 4-fold, 5-fold, 6-fold, 7-fold, 8-fold, 9-fold, 10-fold, or greater than inhibition of wild-type ROS1. In some embodiments, selectivity for a wildtype or D2033N ROS1 kinase over another kinase is measured in an enzyme assay (e.g., an enzyme assay as provided herein). In some embodiments, the compounds provided herein exhibit selective cytotoxicity to ROS1-mutant cells.

[0373] Compounds of Formula I are useful for treating diseases and disorders which can be treated with a ROS1 kinase inhibitor, such as ROS1-associated diseases and disorders, e.g., proliferative disorders such as cancers, including hematological cancers and solid tumors.

[0374] As used herein, terms "treat" or "treatment" refer to therapeutic or palliative measures. Beneficial or desired clinical results include, but are not limited to, alleviation, in whole or in part, of symptoms associated with a disease or disorder or condition, diminishment of the extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state (e.g., one or more symptoms of the disease), and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

[0375] As used herein, the terms "subject," "individual," or "patient," are used interchangeably, refers to any animal, including mammals such as mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, primates, and humans. In some embodiments, the patient is a human. In some embodiments, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. In some embodiments, the subject has been identified or diagnosed as having a cancer with a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same (a ROS1-associated cancer) (e.g., as determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the assay is a liquid biopsy. In some embodiments, the subject has a tumor that is positive for a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same (e.g., as determined using a regulatory agency-approved assay or kit). The subject can be a subject with a tumor(s) that is positive for a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same (e.g., identified as positive using a regulatory agency-approved, e.g., FDA-approved, assay or kit). In some embodiments, the assay is a liquid biopsy. The subject can be a subject whose tumors have a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or a level of the same (e.g., where the tumor is identified as such using a

regulatory agency-approved, e.g., FDA-approved, kit or assay). In some embodiments, the subject is suspected of having a ROS1-associated cancer. In some embodiments, the subject has a clinical record indicating that the subject has a tumor that has a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same (and optionally the clinical record indicates that the subject should be treated with any of the compositions provided herein). In some embodiments, the patient is a pediatric patient.

[0376] The term "pediatric patient" as used herein refers to a patient under the age of 21 years at the time of diagnosis or treatment. The term "pediatric" can be further be divided into various subpopulations including: neonates (from birth through the first month of life); infants (1 month up to two years of age); children (two years of age up to 12 years of age); and adolescents (12 years of age through 21 years of age (up to, but not including, the twenty-second birthday)). Berhman R E, Kliegman R, Arvin A M, Nelson W E. Nelson *Textbook of Pediatrics,* 15th Ed. Philadelphia: W.B. Saunders Company, 1996; Rudolph A M, et al. *Rudolph's Pediatrics,* 21st Ed. New York: McGraw-Hill, 2002; and Avery M D, First L R. *Pediatric Medicine,* 2nd Ed. Baltimore: Williams & Wilkins; 1994. In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than two years of age, from two years of age to less than 12 years of age, or 12 years of age through 21 years of age (up to, but not including, the twenty-second birthday). In some embodiments, a pediatric patient is from birth through the first 28 days of life, from 29 days of age to less than 1 year of age, from one month of age to less than four months of age, from three months of age to less than seven months of age, from six months of age to less than 1 year of age, from 1 year of age to less than 2 years of age, from 2 years of age to less than 3 years of age, from 2 years of age to less than seven years of age, from 3 years of age to less than 5 years of age, from 5 years of age to less than 10 years of age, from 6 years of age to less than 13 years of age, from 10 years of age to less than 15 years of age, or from 15 years of age to less than 22 years of age.

[0377] In certain embodiments, compounds of Formula I are useful for preventing diseases and disorders as defined herein (for example, cancer). The term "preventing" as used herein means the prevention of the onset, recurrence or spread, in whole or in part, of the disease or condition as described herein, or a symptom thereof.

[0378] The term "ROS1-associated disease or disorder" as used herein refers to diseases or disorders associated with or having a dysregulation of a ROS1 gene, a ROS1 kinase (also called herein ROS1 kinase protein), or the expression or activity or level of any (e.g., one or more) of the same (e.g., any of the types of dysregulation of a ROS1 gene, a ROS1 kinase, a ROS1 kinase domain, or the expression or activity or level of any of the same described herein). A non-limiting example of a ROS1-associated disease or disorder includes cancer.

[0379] The term "ROS1-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a ROS1 gene, a ROS1 kinase (also called herein ROS1 kinase protein), or expression or activity, or level of any of the same. Non-limiting examples of a ROS1-associated cancer are described herein.

[0380] The phrase "dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a ROS1 gene translocation that results in the expression of a fusion protein, a deletion in a ROS1 gene that results in the expression of a ROS1 protein that includes a deletion of at least one amino acid as compared to the wild-type ROS1 protein, a mutation in a ROS1 gene that results in the expression of a ROS1 protein with one or more point mutations, or an alternative spliced version of a ROS1 mRNA that results in a ROS1 protein having a deletion of at least one amino acid in the ROS1 protein as compared to the wild-type ROS1 protein) or a ROS1 gene amplification that results in overexpression of a ROS1 protein or an autocrine activity resulting from the overexpression of a ROS1 gene in a cell that results in a pathogenic increase in the activity of a kinase domain of a ROS1 protein (e.g., a constitutively active kinase domain of a ROS1 protein) in a cell. As another example, a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same, can be a mutation in a ROS1 gene that encodes a ROS1 protein that is constitutively active or has increased activity as compared to a protein encoded by a ROS1 gene that does not include the mutation. For example, a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of ROS1 that includes a functional kinase domain, and a second portion of a partner protein that is not ROS1. In some examples, dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity or level of any of the same can be a result of a gene translocation of one ROS1 gene with another non-ROS1 gene. Non-limiting examples of fusion proteins are described in Table 2. Non-limiting examples of ROS1 kinase protein point mutations are described in Table 3 and Table 3a. Additional examples of ROS1 kinase protein mutations (e.g., point mutations) are ROS1 inhibitor resistance mutations. Non-limiting examples of ROS1 inhibitor resistance mutations are described in Table 4.

[0381] The term "wildtype" or "wild-type" when referring to a ROS1 nucleic acid or protein describes a nucleic acid (e.g., a ROS1 gene or a ROS1 mRNA) or protein (e.g., a ROS1 protein) that is found in a subject that does not have a ROS1-associated disease, e.g., a ROS1-associated cancer (and optionally also does not have an increased risk of developing a ROS1-associated disease and/or is not suspected of having a ROS1-associated disease), or is found in a cell or tissue from a subject that does not have a ROS1-associated disease, e.g., a ROS1-associated cancer (and optionally also does not have an increased risk of developing a ROS1-associated disease and/or is not suspected of having a ROS1-associated disease).

[0382] The term "regulatory agency" refers to a country's agency for the approval of the medical use of pharmaceutical agents with the country. For example, a non-limiting example of a regulatory agency is the U.S. Food and Drug Administration (FDA).

[0383] Provided herein is a method of treating cancer (e.g., a ROS1-associated cancer) in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. For example, provided herein are methods for treating a ROS1-associated cancer in a patient in need of such treatment, the

method comprising a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Non-limiting examples of ROS1 gene fusion proteins are described in Table 2. In some embodiments, the fusion protein is one of SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROS1. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same includes one or more ROS1 kinase protein point mutations, insertions, and/or deletions. Non-limiting examples of ROS1 kinase protein point mutations are described in Table 3 and Table 3a. In some embodiments, the ROS1 kinase protein point mutations, insertions, and/or deletions are point mutations selected from the group consisting of A15G, R118N, G1025R, T1735M, R1948H, and R2072N. In some embodiments, a compound of Formula I is selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof.

[0384] In some embodiments of any of the methods or uses described herein, the cancer (e.g., ROS1-associated cancer) is a hematological cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., ROS1-associated cancer) is a solid tumor. In some embodiments of any of the methods or uses described herein, the cancer (e.g., ROS1-associated cancer) is lung cancer (e.g., small cell lung carcinoma or non-small cell lung carcinoma), papillary thyroid cancer, medullary thyroid cancer, differentiated thyroid cancer, recurrent thyroid cancer, refractory differentiated thyroid cancer, lung adenocarcinoma, bronchioles lung cell carcinoma, multiple endocrine neoplasia type 2A or 2B (MEN2A or MEN2B, respectively), pheochromocytoma, parathyroid hyperplasia, breast cancer, colorectal cancer (e.g., metastatic colorectal cancer), papillary renal cell carcinoma, ganglioneuromatosis of the gastroenteric mucosa, inflammatory myofibroblastic tumor, or cervical cancer. In some embodiments of any of the methods or uses described herein, the cancer (e.g., ROS1-associated cancer) is selected from the group of: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), cancer in adolescents, adrenocortical carcinoma, anal cancer, appendix cancer, astrocytoma, atypical teratoid/rhabdoid tumor, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumor, Burkitt lymphoma, carcinoid tumor, unknown primary carcinoma, cardiac tumors, cervical cancer, childhood cancers, chordoma, chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative neoplasms, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, bile duct cancer, ductal carcinoma in situ, embryonal tumors, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, fallopian tube cancer, fibrous histiocytoma of bone, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ cell tumor, gestational trophoblastic disease, glioma, hairy cell tumor, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular cancer, histiocytosis, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, Kaposi sarcoma, kidney cancer, Langerhans cell histiocytosis, laryngeal cancer, leukemia, lip and oral cavity cancer, liver cancer, lung cancer, lymphoma, macroglobulinemia, malignant fibrous histiocytoma of bone, osteocarcinoma, melanoma, Merkel cell carcinoma, mesothelioma, metastatic squamous neck cancer, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, myelogenous leukemia, myeloid leukemia, multiple myeloma, myeloproliferative neoplasms, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer, oral cancer, oral cavity cancer, lip cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromosytoma, pituitary cancer, plasma cell neoplasm, pleuropulmonary blastoma, pregnancy and breast cancer, primary central nervous system lymphoma, primary peritoneal cancer, prostate cancer, rectal cancer, renal cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcoma, Sezary syndrome, skin cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, squamous neck cancer, stomach cancer, T-cell lymphoma, testicular cancer, throat cancer, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, unknown primary carcinoma, urethral cancer, uterine cancer, uterine sarcoma, vaginal cancer, vulvar cancer, and Wilms' tumor.

[0385] In some embodiments, a hematological cancer (e.g., hematological cancers that are ROS1-associated cancers) is selected from the group consisting of leukemias, lymphomas (non-Hodgkin's lymphoma), Hodgkin's disease (also called Hodgkin's lymphoma), and myeloma, for instance, acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), acute promyelocytic leukemia (APL), chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia (CNL), acute undifferentiated leukemia (AUL), anaplastic large-cell lymphoma (ALCL), prolymphocytic leukemia (PML), juvenile myelomonocyctic leukemia (JMML), adult T-cell ALL, AML with trilineage myelodysplasia (AML/TMDS), mixed lineage leukemia (MLL), myelodysplastic syndromes (MDSs), myeloproliferative disorders (MPD), and multiple myeloma (MM). Additional examples of hematological cancers include myeloproliferative disorders (MPD) such as polycythemia vera (PV), essential thrombocytopenia (ET) and idiopathic primary myelofibrosis (IMF/IPF/PMF). In some embodiments, the hematological cancer (e.g., the hematological cancer that is a RET-associated cancer) is AML or CMML.

[0386] In some embodiments, the cancer (e.g., the ROS1-associated cancer) is a solid tumor. Examples of solid tumors (e.g., solid tumors that are ROS1-associated cancers) include, for example, thyroid cancer (e.g., papillary thyroid carcinoma, medullary thyroid carcinoma), lung cancer (e.g., lung adenocarcinoma, small-cell lung carcinoma), pancreatic cancer, pancreatic ductal carcinoma, breast cancer, colon cancer, colorectal cancer, prostate cancer, renal cell carcinoma, head and neck tumors, neuroblastoma, and melanoma. See, for example, Nature Reviews Cancer, 2014, 14, 173-186.

[0387] In some embodiments, the cancer is selected from the group consisting of lung cancer (including, e.g., non-small-cell lung cancer), colorectal cancer, gastric cancer, adenocarcinoma (including, e.g., small bowel adenocarcinoma), cholangiocarcinoma, glioblastoma, ovarian cancer, angiocarcinoma, congenital gliobastoma multiforme, papillary thyroid carcinoma, inflammatory myofibroblastic tumour, a spitzoid neoplasm, anaplastic large cell lymphoma, diffuse large B cell lymphoma, and B-cell acute lymphoblastic leukemia.

[0388] In some embodiments, the patient is a human.

[0389] Compounds of Formula I and pharmaceutically acceptable salts and solvates thereof are also useful for treating a ROS1-associated cancer.

[0390] Accordingly, also provided herein is a method for treating a patient diagnosed with or identified as having a ROS1-associated cancer, e.g., any of the exemplary ROS1-associated cancers disclosed herein, comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein.

[0391] Dysregulation of a ROS1 kinase, a ROS1 gene, or the expression or activity or level of any (e.g., one or more) of the same can contribute to tumorigenesis. For example, a dysregulation of a ROS1 kinase, a ROS1 gene, or expression or activity or level of any of the same can be a translocation, overexpression, activation, amplification, or mutation of a ROS1 kinase, a ROS1 gene, or a ROS1 kinase domain. A translocation can include a translocation involving the ROS1 kinase domain, a mutation can include a mutation involving the ROS1 ligand-binding site, and an amplification can be of a ROS1 gene.

[0392] In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes overexpression of wild-type ROS1 kinase (e.g., leading to autocrine activation). In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase protein, or expression or activity or level of any of the same, includes overexpression, activation, amplification, or mutation in a chromosomal segment comprising the ROS1 gene or a portion thereof, including, for example, the kinase domain portion, or a portion capable of exhibiting kinase activity.

[0393] In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in a ROS1 gene fusion. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-ROS1 partner protein, and includes a minimum of a functional ROS1 kinase domain.

[0394] Non-limiting examples of ROS1 fusion proteins are shown in Table 2.

TABLE 2

Exemplary ROS1 Fusion Proteins

CD74	Non-small-cell lung cancer[1]
SLC34A2 including SLC34A2-ROS(S)[28], SLC34A2-ROS(L)[28], and SLC34A2-ROS(VS)[28],	Non-small-cell lung cancer[1], Colorectal cancer[14], Gastric cancer[15], Lung adenocarcinoma[24]
SLC34A2-ROS (with a breakpoint at chr6: 117653720, chr4: 25678781)[24]	
TPM3	Non-small-cell lung cancer[1]
SDC4	Non-small-cell lung cancer[1], Adenocarcinoma[10]
EZR	Non-small-cell lung cancer[1]
LRIG3	Non-small-cell lung cancer[1]
KDELR2	Non-small-cell lung cancer[1]
CCDC6	Non-small-cell lung cancer[1]
FIG (GOPC, PIST) including FIG-ROS1(L)[29], FIG-ROS1(S)[29], and FIG-ROS1(VL)[29], FIG-ROS1 (XL)[30]	Non-small-cell lung cancer[2], Cholangiocarcinoma[5], Glioblastoma[8], Ovarian cancer[16], Small bowel adenocarcinomas (SBAs)[22], Acral lentiginous melanoma (ALM)[25]
TPD52L1	Non-small-cell lung cancer[3]
CEP85L	Angiosarcoma[4] Pediatric gliomas[31]
ZCCHC8	Congenital gliobastoma multiforme[6]
CCDC30	Papillary thyroid carcinoma[7]
TFG	Inflammatory myofibroblastic tumour[9], Sarcomas[26]
TMEM106B	Adenocarcinoma[11]
YWHAE	Inflammatory myofibroblastic tumor[12]
MSN	Lung cancer[13]
PWWP2A	Spitzoid neoplasm[17]
FYN	Non-small-cell lung cancer[18]
MKX	Non-small-cell lung cancer[18]
PPFIBP1	Spitzoid neoplasm[19]
ERC1	Spitzoid neoplasm[19]
MY05A	Spitzoid neoplasm[19]
CLIP1	Spitzoid neoplasm[19]
HLA-A	Spitzoid neoplasm[19]
KIAA1598 (SHTN1)	Spitzoid neoplasm[19]
ZCCHC8	Spitzoid neoplasm[19]
CLTC	Non-small-cell lung cancer[20]
LIMA1	Non-small-cell lung cancer[20]
NFkB2	Anaplastic Large Cell Lymphoma[21]
NCOR2	Anaplastic Large Cell Lymphoma[21]
KLC1	Pediatric low-grade glioma[24]
TBL1XR1	Juvenile myelomonocytic leukemia (JMML)[27]

TABLE 2-continued

Exemplary ROS1 Fusion Proteins

[1]Davies and Dobele, *Clin. Cancer Res*, 19(15):4040-5, 2013.

[2]Rimkunas et al., *Clin. Cancer Res.*, 18:4449-58, 2012.

[3]Zhu et al., *Lung Cancer*, 97:48-50, doi: 10.1016/j.lungcan.2016.04.013, 2012.

[4]Giacomini et al., *PLoS Gene.t*, 9(4):e1003464, 2013.

[5]Saborowski et al., *Proc.Natl. Acad. Sci.* U.S.A., 110(48):19513-19518, 2013.

[6]Cocce et al., *Genes Chromosomes Cancer*, 55(9):677-87, 2016.

[7]Ritterhouse et al., *Thyroid*, 26(6):794-7, 2016.

[8]Das et al., *Cancer Growth Metastasis*, 8:51-60, doi: 10.4137/CGM.S32801, 2015.

[9]Yamamoto et al., *Histopathology*, 69(1):72-83, 2016.

[10]Fu et al., *PLoS One*, 10(4):e0124354, 2015.

[11]Ou et al., *Lung Cancer*, 88(3):352-4, 2015.

[12]Hornick et al., *Mod. Pathol.*, 28(5):732-9, 2015.

[13]Zheng et al.,*Nat Med.*, (12):1479-84, 2014.

[14]Aisner et al., *Mol. Cancer Res.*, 12(1):111-8, 2014.

[15]Lee et al., *Cancer*, 119(9):1627-1635, 2013.

[16]Birch et al., *PLoS One*, 6(12):e28250, 2011.

[17]Weisner et al., *Nature Comm.*, 5:3116, doi:10.1038/ncomms4116, 2014.

[18]U.S. Patent Application Publication No. 2016/0032396A1.

[19]PCT Patent Application Publication No. WO 2014/130975A1.

[20]Australian Patent Application Publication No. AU 2015/101722A4

[21]Crescenzo et al., *Cancer Cell.*, 27(4):516-32, 2015.

[22]Schrock et al., *Annals of Oncology*. Vol. 27, Supp_6, 613O, 2016.

[24]Nakano et al. *Pediatr Blood Cancer*. Vol. 64, S54-S55 Suppe. 4. O13-1-7, 2017.

[25]Couts et al. *Pigment Cell Melanoma Res.* Vol. 30, No. 5, pp. e61, 2017.

[26]Ikeda et al. *Annals of Oncology*. Vol. 28 (suppl_10): x1-x6. 10.1093/annonc/mdx652, 2017.

[27]Murakami et al. *Blood*, blood-2017-07-798157; DOI: 10.1182/blood-2017-07-798157, 2018.

[28]EP Patent Application Publication No. EP3266795A1

[29]U.S. Patent Publication No. US9782400B2

[30]PCT Patent Application Publication No. WO 2010/093928

[31]Johnson et al., *Oncologist*. 22(12):1478-1490, doi:10.1634/theoncologist.2017-0242, 2017.

[0395] In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes one or more deletions, insertions, or point mutation(s) in a ROS1 kinase. In some

embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes a deletion of one or more residues from the ROS1 kinase, resulting in constitutive activity of the ROS1 kinase domain.

[0396] In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a ROS1 gene that results in the production of a ROS1 kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type ROS1 kinase (see, for example, the point mutations listed in Table 3).

TABLE 3

Exemplary ROS1 Point Mutations

ROS1 Mutation	ROS1-Associated Cancer
Amino acid position 15 (e.g., A15G)	Diffuse large B cell lymphoma[1]
Amino acid position 118 (e.g., R118N)	B-cell acute lymphoblastic leukemia[2]
Amino acid position 122 (e.g., A122T)	Gastrointestinal stromal tumors (GISTs)[3]
Amino acid position 245 (e.g., R245I)	Uterine Corpus Endometrioid Carcinoma[4]
Amino acid position 1025 (e.g., G1025R)	B-cell acute lymphoblastic leukemia[2]
Amino acid position 1186 (e.g., S1186F)	Non-Small-Cell Lung Cancer[5]
Amino acid position 1539 (e.g., P1539S)	Skin Cutaneous Melanoma[7]
Amino acid position 1735 (e.g., T1735M)	B-cell acute lymphoblastic leukemia[2]
Amino acid position 1948 (e.g., R1948H)	Diffuse large B cell lymphoma[1]
Amino acid position 2033 (e.g., D2033Y)	Colorectal adenocarcinoma[6]
Amino acid position 2072 (e.g., R2072N)	B-cell acute lymphoblastic leukemia[2]
Amino acid position 2126 (e.g., R2126W, R2126Q, R2126L)	Breast, melanoma[6]
Amino acid position 2308 (e.g., E2308, E2308Q)	Kidney renal clear cell carcinoma, Skin cutaneous melanoma, Head and neck squamous cell carcinoma[7]

[1]U.S. Patent Application Publication No. 2016/0032404A1.

[2]de Smith et al., *Oncotarget*., doi: 10.18632/oncotarget. 12238, 2016.

[3]Qiu et al., *J. Clin. Oncol.* 35:15_suppl, e22507-e22507, 2017.

[4]PCT Patent Application Publication No. WO 2016/187508A2

[5]Gainor et al., *JCO Precis Oncol.* 10.1200/PO.17.00063, 2017.

[6]The Cancer Genome Atlas: http://cancergenome.nih.gov/

[7]Wang, University of Hong Kong, Pokfulam, Hong Kong SAR (Thesis). Retrieved from http://dx.doi.org/10.5353/th_b5659723.

[0397] Additional exemplary ROS1 mutations are provided in Table 3a.

TABLE 3a

Exemplary ROS1 Mutations

Amino acid position 1186 (e.g., S1186F[11])
Amino acid position 1935 (e.g., E1935G[10])
Amino acid position 1945 (e.g., L1945Q[7])
Amino acid position 1946 (e.g., T1946S[7])
Amino acid position 1947 (e.g., L1947R[6, 10], L1947M[7])
Amino acid position 1948 (e.g., R1948S[7])
Amino acid position 1951 (e.g., L1951R[5], L1951V[7])
Amino acid position 1958 (e.g., E1958V[7])
Amino acid position 1959 (e.g., V1959E[7])
Amino acid position 1961 (e.g., E1961K[7])

TABLE 3a-continued

Exemplary ROS1 Mutations

Amino acid position 1962 (e.g., G1962E[7])
Amino acid position 1971 (e.g., G1971E[6, 10])
Amino acid position 1974 (e.g., E1974K[9])
Amino acid position 1981 (e.g., T1981M[7])
Amino acid position 1982 (e.g., L1982F[5, 10], L1982R[6])
Amino acid position 1986 (e.g., S1986Y[1], S1986F[1])
Amino acid position 1990 (e.g., E1990G[5], E1990L[7])
Amino acid position 1993 (e.g., E1993K[7])
Amino acid position 1994 (e.g., F1994L[5])
Amino acid position 2000 (e.g., L2000V[7])
Amino acid position 2002 (e.g., S2002N[7])
Amino acid position 2004 (e.g., F2004L[7], F2004I[9], F2004V[9], F2004C[9])
Amino acid position 2008 (e.g., N2008H[7])
Amino acid position 2009 (e.g., I2009L[7])
Amino acid position 2010 (e.g., L2010M[7])
Amino acid position 2011 (e.g., K2011N[7])
Amino acid position 2016 (e.g., C2016G[7])
Amino acid position 2019 (e.g., N2019D[7], N2019Y[7])
Amino acid position 2020 (e.g., E2020k[9])
Amino acid position 2022 (e.g., Q2022H[7])
Amino acid position 2026 (e.g., L2026M[3])
Amino acid position 2028 (e.g., L2028M[7])
Amino acid position 2029 (e.g., M2029K[7])
Amino acid position 2030 (e.g., E2030K[7])
Amino acid position 2032 (e.g., G2032R[2])
Amino acid position 2033 (e.g., D2033G[7], D2033N[8])
Amino acid position 2035 (e.g., L2035I[7])
Amino acid position 2036 (e.g., T2036I[7], T2036N[7])
Amino acid position 2039 (e.g., R2039G[7], R2039H[7], R2039M[7], R2039N[7], R2039S[7])
Amino acid position 2040 (e.g., K2040E[7], K2040Q[7])
Amino acid position 2052 (e.g., T2052S[7])
Amino acid position 2059 (e.g., L2059P[7])
Amino acid position 2060 (e.g., C2060G[6, 10])
Amino acid position 2075 (e.g., F2075C[9], F2075I[9], F2075V[9])
Amino acid position 2077 (e.g., H2077P[7])
Amino acid position 2078 (e.g., R2078W[7])
Amino acid position 2087 (e.g., V2087I[7])
Amino acid position 2091 (e.g., D2091N[7])
Amino acid position 2092 (e.g., Y2092N[7])
Amino acid position 2094 (e.g., S2094N[7])
Amino acid position 2098 (e.g., V2098I[6, 10])
Amino acid position 2099 (e.g., K2099N[7])
Amino acid position 2100 (e.g., I2100V[7])
Amino acid position 2101 (e.g., G2101A[7])
Amino acid position 2106 (e.g., A2106P[7])
Amino acid position 2107 (e.g., R2107T[7])
Amino acid position 2112 (e.g., N2112K[9])
Amino acid position 2113 (e.g., D2113N[9] D2113G[9])
Amino acid position 2116 (e.g., R2116T[7], R2116K[9])
Amino acid position 2125 (e.g., V2125G[7], V2125L[7])
Amino acid position 2127 (e.g., W2127G[7], W2127[9])
Amino acid position 2128 (e.g., M2128T[9])
Amino acid position 2131 (e.g., E2131D[7], E2131K[7])
Amino acid position 2134 (e.g., M2134I[7])
Amino acid position 2139 (e.g., T2139I[7], T2139S[7])
Amino acid position 2141 (e.g., Q2141H[7])
Amino acid position 2142 (e.g., S2142Y[7])
Amino acid position 2148 (e.g., G2148E[7])
Amino acid position 2151 (e.g., I2151N[7])
Amino acid position 2154 (e.g., I2154M[7])
Amino acid position 2155 (e.g., L2155S[4])
Amino acid position 2160 (e.g., Q2160H[7])
Amino acid position 2165 (e.g., H2165D[7])
Amino acid position 2181 (e.g., E2181D[7])
Amino acid position 2184 (e.g., R2184T[7])
Amino acid position 2201 (e.g., E2201D[7])
Amino acid position 2205 (e.g., R2205I[7])
Amino acid position 2207 (e.g., T2207I[7])
Amino acid position 2209 (e.g., H2209P[7])
Amino acid position 2212 (e.g., Q2212H[7], Q2212P[7])

TABLE 3a-continued

Exemplary ROS1 Mutations
Amino acid position 2223 (e.g., L2223[9])
Amino acid position 2224 (e.g., N2224K[9])

[1]Facchinetti et al., *Clin.Cancer Res.*, DOI: 10.1158/1078-0432.CCR-16-0917, 2016.
[2]Awad et al.,*N. Engl. J. Med.*, 368(25):2395-401, 2013.
[3]Zou et al., *Proc. Natl.Acad.Sci.* U.S.A., 112(11):3493-8, 2015.
[4]Song et al., *Clin. Cancer Res.*, 21(10):2379-87, 2015.
[5]Katayama et al., *Clin. Cancer Res.*, 21(1):166-74, 2015.
[6]PCT Patent Application Publication No. WO 2014/134096A1.
[7]PCT Patent Application Publication No. WO 2014/152777A2.
[8]Drilon et al., *Clin. Cancer Res.*, 22(10):2351-8, 2016.
[9]Davare et al., *Proc. Natl. Acad. Sci.* U.S.A., 112(39):E5381-90, 2015.
[10]Davare et al., *Proc. Natl. Acad. Sci.* U.S.A., 110(48):19519-24, 2013.
[11]Gainor et al., *JCO Precis Oncol.* 10.1200/PO.17.00063, 2017.

[0398] In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes a splice variation in a ROS1 mRNA which results in an expressed protein that is an alternatively spliced variant of ROS1 having at least one residue deleted (as compared to the wild-type ROS1 kinase) resulting in a constitutive activity of a ROS1 kinase domain. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes a splice variation in a ROS1 mRNA which results in an expressed protein that is an alternatively spliced variant of ROS1 having at least one residue added (as compared to the wild-type ROS1 kinase) resulting in a constitutive activity of a ROS1 kinase domain.

[0399] A "ROS1 kinase inhibitor" as defined herein includes any compound exhibiting ROS1 inhibition activity. In some embodiments, a ROS1 kinase inhibitor is selective for a wild type and/or mutant ROS1 kinase. In some embodiments, ROS1 kinase inhibitors can exhibit inhibition activity (IC_{50}) against a ROS1 kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a ROS1 kinase inhibitors can exhibit inhibition activity (IC_{50}) against a ROS1 kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein. In some embodiments, the ROS1 kinase inhibitor is a compound of Formula I.

[0400] As used herein, a "first ROS1 kinase inhibitor" or "first ROS1 inhibitor" is a ROS1 kinase inhibitor as defined herein, but which does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. As used herein, a "second ROS1 kinase inhibitor" or a "second ROS1 inhibitor" is a ROS1 kinase inhibitor as defined herein. In some embodiments, a second ROS1 inhibitor does not include a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as defined herein. When more than one ROS1 inhibitor is present in a method provided herein (e.g., both a first and a second ROS1 inhibitor are present in a method provided herein), the two ROS1 inhibitors are different (e.g., the first and second ROS1 kinase inhibitor are different). As provided herein, different ROS1 inhibitors are structurally distinct from one another.

[0401] In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a ROS1 gene that results in the production of a ROS1 kinase that has one or more amino acid substitutions or insertions or deletions as compared to the wild-type ROS1 kinase. In some cases, the resulting ROS1 kinase is more resistant to inhibition of its phosphotransferase activity by one or more first ROS1 kinase inhibitor(s), as compared to a wildtype ROS1 kinase or a ROS1 kinase not including the same mutation. Such mutations, optionally, do not decrease the sensitivity of the cancer cell or tumor having the ROS1 kinase to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof (e.g., as compared to a cancer cell or a tumor that does not include the particular ROS1 inhibitor resistance mutation). In such embodiments, a ROS1 inhibitor resistance mutation can result in a ROS1 kinase that has one or more of an increased V_{max}, a decreased K_m for ATP, and an increased K_D for a first ROS1 kinase inhibitor, when in the presence of a first ROS1 kinase inhibitor, as compared to a wildtype ROS1 kinase or a ROS1 kinase not having the same mutation in the presence of the same first ROS1 kinase inhibitor.

[0402] In other embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, includes at least one point mutation in a ROS1 gene that results in the production of a ROS1 kinase that has one or more amino acid substitutions as compared to the wild-type ROS1 kinase, and which has increased resistance to a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as compared to a wildtype ROS1 kinase or a ROS1 kinase not including the same mutation. In such embodiments, a ROS1 inhibitor resistance mutation can result in a ROS1 kinase that has one or more of an increased V_{max}, a decreased K_m, and a decreased K_D in the presence of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as compared to a wildtype ROS1 kinase or a ROS1 kinase not having the same mutation in the presence of the same compound of Formula I or a pharmaceutically acceptable salt or solvate thereof.

[0403] Examples of ROS1 inhibitor resistance mutations can, e.g., include point mutations, insertions, or deletions in and near the ATP binding site in the tertiary structure of ROS1 kinase, including but not limited to the gatekeeper residue, P-loop residues, residues in or near the DFG motif, and ATP cleft solvent front amino acid residues. Additional examples of these types of mutations include changes in residues that may affect enzyme activity and/or drug binding including but are not limited to residues in the activation loop, residues near or interacting with the activation loop, residues contributing to active or inactive enzyme conformations, changes including mutations, deletions, and insertions in the loop proceeding the C-helix and in the C-helix. Specific residues or residue regions that may be changed (e.g., ROS1 inhibitor resistance mutations) include but are not limited to those listed in Table 4 based on the human wildtype ROS1 protein sequence (e.g., SEQ ID NO: 1). Changes to these residues may include single or multiple amino acid changes, insertions within or flanking the sequences, and deletions within or flanking the sequences.

[0404] In some embodiments, compounds of Formula I and pharmaceutically acceptable salts and solvates are useful in treating patients that develop cancers with ROS1 inhibitor resistance mutations (e.g., that result in an increased resistance to a first ROS1 inhibitor, e.g., a substitution at amino acid position 2032 (e.g., G2032R), amino

acid position 2026 (e.g., L2026M), amino acid position 2033 (e.g., D2033N), and/or one or more ROS1 inhibitor resistance mutations listed in Table 4) by either dosing in combination or as a follow-up therapy to existing drug treatments (e.g., ALK kinase inhibitors, TRK kinase inhibitors, other ROS1 kinase inhibitors, e.g., first and/or second ROS1 kinase inhibitors). Exemplary ALK kinase inhibitors are described herein. Exemplary TRK kinase inhibitors are described herein. Exemplary first and second ROS1 kinase inhibitors are described herein. In some embodiments, a first or second ROS1 kinase inhibitor can be selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib.

[0405] In some embodiments, compounds of Formula I or pharmaceutically acceptable salts and solvates thereof are useful for treating a cancer that has been identified as having one or more ROS1 inhibitor resistance mutations (that result in an increased resistance to a first or second ROS1 inhibitor, e.g., a substitution at amino acid position 2032 (e.g., G2032R), amino acid position 2026 (e.g., L2026M), amino acid position 2033 (e.g., D2033N)). Non-limiting examples of ROS1 inhibitor resistance mutations are listed in Table 4.

TABLE 4

Exemplary ROS1 Resistance Mutations
Amino acid position 1186 (e.g., S1186F[11])
Amino acid position 1935 (e.g., E1935G6[10])
Amino acid position 1945 (e.g., L1945Q[7])
Amino acid position 1946 (e.g., T1946S[7])
Amino acid position 1947 (e.g., L1947R[6, 10], L1947M[7])
Amino acid position 1948 (e.g., R1948S[7])
Amino acid position 1951 (e.g., L1951R[5], L1951V[7])
Amino acid position 1958 (e.g., E1958V[7])
Amino acid position 1959 (e.g., V1959E[7])
Amino acid position 1961 (e.g., E1961K[7])
Amino acid position 1962 (e.g., G1962E[7])
Amino acid position 1971 (e.g., G1971E[6, 10])
Amino acid position 1974 (e.g., E1974K[9])
Amino acid position 1981 (e.g., T1981M[7])
Amino acid position 1982 (e.g., L1982F[5, 10], L1982R[6])
Amino acid position 1986 (e.g., S1986Y[1], S1986F[1])
Amino acid position 1990 (e.g., E1990G[5], E1990L[7])
Amino acid position 1993 (e.g., E1993K[7])
Amino acid position 1994 (e.g., F1994L[5])
Amino acid position 2000 (e.g., L2000V[7])
Amino acid position 2002 (e.g., S2002N[7])
Amino acid position 2004 (e.g., F2004L[7], F2004I[9], F2004V[9], F2004C[9])
Amino acid position 2008 (e.g., N2008H[7])
Amino acid position 2009 (e.g., I2009L[7])
Amino acid position 2010 (e.g., L2010M[7])
Amino acid position 2011 (e.g., K2011N[7])
Amino acid position 2016 (e.g., C2016G[7])
Amino acid position 2019 (e.g., N2019D[7], N2019Y[7])
Amino acid position 2020 (e.g., E2020k[9])
Amino acid position 2022 (e.g., Q2022H[7])
Amino acid position 2026 (e.g., L2026M[3])
Amino acid position 2028 (e.g., L2028M[7])
Amino acid position 2029 (e.g., M2029K[7])
Amino acid position 2030 (e.g., E2030K[7])
Amino acid position 2032 (e.g., G2032R[2])
Amino acid position 2033 (e.g., D2033G[7], D2033N[8])
Amino acid position 2035 (e.g., L2035I[7])
Amino acid position 2036 (e.g., T2036I[7], T2036N[7])
Amino acid position 2039 (e.g., R2039G[7], R2039H[7], R2039M[7], R2039N[7], R2039S[7])
Amino acid position 2040 (e.g., K2040E[7], K2040Q[7])
Amino acid position 2052 (e.g., T2052S[7])
Amino acid position 2059 (e.g., L2059P[7])
Amino acid position 2060 (e.g., C2060G[6, 10])

TABLE 4-continued

Exemplary ROS1 Resistance Mutations
Amino acid position 2075 (e.g., F2075C[9], F2075I[9], F2075V[9])
Amino acid position 2077 (e.g., H2077P[7])
Amino acid position 2078 (e.g., R2078W[7])
Amino acid position 2087 (e.g., V2087I[7])
Amino acid position 2091 (e.g., D2091N[7])
Amino acid position 2092 (e.g., Y2092N[7])
Amino acid position 2094 (e.g., S2094N[7])
Amino acid position 2098 (e.g., V2098I[6, 10])
Amino acid position 2099 (e.g., K2099N[7])
Amino acid position 2100 (e.g., I2100V[7])
Amino acid position 2101 (e.g., G2101A[7])
Amino acid position 2106 (e.g., A2106P[7])
Amino acid position 2107 (e.g., R2107T[7])
Amino acid position 2112 (e.g., N2112K[9])
Amino acid position 2113 (e.g., D2113N[9] D2113G[9])
Amino acid position 2116 (e.g., R2116T[7], R2116K[9])
Amino acid position 2125 (e.g., V2125G[7], V2125L[7])
Amino acid position 2127 (e.g., W2127G[7], W2127[9])
Amino acid position 2128 (e.g., M2128T[9])
Amino acid position 2131 (e.g., E2131D[7], E2131K[7])
Amino acid position 2134 (e.g., M2134I[7])
Amino acid position 2139 (e.g., T2139I[7], T2139S[7])
Amino acid position 2141 (e.g., Q2141H[7])
Amino acid position 2142 (e.g., S2142Y[7])
Amino acid position 2148 (e.g., G2148E[7])
Amino acid position 2151 (e.g., I2151N[7])
Amino acid position 2154 (e.g., I2154M[7])
Amino acid position 2155 (e.g., L2155S[4])
Amino acid position 2160 (e.g., Q2160H[7])
Amino acid position 2165 (e.g., H2165D[7])
Amino acid position 2181 (e.g., E2181D[7])
Amino acid position 2184 (e.g., R2184T[7])
Amino acid position 2201 (e.g., E2201D[7])
Amino acid position 2205 (e.g., R2205I[7])
Amino acid position 2207 (e.g., T2207I[7])
Amino acid position 2209 (e.g., H2209P[7])
Amino acid position 2212 (e.g., Q2212H[7], Q2212P[7])
Amino acid position 2223 (e.g., L2223[9])
Amino acid position 2224 (e.g., N2224K[9])

[1]Facchinetti et al., *Clin. Cancer Res.*, DOI: 10.1158/1078-0432.CCR-16-0917, 2016.
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[3]Zou et al., *Proc. Natl. Acad. Sci.* U.S.A., 112(11):3493-8, 2015.
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[6]PCT Patent Application Publication No. WO 2014/134096A1.
[7]PCT Patent Application Publication No. WO 2014/152777A2.
[8]Drilon et al., *Clin. Cancer Res.*, 22(10):2351-8, 2016.
[9]Davare et al., *Proc. Natl. Acad. Sci.* U.S.A., 112(39):E5381-90, 2015.
[10]Davare et al., *Proc. Natl. Acad. Sci.* U.S.A., 110(48):19519-24, 2013.
[11]Gainor et al., *JCO Precis Oncol.* 10.1200/PO.17.00063, 2017.

[0406] The ROS1 proto-oncogene is expressed in a variety of tumor types, and belongs to the sevenless subfamily of tyrosine kinase insulin receptor genes. The protein encoded by this gene is a type I integral membrane protein with tyrosine kinase activity. ROS1 shares structural similarity with the anaplastic lymphoma kinase (ALK) protein. Gene rearrangements involving ROS1 have been identified in a variety of cancers. The small molecule tyrosine kinase inhibitor, crizotinib, has been approved for the treatment of patients with metastatic NSCLC whose tumors are ROS1-positive or ALK-positive. Although the most preclinical and clinical studies of ROS1 gene fusions have been performed in lung cancer, ROS1 fusions have been detected in multiple other tumor histologies, including ovarian carcinoma, sarcoma, cholangiocarcinomas and others.

[0407] ALK is a receptor tyrosine kinase that belongs to the insulin growth factor receptor superfamily. ALK is believed to play a role in the development of the nervous

system. A variety of ALK gene fusions have been described, such as EML4, KIF5B, KLC1, and TRK-fused gene (TFG). Such fusion products result in kinase activation and oncogenesis. Non-small-cell lung cancer (NSCLC) harboring the anaplastic lymphoma kinase gene (ALK) rearrangement is sensitive to the small molecule tyrosine kinase inhibitor crizotinib, which is an inhibitor of ALK and ROS1.

[0408] In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same. In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of an ALK gene, an ALK protein, or expression or activity, or level of any of the same (e.g., an ALK-associated cancer). In some embodiments, the additional therapeutic agent(s) includes any one of the above listed therapies or therapeutic agents which are standards of care in cancers wherein the cancer has a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same (e.g., a TRK-associated cancer).

[0409] The term "ALK-associated cancer" as used herein refers to cancers associated with or having a dysregulation of an ALK gene, an ALK protein, or expression or activity, or level of any of the same. Exemplary ALK-associated cancers are provided herein.

[0410] The phrase "dysregulation of an ALK gene, an ALK kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., an ALK gene translocation that results in the expression of a fusion protein, a deletion in an ALK gene that results in the expression of an ALK protein that includes a deletion of at least one amino acid as compared to the wild-type ALK protein, a mutation in an ALK gene that results in the expression of an ALK protein with one or more point mutations, or an alternative spliced version of an ALK mRNA that results in an ALK protein having a deletion of at least one amino acid in the ALK protein as compared to the wild-type ALK protein) or an ALK gene amplification that results in overexpression of an ALK protein or an autocrine activity resulting from the overexpression of an ALK gene in a cell that results in a pathogenic increase in the activity of a kinase domain of an ALK protein (e.g., a constitutively active kinase domain of an ALK protein) in a cell. As another example, a dysregulation of an ALK gene, an ALK protein, or expression or activity, or level of any of the same, can be a mutation in an ALK gene that encodes an ALK protein that is constitutively active or has increased activity as compared to a protein encoded by an ALK gene that does not include the mutation. For example, a dysregulation of an ALK gene, an ALK protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of ALK that includes a functional kinase domain, and a second portion of a partner protein that is not ALK. In some examples, dysregulation of an ALK gene, an ALK protein, or expression or activity or level of any of the same can be a result of a gene translocation of one ALK gene with another non-ALK gene. Non-limiting examples of fusion proteins are described in Table 5. Additional examples of ALK kinase protein mutations (e.g., point mutations) are ALK inhibitor resistance mutations.

[0411] The term "wildtype" or "wild-type" when referring to an ALK nucleic acid or protein describes a nucleic acid (e.g., an ALK gene or an ALK mRNA) or protein (e.g., an ALK protein) that is found in a subject that does not have an ALK-associated disease, e.g., an ALK-associated cancer (and optionally also does not have an increased risk of developing an ALK-associated disease and/or is not suspected of having an ALK-associated disease), or is found in a cell or tissue from a subject that does not have an ALK-associated disease, e.g., an ALK-associated cancer (and optionally also does not have an increased risk of developing an ALK-associated disease and/or is not suspected of having an ALK-associated disease).

[0412] In some embodiments, the dysregulation of an ALK gene, an ALK kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in an ALK gene fusion. In some embodiments, the dysregulation of an ALK gene, an ALK kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-ALK partner protein, and includes a minimum of a functional ALK kinase domain.

[0413] Non-limiting examples of ALK fusion proteins are shown in Table 5.

TABLE 5

Exemplary ALK Fusion Proteins

ALK Partner	ALK-Associated Cancer
NPM/NPM1	Anaplastic large cell lymphoma[1], Diffuse large B-cell lymphoma[1], Neuroblastoma[8], Lung adenocarcinoma[9]
ALO17/RNF213	Anaplastic large cell lymphoma[1]
TFG (e.g., TFGs, TFG_L, TFG_{XL})[38]	Anaplastic large cell lymphoma[1], Non-small cell lung cancer[1], Anaplastic thyroid carcinoma[1]
MSN (e.g., MSNa and MSNb)[38]	Anaplastic large cell lymphoma[1]
TPM3	Anaplastic large cell lymphoma[1], Inflammatory myofibroblastic tumour[1], Renal medulla carcinoma/renal cell carcinoma[1], Spitzoid neoplasm[5]
TPM4 (e.g., type 1 and type 2)[38]	Anaplastic large cell lymphoma[1], Inflammatory myofibroblastic tumour[1], Oesophageal squamous cell carcinoma[1]
ATIC	Anaplastic large cell lymphoma[1]. Inflammatory myofibroblastic tumour[1]
MYH9	Anaplastic large cell lymphoma[1]
CLTC	Anaplastic large cell lymphoma[1], Inflammatory myofibroblastic tumour[1], Diffuse large B-cell lymphoma[1]
TRAF1	Anaplastic large cell lymphoma[1]
EML4*	Non-small cell lung cancer[1], Renal medulla carcinoma/renal cell carcinoma[1], Breast cancer[1], Colon cancer[1], Anaplastic thyroid carcinoma[1], Squamous cell carcinoma[14], Lung adenocarcinoma[18], Colorectal Adenocarcinoma[19]
KIF5B	Non-small cell lung cancer[1]
KLC1	Non-small cell lung cancer[1]

TABLE 5-continued

Exemplary ALK Fusion Proteins

ALK Partner	ALK-Associated Cancer
PTPN3	Non-small cell lung cancer[1]
HIP1	Non-small cell lung cancer[1]
TPR	Non-small cell lung cancer[1]
STRN	Non-small cell lung cancer[1], Anaplastic thyroid carcinoma[1], Colorectal Adenocarcinoma[19], Renal Cell Carcinoma[20]
SEC31A/SEC31L1[38] (e.g., type 1 and type 2)[38]	Inflammatory myofibroblastic tumour[1], Diffuse large B-cell lymphoma[1], Lung adenocarcinoma[21]
RANBP2	Inflammatory myofibroblastic tumour[1], Pediatric acute myeloid leukemia[11]
PPFIBP1	Inflammatory myofibroblastic tumour[1]
CARS	Inflammatory myofibroblastic tumour[1]
SQSTM1	Diffuse large B-cell lymphoma[1]
VCL	Renal medulla carcinoma/renal cell carcinoma[1]
C2orf44	Colon cancer[1]
FN1	Serous ovarian carcinoma[1], Gastrointestinal leiomyoma[36]
GFPT1	Anaplastic thyroid carcinoma[1]
KIAA1618	Blood Cancer[2]
MEL4	Unspecified[3]
ROS1	Unspecified[4]
DCTN1	Spitzoid neoplasm[5], Sarcoma[26]
MDCF2	Lung adenocarcinoma[6]
STK32B	Breast cancer[6]
TPM1	Unspecified[7]
PRKAR1A	Unspecified[7]
NCOA1	Unspecified[7]
GTF2IRD1	Unspecified[7]
CLTCL1	Neuroblastoma[8]
LMNA	Neuroblastoma[8]
PRKAR1A	Neuroblastoma[8], Non-small cell lung cancer[15], Colorectal Adenocarcinoma[19]
SPTBN1	Lung adenocarcinoma[10]
EIF2AK3	Lung adenocarincoma[12], Non-small cell lung cancer[15]
EML4-EXOC6B	Lung adenocarincoma[13]
PPM1B	Non-small cell lung cancer[15]
MALAT1 (lncRNA gene fusion)	Triple-negative breast cancer[16]
HOOK1	Renal cell carcinoma[17]
CAD	Colorectal Adenocarcinoma[19]
PPP1T21	Colorectal Adenocarcinoma[19]
SENPF	Colorectal Adenocarcinoma[19]
MAPRE3	Colorectal Adenocarcinoma[19]
SPDYA	Non-small cell lung cancer[22]
ASXL2	Non-small cell lung cancer[22]
IGL@	Diffuse large B-cell lymphoma[23]
PPP1R21	Colorectal Adenocarcinoma[24]
PRKAP1B	Colorectal Adenocarcinoma[24]
BIRC6	Non-small cell lung cancer[25]
PICALM	Non-small cell lung cancer[25]
KCL	Lung adenocarcinoma[27]
CRIM1	Non-small cell lung cancer[28]
EEF1G	Anaplastic large cell lymphoma[29]
DCTN1	Advanced Sarcoma[30], Inflammatory myofibroblastic tumor[33], Spitzoid tumors[33]
GTF2IRD1	Pediatric, adolescent and young adult (PAYA) thyroid carcinoma[31]
BEND5	Neuroblastoma[32]
PPP1CB	Astrocytoma[32]
CUX	Non-small-cell Lung cancer[34]
FAM179A	Non-small-cell Lung cancer[35]
COL25A1	Non-small-cell Lung cancer[35]
BIRC6	Non-small-cell Lung Cancer[37]
PICALM	Non-small-cell Lung Cancer[37]

TABLE 5-continued

Exemplary ALK Fusion Proteins

ALK Partner	ALK-Associated Cancer
GTF3C2	Spitz tumor[39]
IGFBP5	Soft Tissue Sarcoma[40]
MYO18A	Adenosarcoma[41]

*There are a number of different ALK-EML4 fusion variants: 1, 2, 3a, 3b, 4, 5a, 5b, 6, 7, 8a, 8b, 4', 5' (Ann. Oncol., 27(3):iii6-iii24, 2016)

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[3]U.S. Patent Application Publication No. 2016/0145237A1.

[4]U.S. Patent Application Publication No. 2016/0108123A1.

[5]U.S. Patent Application Publication No. 2016/0010068A1.

[6]U.S. Patent Application Publication No. 2016/00009785A1.

[7]European Patent Application Publication No. 2986736A2.

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[35]Cui et al., *Oncotarget*. 2016 Dec 1. doi: 10.18632/oncotarget.13741.

[36]Panagopoulos et al., *Modern Pathology* 29: 1415-1423, 2016

[37]Li et al., *J. Thorac. Oncol.* 2017 Jan;12(1):94-101. doi: 10.1016/j.jtho.2016.08.145.

[38]European Patent Application Number EP2558490B1.

[39]PCT Application No. WO2017001491A2.

[40]Chmielecki et al., *Cancer Research*, Vol. 76, No. 14, Supp. Supplement. Abstract Number: LB-178. 107th Annual meeting of the American Association for Cancer Research, AACR. New Orleans, LA. April 16-20 2016.

[41]Majweska et al., *Cancer Research*, Vol. 76, No. 14, Supp. Supplement. Abstract Number: 3190. 107th Annual meeting of the American Association for Cancer Research, AACR. New Orleans, LA. April 16-20 2016.

[0414] In some embodiments, the dysregulation of an ALK gene, an ALK kinase, or expression or activity or level of any of the same, includes at least one point mutation in an ALK gene that results in the production of an ALK kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type ALK kinase.

[0415] In some embodiments, an ALK-associated cancer has been identified as having one or more ALK inhibitor resistance mutations (that result in an increased resistance to an ALK inhibitor.

[0416] Tropomyosin-related kinase (TRK) is a receptor tyrosine kinase family of neurotrophin receptors that are found in multiple tissues types. Three members of the TRK proto-oncogene family have been described: TrkA, TrkB, and TrkC, encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively. The TRK receptor family is involved in neuronal development, including the growth and function of neuronal synapses, memory development, and maintenance, and the protection of neurons after ischemia or other types of injury (Nakagawara, *Cancer Lett.* 169:107-114, 2001).

[0417] TRK was originally identified from a colorectal cancer cell line as an oncogene fusion containing 5' sequences from tropomyosin-3 (TPM3) gene and the kinase domain encoded by the 3' region of the neurotrophic tyrosine kinase, receptor, type 1 gene (NTRK1) (Pulciani et al., *Nature* 300:539-542, 1982; Martin-Zanca et al., *Nature* 319:743-748, 1986). TRK gene fusions follow the well-established paradigm of other oncogenic fusions, such as those involving ALK and ROS1, which have been shown to drive the growth of tumors and can be successfully inhibited in the clinic by targeted drugs (Shaw et al., *New Engl. J. Med.* 371:1963-1971, 2014; Shaw et al., *New Engl. J. Med.* 370:1189-1197, 2014). Oncogenic TRK fusions induce cancer cell proliferation and engage critical cancer-related downstream signaling pathways such as mitogen activated protein kinase (MAPK) and AKT (Vaishnavi et al., *Cancer Discov.* 5:25-34, 2015). Numerous oncogenic rearrangements involving NTRK1 and its related TRK family members NTRK2 and NTRK3 have been described (Vaishnavi et al., *Cancer Disc.* 5:25-34, 2015; Vaishnavi et al., *Nature Med.* 19:1469-1472, 2013). Although there are numerous different 5' gene fusion partners identified, all share an in-frame, intact TRK kinase domain. A variety of different Trk inhibitors have been developed to treat cancer (see, e.g., U.S. Patent Application Publication No. 62/080,374, International Application Publication Nos. WO 11/006074, WO 11/146336, WO 10/033941, and WO 10/048314, and U.S. Pat. Nos. 8,933,084, 8,791,123, 8,637,516, 8,513,263, 8,450,322, 7,615,383, 7,384,632, 6,153,189, 6,027,927, 6,025,166, 5,910,574, 5,877,016, and 5,844,092).

[0418] The term "TRK-associated cancer" as used herein refers to cancers associated with or having a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same. Exemplary TRK-associated cancers are provided herein.

[0419] The phrase "dysregulation of a TRK gene, a TRK kinase, or the expression or activity or level of any of the same" refers to a genetic mutation (e.g., a TRK gene translocation that results in the expression of a fusion protein, a deletion in a TRK gene that results in the expression of a TRK protein that includes a deletion of at least one amino acid as compared to the wild-type TRK protein, a mutation in a TRK gene that results in the expression of a TRK protein with one or more point mutations, or an alternative spliced version of a TRK mRNA that results in a TRK protein having a deletion of at least one amino acid in the TRK protein as compared to the wild-type TRK protein) or a TRK gene amplification that results in overexpression of a TRK protein or an autocrine activity resulting from the overexpression of a TRK gene in a cell that results in a pathogenic increase in the activity of a kinase domain of a TRK protein (e.g., a constitutively active kinase domain of a TRK protein) in a cell. As another example, a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same, can be a mutation in a TRK gene that encodes a TRK protein that is constitutively active or has increased activity as compared to a protein encoded by a TRK gene that does not include the mutation. For example, a dysregulation of a TRK gene, a TRK protein, or expression or activity, or level of any of the same, can be the result of a gene or chromosome translocation which results in the expression of a fusion protein that contains a first portion of TRK that includes a functional kinase domain, and a second portion of a partner protein that is not TRK. In some examples, dysregulation of a TRK gene, a TRK protein, or expression or activity or level of any of the same can be a result of a gene translocation of one TRK gene with another non-TRK gene. Non-limiting examples of fusion proteins are described in Tables 6-8. Additional examples of TRK kinase protein mutations (e.g., point mutations) are TRK inhibitor resistance mutations.

[0420] The term "wildtype" or "wild-type" when referring to a TRK nucleic acid or protein describes a nucleic acid (e.g., a TRK gene or a TRK mRNA) or protein (e.g., a TRK protein) that is found in a subject that does not have a TRK-associated disease, e.g., a TRK-associated cancer (and optionally also does not have an increased risk of developing a TRK-associated disease and/or is not suspected of having a TRK-associated disease), or is found in a cell or tissue from a subject that does not have a TRK-associated disease, e.g., a TRK-associated cancer (and optionally also does not have an increased risk of developing a TRK-associated disease and/or is not suspected of having a TRK-associated disease).

[0421] In some embodiments, the dysregulation of a TRK gene, a TRK kinase protein, or expression or activity or level of any of the same, includes one or more chromosome translocations or inversions resulting in a TRK gene fusion. In some embodiments, the dysregulation of a TRK gene, a TRK kinase protein, or expression or activity or level of any of the same, is a result of genetic translocations in which the expressed protein is a fusion protein containing residues from a non-TRK partner protein, and includes a minimum of a functional TRK kinase domain. See, for example, Tables 6-8.

TABLE 6

Exemplary TrkA Fusion Proteins and Cancers

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
TP53-TrkA[1,11]	Tumor Protein P53	Spitzoid Melanoma, Spitz tumors
LMNA-TrkA[1, 12]	Lamin A/C	Spitzoid Melanoma, Spitz tumors, Undifferentiated Sarcoma, Adult Soft Tissue Sarcoma (e.g., Soft Tissue Sarcoma Metastatic to Lung), Soft Tissue Fibrosarcoma, Spindle Cell Sarcoma[G], Congenital Infantile Fibrosarcoma[H], Pediatric haemangiopericytoma-like sarcoma[I], Colorectal Cancer[K]

TABLE 6-continued

Exemplary TrkA Fusion Proteins and Cancers

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
CD74-TrkA[2]	MHC class II invariant chain	Non-Small Cell Lung Cancer (NSCLC) Lung adenocarcimona
TFG-TrkA (TRK-T3)[3]	TRK-Fused Gene	Papillary Thyroid Carcinoma (PTC), Soft Tissue Solitary Fibrous Tumor
TPM3-TrkA[3]	Tropomyosin 3	Lung Cancer, Papillary Thyroid Carcinoma (PTC), Acute Myeloid Leukemia (AML), Sarcoma, Pediatric Gliomas, Colorectal Cancer (CRC), Soft Tissue Schwannoma, Spitzoid melanocytic tumors[J]
NFASC-TrkA[4]	Neurofascin	Gliobastoma multiforme (GBM); Glioblastoma
BCAN-TrkA[4]	Brevican	Glioblastoma multiforme (GBM)
MPRIP-TrkA[5, E]	Myosin Phosphatase Rho Interacting Protein or Rho Interacting Protein 3	Non-small cell lung cancer (NSCLC), Lung adenocarcinoma
TPR-TrkA (TRK-T1 or TRK-T2)[3]	Translocated Promoter Region, Nuclear Basket Protein	Papillary Thyroid Carcinoma (PTC), Colorectal Cancer (CRC)[4], Non-small cell lung cancer (NSCLC)
RFWD2-TrkA[6]	Ring Finger and WD Repeat Domain 2	Large Cell Neuroendrocine Cancer (LCNEC); NSCLC
IRF2BP2-TrkA[7]	Interferon Regulatory Factor 2 Binding Protein 2	Thyroid Cancer; Thyroid Gland Carcinoma
SQSTM1-TrkA[7]	Sequestosome 1	Thyroid Cancer (e.g., Papillary Thyroid Cancer), Thyroid Gland Carcinoma, Soft Tissue Fibrosarcoma, Non-small-cell lung cancer[L]
SSBP2-TrkA[7]	Single-Stranded DNA Binding Protein 2	Thyroid Cancer (e.g., Papillary Thyroid Cancer); Thyroid Gland Carcinoma
RABGAP1L-TrkA[8]	RAB GTPase Activating Protein 1-Like	Intrahepatic Cholangicarcinoma (ICC)
C18ORF8-TrkA[9]	Chromosome 18 Open Reading Frame 8	Non-Small Cell Lung Cancer (NSCLC)
RNF213-TrkA[9]	Ring Finger Protein 213	Non-Small Cell Lung Cancer (NSCLC)
TBC1D22A-TrkA[9]	TBC1 Domain Family, Member 22A	Non-Small Cell Lung Cancer (NSCLC)
C20ORF112-TrkA[9]	Chromosome 20 Open Reading Frame 112	Non-Small Cell Lung Cancer (NSCLC)
DNER-TrkA[9]	Delta/Notch-Like EGF Repeat Containing	Non-Small Cell Lung Cancer (NSCLC)
ARHGEF2-TrkA[13]	Rho Guanine Nucleotide Exchange Factor 2	Glioblastoma
CHTOP-TrkA[13]	Chromatin Target of PRMT1	Glioblastoma
PPL-TrkA[13]	Periplakin	Thyroid Carcinoma
PLEKHA6-TrkA	Pleckstrin Homology Domain-Containing Family A Member 6	
PEAR1-TrkA	Platelet Endothelial Aggregation Receptor 1	
MRPL24-TrkA	39S Ribosomal Protein L24, Mitochondrial	
MDM4-TrkA	Human Homolg of Mouse Double Minute 4	
LRRC71-TrkA	Leucine Rich Repeat Containing 71	
GRIPAP1-TrkA	GRIP1 Associated Protein 1	
EPS15-TrkA	Epidermal Growth Factor Receptor Substrate 15	
DYNC2H1-TrkA[B]	Dynein, Cytoplasmic 2, Heavy Chain 1	Sarcoma
CEL-TrkA	Carboxyl Ester Lipase	Pancreatic adenocarcinoma sample[D]
EPHB2-TrkA[B]	EPH Receptor B2	Lower Grade Glioma
TGF-TrkA[C]	Transforming Growth Factor	Papillary Thyroid Cancer
NELL1-TrkA[F]	Cytoplasmic Protein That Contains Epidermal Growth Factor (Egf)-Like Repeats	Non-Small Cell Lung Cancer (NSCLC)
EPL4-TrkA[F]	EPH-Related Receptor Tyrosine Kinase Ligand 4/Ephrin-A4 Protein	Non-Small Cell Lung Cancer (NSCLC)
CTNND2-TrkA[F]	Catenin (Cadherin-Associated Protein), Delta 2	Non-Small Cell Lung Cancer (NSCLC)

TABLE 6-continued

Exemplary TrkA Fusion Proteins and Cancers

Fusion Protein	Non-TrkA Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
TCEANC2-TrkA[F]	Transcription Elongation Factor A (SII) N-Terminal And Central Domain	Non-Small Cell Lung Cancer (NSCLC)

[A]Créancier et al., *Cancer Lett.* 365(1):107-111, 2015.J
[B]U.S. Patent Application Publication No. 2015/0315657.
[C]U.S. Patent Application Publication No. 2015/0283132.
[D]Egren et al., *Cancer Res.* 75(15 Supplement): 4793, 2015.
[E]U.S. Patent Application Publication No. 2015/0073036.
[F]P.C.T. Patent Application Publication No. WO2015184443A1.
[G]Haller et al., The Journal of pathology 238.5 (2016): 700-710.
[H]Wong et al., *J Natl Cancer* Inst 2016;108: djv307.
[I]Haller et al., J. Pathol. 238(5): 700-10.
[J]Gang et al., Mod Pathol. 2016 Apr;29(4):359-69.
[K]Konicek et al., *Cancer research*, Vol. 76, No. 14, Supp. Supplement. Abstract Number: 2647; 107th Annual Meeting of the American Association for Cancer Research, AACR 2016. New Orleans,LA; 16-20 Apr 2016.
[L]Dtilon et al., *Cancer research*, Vol. 76, No. 14, Supp. Supplement. Abstract Number: CT007; 107th Annual Meeting of the American Association for Cancer Research, AACR 2016. New Orleans,LA; 16-20 Apr 2016.

TABLE 7

Exemplary TrkB Fusion Proteins and Cancers

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
NACC2-TrkB[10]	NACC Family Member 2, BEN and BTB (POZ) Domain Containing	Pilocytic Astrocytoma
QKI-TrkB[10]	QKI, KH Domain Containing, RNA Binding	Pilocytic Astrocytoma
AFAP1-TrkB[7]	Actin Filament Associated Protein 1	Lower-grade Glioma, In vitro (murine Ba/F3 cells)[B], Pilocytic astrocytoma with anaplasia (PAA)[E]
PAN3-TrkB[7]	PAN3 Poly(A) Specific Ribonuclease Subunit	Head and Neck Squamous Cell Carcinoma
SQSTM1-TrkB[7]	Sequestosome 1	Lower-Grade Glioma
TRIM24-TrkB[7]	Tripartite Motif Containing 24	Lung adenocarcinoma
VCL-TrkB[11]	Vinculin	Pediatric gliomas

TABLE 7-continued

Exemplary TrkB Fusion Proteins and Cancers

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
AGBL4-TrkB[11]	ATP/GTP Binding Protein-Like 4	Pediatric gliomas
DAB2IP-TrkB	Disabled Homolog 2-Interacting Protein	
NTRK2-TERT[A]	Telomerase Reverse Transcriptase	Thyroid Cancer
TEL-TrkB[C] (ETV6)	ETS Variant 6	In vitro (murine Ba/F3 cells)
QKI-TrkB[D]	Protein Quaking	Astrocytoma

[A]PCT Patent Application Publication No. WO 2015/183836A1
[B]Drilon et al., *Ann Oncol.* 2016 May;27(5):920-6.
[C]Yuzugullu et al., *Cell Discov.* 2: 16030, 2016.
[D]Ni et al., *Neuro Oncol.* 2017 Jan;19(1):22-30.
[E]Lin et al., *Neuro-Oncol*, Vol. 18, Supp. Supplement 3, pp. iii58, Abstract Number: HG-48; 17th International Symposium on Pediatric Neuro-Oncology, ISPNO 2016. Liverpool, UK, 12 Jun 2016-15 Jun 2016.

TABLE 8

Exemplary TrkC Fusion Proteins and Cancers

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
ETV6-TrkC[11] (TEL; or chromosomal translocation t(12;15) (p13;q25))[J]	ETS Variant 6	Salivary Gland Cancer, Secretory Breast Carcinoma, Acute Myeloid Leukemia, Fibrosarcoma, Nephroma, Melanoma, Colorectal Cancer (CRC), Breast Cancer, Pediatric Gliomas, Thyroid Cancer (e.g., Papillary Thyroid Cancer), Infantile Fibrosarcoma, Soft Tissue Hemangioma, Gastrointestinal Stromal Tumor (GIST) (e.g., c-kit-negative GIST), Mammary Carcinoma (e.g., Mammary Analogue Secretory Carcinoma, Secretory Breast Carcinoma (SBSC)[K], Congenital Fibrosarcoma, Acute Myelogenous Leukemia, Polymorphous low-grade adenocarcinoma[D], ALK-negative inflammatory myofibroblastic tumors (IMT)[E], Infantile Fibrosarcoma (IFS)[F], Acinic cell carcinoma (AcCC)[G], Cellular mesoblastic nephroma[H], Promyelocytic leukemia[I], Burkitt Lymphoma[I], B-cell lymphoma[I], multiple myeloma[I], medulloblastoma[I], neuroblastoma[I], ovarian cancer[I], intestinal cancer[J]
BTBD1-TrkC[11]	BTB (POZ) Domain Containing 1	Pediatric Gliomas
LYN-TrkC[7]	V-Yes-1 Yamaguchi Sarcoma Viral Related Oncogene Homolog (also known as Lck/Yes-Related Novel Protein Tyrosine Kinase)	Head and Neck Squamous Cell Carcinoma

TABLE 8-continued

Exemplary TrkC Fusion Proteins and Cancers

Fusion Protein	Non-TrkB Fusion Partner	Non-limiting Exemplary Trk-and Synonyms of Associated Cancer(s)
RBPMS-TrkC[I]	RNA Binding Protein with Multiple Splicing	Thyroid Cancer (e.g., Papillary Thyroid Cancer)
EML4-TrkC[A]	Echinoderm Microtubule-Associated Protein-Like 4	Fibrosarcoma (e.g., Pediatric Fibrosarcoma[L])
HOMER2-TrkC	Homer Protein Homolog 2	Soft Tissue Sarcoma
TFG-TrkC	TRK-Fused Gene	Soft Tissue Solitary Fibrous Tumor
FAT1-TrkC	FAT Atypical Cadherin 1	Cervical Squamous Cell Carcinoma[B]
MYO5A-TrkC	Myosin VA	Spitz tumor[C]
MYH9-TrkC	Myosin Heavy Chain 9	Spitz tumor[C]

[A]Tannenbaum et al., *Cold Spring Harb. Mol. Case Stud.* 1: a000471, 2015.
[B]U.S. Patent Application Publication No. 2015/0315657.
[C]Yeh et al., *J Pathol.* 240(3): 282-90, 2016
[D]Montalli et al., *J Oral Pathol Med.* doi: 10.1111/jop.12491, 2016
[E]Alassiri et al., *Am J Surg Pathol.* 2016 Aug;40(8):1051-61.
[F]Nagasubramanian et al., *Pediatr Blood Cancer.* 2016 Aug;63(8):1468-70.
[G]Chintakuntlawar et al., *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016 May;121(5):542-549.e1.
[H]U.S. Patent Application Publication No. US15030713A.
[I]U.S. Patent Application Publication No. US9447135B2.
[J]Skalova et al., *Modern Pathology* 30, S27-S43, 2017.
[K]Hyrcza et al., Vol. 469, Supp. Supplement 1, pp. S17. Abstract Number: OFP-1997-7; 31st International Congress of the International Academy of Pathology and the 28th Congress of the European Society of Pathology, Cologne, Germany. 25-29 September 2016.
[L]Sims et al., *Journal of Immunotherapy of Cancer*, Vol. 4, Supp. Supplement 1; Abstract Number: P280; 31st Annual Meeting and Associated Programs of the Society for Immunotherapy of Cancer, SITC 2016. National Harbor, MD; 9-13 November 2016.

[0422] In some embodiments, the dysregulation of a TRK gene, a TRK kinase, or expression or activity or level of any of the same, includes at least one point mutation in a TRK gene that results in the production of a TRK kinase that has one or more amino acid substitutions, insertions, or deletions as compared to the wild-type TRK kinase.

[0423] In some embodiments, a TRK-associated cancer has been identified as having one or more TRK inhibitor resistance mutations (that result in an increased resistance to a TRK inhibitor.

[0424] Accordingly, provided herein are methods for treating a patient diagnosed with (or identified as having) a cancer that include administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided herein are methods for treating a patient identified or diagnosed as having a ROS1-associated cancer that include administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the patient that has been identified or diagnosed as having a ROS1-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient or by performing any of the non-limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the cancer is a ROS1-associated cancer. For example, the ROS1-associated cancer can be a cancer that includes one or more ROS1 inhibitor resistance mutations.

[0425] Also provided are methods for treating cancer in a patient in need thereof, the method comprising: (a) determining if the cancer in the patient is associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same; and (b) if the cancer is determined to be associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. Some embodiments of these methods further include administering to the subject one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor). In some embodiments, one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor) are administered before a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor) are administered after a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor) are administered with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the subject was previously treated with a first ROS1 inhibitor or previously treated with another anticancer treatment, e.g., treatment with another anticancer agent, resection of the tumor or radiation therapy. In some embodiments, the subject was previously treated with an ALK inhibitor, a TRK inhibitor, or both. In some embodiments, the patient is determined to have a ROS1-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved test or assay for identifying dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient or by performing any of the non-

limiting examples of assays described herein. In some embodiments, the test or assay is provided as a kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the cancer is a ROS1-associated cancer. For example, the ROS1-associated cancer can be a cancer that includes one or more ROS1 inhibitor resistance mutations.

[0426] Also provided are methods of treating a patient that include performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, and administering (e.g., specifically or selectively administering) a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof to the patient determined to have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. Some embodiments of these methods further include administering to the subject one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor). In some embodiments, one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor) are administered before a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, one or more additional anticancer agents (e.g., a second ROS1 inhibitor (e.g., a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof), an ALK inhibitor, and/or a TRK inhibitor) are administered after a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, one or more additional anticancer agents (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor) are administered with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments of these methods, the subject was previously treated with a first ROS1 inhibitor or previously treated with another anticancer treatment, e.g., treatment with another anticancer agent, resection of a tumor or radiation therapy. In some embodiments, the subject was previously treated with an ALK inhibitor, a TRK inhibitor, or both. In some embodiments, the patient is a patient suspected of having a ROS1-associated cancer, a patient presenting with one or more symptoms of a ROS1-associated cancer, or a patient having an elevated risk of developing a ROS1-associated cancer. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH). In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. Additional, non-limiting assays that may be used in these methods are described herein. Additional assays are also known in the art. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations.

[0427] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof for use in treating a ROS1-associated cancer in a patient identified or diagnosed as having a ROS1-associated cancer through a step of performing an assay (e.g., an in vitro assay) on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, where the presence of a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, identifies that the patient has a ROS1-associated cancer. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a ROS1-associated cancer in a patient identified or diagnosed as having a ROS1-associated cancer through a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same where the presence of dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, identifies that the patient has a ROS1-associated cancer. Some embodiments of any of the methods or uses described herein further include recording in the patient's clinical record (e.g., a computer readable medium) that the patient is determined to have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, through the performance of the assay, should be administered a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the assay utilizes next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH). In some embodiments, the assay is a regulatory agency-approved assay, e.g., FDA-approved kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations.

[0428] Also provided is a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, for use in the treatment of a cancer in a patient in need thereof or a patient identified or diagnosed as having a ROS1-associated cancer. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a cancer in a patient identified or diagnosed as having a ROS1-associated cancer. In some embodiments, the cancer is a ROS1-associated cancer, for example, a ROS1-associated cancer having one or more ROS1 inhibitor resistance mutations. In some embodiments, a patient is identified or diagnosed as having a ROS1-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the sample. As provided herein, a ROS1-associated cancer includes those described herein and known in the art.

[0429] In some embodiments of any of the methods or uses described herein, the patient has been identified or diagnosed as having a cancer with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. In some embodiments of any of the

methods or uses described herein, the patient has a tumor that is positive for a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient can be a patient with a tumor(s) that is positive for a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient can be a patient whose tumors have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. In some embodiments of any of the methods or uses described herein, the patient is suspected of having a ROS1-associated cancer (e.g., a cancer having one or more ROS1 inhibitor resistance mutations). In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a patient in need of such treatment, the method comprising a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the patient; and b) administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same includes one or more fusion proteins. Non-limiting examples of ROS1 gene fusion proteins are described in Table 2. In some embodiments, the fusion protein is SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROS1. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same includes one or more ROS1 kinase protein point mutations, insertions, and/or deletions. Non-limiting examples of ROS1 kinase protein point mutations are described in Table 3 and Table 3a. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations. Non-limiting examples of ROS1 inhibitor resistance mutations are described in Table 4. In some embodiments, the ROS1 inhibitor resistance mutation is selected from the group consisting of L2026M, G2032R, and D2033N. In some embodiments, the cancer with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the tumor that is positive for a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is a tumor positive for one or more ROS1 inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the assay is a liquid biopsy.

[0430] In some embodiments of any of the methods or uses described herein, the patient has a clinical record indicating that the patient has a tumor that has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same (e.g., a tumor having one or more ROS1 inhibitor resistance mutations). In some embodiments, the clinical record indicates that the patient should be treated with one or more of the compounds of Formula I or a pharmaceutically acceptable salts or solvates thereof or compositions provided herein. In some embodiments, the cancer with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is a cancer having one or more ROS1 inhibitor resistance mutations. In some embodiments, the cancer with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the tumor that is positive for a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is a tumor positive for one or more ROS1 inhibitor resistance mutations. In some embodiments, the tumor with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same is determined using a regulatory agency-approved, e.g., FDA-approved, assay or kit. In some embodiments, the assay is a liquid biopsy.

[0431] Also provided are methods of treating a patient that include administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to a patient having a clinical record that indicates that the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. Also provided is the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for treating a ROS1-associated cancer in a patient having a clinical record that indicates that the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. Some embodiments of these methods and uses can further include: a step of performing an on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, and recording the information in a patient's clinical file (e.g., a computer readable medium) that the patient has been identified to have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH). In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of a ROS1 gene, ROS1 kinase, or expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations.

[0432] Also provided herein is a method of treating a subject. The method includes performing an assay on a sample obtained from the subject to determine whether the subject has a dysregulation of a ROS1 gene, a ROS1 protein, or expression or level of any of the same. The method also includes administering to a subject determined to have a dysregulation of a ROS1 gene, a ROS1 protein, or expression or activity, or level of any of the same a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the dysregulation in a ROS1 gene, a ROS1 kinase protein, or expression or activity of the same is a gene or chromosome translocation that results in the expression of a ROS1 fusion protein (e.g., any of the ROS1 fusion proteins

described herein). In some embodiments, the ROS1 fusion can be selected from a SLC34A2 fusion, a CD74 fusion, a EZR fusion, a TPM3 fusion, or a SDC4 fusion. In some embodiments, the dysregulation in a ROS1 gene, a ROS1 kinase protein, or expression or activity or level of any of the same is one or more point mutation in the ROS1 gene (e.g., any of the one or more of the ROS1 point mutations described herein). The one or more point mutations in a ROS1 gene can result, e.g., in the translation of a ROS1 protein having one or more of the following amino acid substitutions: A15G, R118N, G1025R, T1735M, R1948H, and R2072N. In some embodiments, the dysregulation in a ROS1 gene, a ROS1 kinase protein, or expression or activity or level of any of the same is one or more ROS1 inhibitor resistance mutations (e.g., any combination of the one or more ROS1 inhibitor resistance mutations described herein). The one or more point mutations in a ROS1 gene can result, e.g., in the translation of a ROS1 protein having one or more of the following amino acid substitutions: L2026M, G2032R, and D2033N. Some embodiments of these methods further include administering to the subject another anticancer agent (e.g., a second ROS1 inhibitor, a second compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, an ALK inhibitor, and/or a TRK inhibitor).

[0433] Also provided are methods (e.g., in vitro methods) of selecting a treatment for a patient identified or diagnosed as having a ROS1-associated cancer. Some embodiments can further include administering the selected treatment to the patient identified or diagnosed as having a ROS1-associated cancer. For example, the selected treatment can include administration of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Some embodiments can further include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, and identifying and diagnosing a patient determined to have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, as having a ROS1-associated cancer. In some embodiments, the cancer is a ROS1-associated cancer having one or more ROS1 inhibitor resistance mutations. In some embodiments, the patient has been identified or diagnosed as having a ROS1-associated cancer through the use of a regulatory agency-approved, e.g., FDA-approved, kit for identifying dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, in a patient or a biopsy sample from the patient. In some embodiments, the assay is a liquid biopsy. In some embodiments, the ROS1-associated cancers is a cancer described herein or known in the art. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH). In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy.

[0434] Also provided herein are methods of selecting a treatment for a patient, wherein the methods include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same (e.g., one or more ROS1 inhibitor resistance mutations), and identifying or diagnosing a patient determined to have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, as having a ROS1-associated cancer. Some embodiments further include administering the selected treatment to the patient identified or diagnosed as having a ROS1-associated cancer. For example, the selected treatment can include administration of a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to the patient identified or diagnosed as having a ROS1-associated cancer. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH). In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy.

[0435] Also provided are methods of selecting a patient for treatment, wherein the methods include selecting, identifying, or diagnosing a patient having a ROS1-associated cancer, and selecting the patient for treatment including administration of a therapeutically-effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, identifying or diagnosing a patient as having a ROS1-associated cancer can include a step of performing an assay on a sample obtained from the patient to determine whether the patient has a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, and identifying or diagnosing a patient determined to have a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same, as having a ROS1-associated cancer. In some embodiments, the method of selecting a treatment can be used as a part of a clinical study that includes administration of various treatments of a ROS1-associated cancer. In some embodiments, a ROS1-associated cancer is a cancer having one or more ROS1 inhibitor resistance mutations. In some embodiments, the assay is an in vitro assay. For example, an assay that utilizes next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH). In some embodiments, the assay is a regulatory agency-approved, e.g., FDA-approved, kit. In some embodiments, the assay is a liquid biopsy. In some embodiments, the dysregulation of the ROS1 gene, the ROS1 kinase, or expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations.

[0436] In some embodiments of any of the methods or uses described herein, an assay used to determine whether the patient has a dysregulation of a ROS1 gene, or a ROS1 kinase, or expression or activity or level of any of the same, using a sample from a patient can include, for example, next generation sequencing, pyrosequencing, immunohistochemistry, an enzyme-linked immunosorbent assay, and/or fluorescence in situ hybridization (FISH) (e.g., break apart FISH or dual-fusion FISH), fluorescence microscopy, Southern blotting, Western blotting, FACS analysis, Northern blotting, and PCR-based amplification (e.g., RT-PCR and quan-

titative real-time RT-PCR). As is well-known in the art, the assays are typically performed, e.g., with at least one labelled nucleic acid probe or at least one labelled antibody or antigen-binding fragment thereof. Assays can utilize other detection methods known in the art for detecting dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or levels of any of the same (see, e.g., the references cited herein). In some embodiments, the dysregulation of the ROS1 gene, the ROS1 kinase, or expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations. In some embodiments, the sample is a biological sample or a biopsy sample (e.g., a paraffin-embedded biopsy sample) from the patient. In some embodiments, the patient is a patient suspected of having a ROS1-associated cancer, a patient having one or more symptoms of a ROS1-associated cancer, and/or a patient that has an increased risk of developing a ROS1-associated cancer).

[0437] In some embodiments, dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same can be identified using a liquid biopsy (variously referred to as a fluid biopsy or fluid phase biopsy). See, e.g., Karachialiou et al., "Real-time liquid biopsies become a reality in cancer treatment", *Ann. Transl. Med.,* 3(3):36, 2016. Liquid biopsy methods can be used to detect total tumor burden and/or the dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same. Liquid biopsies can be performed on biological samples obtained relatively easily from a subject (e.g., via a simple blood draw) and are generally less invasive than traditional methods used to detect tumor burden and/or dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same. In some embodiments, liquid biopsies can be used to detect the presence of dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same at an earlier stage than traditional methods. In some embodiments, the biological sample to be used in a liquid biopsy can include, blood, plasma, urine, cerebrospinal fluid, saliva, sputum, broncho-alveolar lavage, bile, lymphatic fluid, cyst fluid, stool, ascites, and combinations thereof. In some embodiments, a liquid biopsy can be used to detect circulating tumor cells (CTCs). In some embodiments, a liquid biopsy can be used to detect cell-free DNA. In some embodiments, cell-free DNA detected using a liquid biopsy is circulating tumor DNA (ctDNA) that is derived from tumor cells. Analysis of ctDNA (e.g., using sensitive detection techniques such as, without limitation, next-generation sequencing (NGS), traditional PCR, digital PCR, or microarray analysis) can be used to identify dysregulation of a RET gene, a RET kinase, or the expression or activity or level of any of the same.

[0438] In some embodiments, ctDNA derived from a single gene can be detected using a liquid biopsy. In some embodiments, ctDNA derived from a plurality of genes (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 or more, or any number of genes in between these numbers) can be detected using a liquid biopsy. In some embodiments, ctDNA derived from a plurality of genes can be detected using any of a variety of commercially-available testing panels (e.g., commercially-available testing panels designed to detect dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same). Liquid biopsies can be used to detect dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same including, without limitation, point mutations or single nucleotide variants (SNVs), copy number variants (CNVs), genetic fusions (e.g., translocations or rearrangements), insertions, deletions, or any combination thereof. In some embodiments, a liquid biopsy can be used to detect a germline mutation. In some embodiments, a liquid biopsy can be used to detect a somatic mutation. In some embodiments, a liquid biopsy can be used to detect a primary genetic mutation (e.g., a primary mutation or a primary fusion that is associated with initial development of a disease, e.g., cancer). In some embodiments, a liquid biopsy can be used to detect a genetic mutation that develops after development of the primary genetic mutation (e.g., a resistance mutation that arises in response to a treatment administered to a subject). In some embodiments, a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same identified using a liquid biopsy is also present in a cancer cell that is present in the subject (e.g., in a tumor). In some embodiments, any of the types of dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same described herein can be detected using a liquid biopsy. In some embodiments, a genetic mutation identified via a liquid biopsy can be used to identify the subject as a candidate for a particular treatment. For example, detection of dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in the subject can indicate that the subject will be responsive to a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0439] Liquid biopsies can be performed at multiple times during a course of diagnosis, a course of monitoring, and/or a course of treatment to determine one or more clinically relevant parameters including, without limitation, progression of the disease, efficacy of a treatment, or development of resistance mutations after administering a treatment to the subject. For example, a first liquid biopsy can be performed at a first time point and a second liquid biopsy can be performed at a second time point during a course of diagnosis, a course of monitoring, and/or a course of treatment. In some embodiments, the first time point can be a time point prior to diagnosing a subject with a disease (e.g., when the subject is healthy), and the second time point can be a time point after subject has developed the disease (e.g., the second time point can be used to diagnose the subject with the disease). In some embodiments, the first time point can be a time point prior to diagnosing a subject with a disease (e.g., when the subject is healthy), after which the subject is monitored, and the second time point can be a time point after monitoring the subject. In some embodiments, the first time point can be a time point after diagnosing a subject with a disease, after which a treatment is administered to the subject, and the second time point can be a time point after the treatment is administered; in such cases, the second time point can be used to assess the efficacy of the treatment (e.g., if the genetic mutation(s) detected at the first time point are reduced in abundance or are undetectable) or to determine the presence of a resistance mutation that has arisen as a result of the treatment. In some embodiments, a treatment to be administered to a subject can include a compound of Formula I or a pharmaceutically acceptable salt thereof.

[0440] In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment or therapy in addition to compositions provided herein may be, for example, surgery, radiotherapy, and chemotherapeutic agents, such as kinase inhibitors, signal transduction inhibitors and/or monoclonal antibodies. Compounds of Formula I therefore may also be useful as adjuvants to cancer treatment, that is, they can be used in combination with one or more additional therapies or therapeutic agents, for example a chemotherapeutic agent that works by the same or by a different mechanism of action.

[0441] In some embodiments of any the methods described herein, the compound of Formula I (or a pharmaceutically acceptable salt or solvate thereof) is administered in combination with a therapeutically effective amount of at least one additional therapeutic agent selected from one or more additional therapies or therapeutic (e.g., chemotherapeutic) agents.

[0442] Non-limiting examples of additional therapeutic agents include: other ROS1-targeted therapeutic agents (i.e. a first or second ROS1 kinase inhibitor), ALK-targeted therapeutic agents (e.g., ALK kinase inhibitors), receptor tyrosine kinase-targeted therapeutic agents (e.g., TRK kinase inhibitors), kinase targeted therapeutics, signal transduction pathway inhibitors, checkpoint inhibitors, modulators of the apoptosis pathway (e.g. obataclax); cytotoxic chemotherapeutics, angiogenesis-targeted therapies, immune-targeted agents, including immunotherapy, and radiotherapy.

[0443] In some embodiments, the other ROS1-targeted therapeutic is a multikinase inhibitor exhibiting ROS1 inhibition activity. In some embodiments, the other ROS1-targeted therapeutic inhibitor is selective for a ROS1 kinase. Exemplary ROS1 kinase inhibitors can exhibit inhibition activity (IC_{50}) against a ROS1 kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a ROS1 kinase inhibitor can exhibit inhibition activity (IC_{50}) against a ROS1 kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein.

[0444] Non-limiting examples of ROS1-targeted therapeutic agents include (E)-5-chloro-2-(2-(1-(4-fluorophenyl) ethylidene)hydrazinyl)-N-(2-(isopropylsulfonyl)phenyl)pyrimidin-4-amine (*Eur. J. Org. Chem.* 2016, 123, 80-89); alectinib; brigatinib; cabozantinib; ceritinib; crizotinib; entrectinib; foretinib; herbimycin A; lorlatinib; lorlatinib des-methyl analogs; merestinib; ASP3026 (NCT01284192; Astellas Pharma); AZD3634 (AstraZeneca); and ASP3026 (Astrellas Pharma).

[0445] In some embodiments, an ALK-targeted therapeutic is a multikinase inhibitor exhibiting ALK inhibition activity. In some embodiments, the ALK-targeted therapeutic inhibitor is selective for an ALK kinase. Exemplary ALK kinase inhibitors can exhibit inhibition activity (IC_{50}) against an ALK kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, an ALK kinase inhibitor can exhibit inhibition activity (IC_{50}) against an ALK kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay.

[0446] Non-limiting examples of ALK-targeted therapeutic agents include "Amgen 36"; "Amgen 49"; "Cephalon 30"; "Chugai 13d"; 4-arylaminopyrimidine derivatives (see, e.g., *Eur. J. Med. Chem.* 2016, 123, 80-99); alectinib; anti-ALK monoclonal antibodies; brigatinib; ceritinib; crizotinib; dorsomorphin; ensartinib; entrectinib; ganetespib; lorlatinib; PF-02341066 (Pfizer); IPI-504 (Infinity); TSR-011 (Tesaro, Inc.); CT-707 (Centaurus Biopharma); AUY922; TEW-7197 (Medpacto); CEP-28122 (Teva Pharmaceuticals); CEP-37440 (Teva Pharmaceuticals); ASP3026 (Astellas Pharma); 17-AAG; IPI-504; GSK 1838705 (GlaxoSmithKline); KRCA 0008; AZD3463 (AstraZeneca); NVP-TAE684 (Novartis); "3-39" (Novartis); LDN193189; SB 525334; SB 505124; and TAE684.

[0447] In some embodiments, a receptor tyrosine kinase targeted therapeutic is a multikinase inhibitor (e.g., TRK-targeted therapeutic inhibitor) exhibiting TRK inhibition activity. In some embodiments, the TRK-targeted therapeutic inhibitor is selective for a TRK kinase. Exemplary TRK kinase inhibitors can exhibit inhibition activity (IC_{50}) against a TRK kinase of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, a TRK kinase inhibitor can exhibit inhibition activity (IC_{50}) against a TRK kinase of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay. For example, a TRK inhibitor assay can be any of those provided in U.S. Pat. No. 8,933,084 (e.g., Example A or B).

[0448] Non-limiting examples of receptor tyrosine kinase (e.g., Trk) targeted therapeutic agents, include afatinib, cabozantinib, cetuximab, crizotinib, dabrafenib, entrectinib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, pazopanib, panitumumab, pertuzumab, sunitinib, trastuzumab, 1-((3 S,4R)-4-(3-fluorophenyl)-1-(2-methoxyethyl) pyrrolidin-3-yl)-3-(4-methyl-3-(2-methylpyrimidin-5-yl)-1-phenyl-1H-pyrazol-5-yl)urea, AG 879, AR-772, AR-786, AR-256, AR-618, AZ-23, AZ623, DS-6051, Go 6976, GNF-5837, GTx-186, GW 441756, LOXO-101, MGCD516, PLX7486, RXDX101, TPX-0005, and TSR-011. Additional Trk targeted therapeutic agents include those described in U.S. Pat. Nos. 8,450,322; 8,513,263; 8,933,084; 8,791,123; 8,946,226; 8,450,322; 8,299,057; and 8,912,194; U.S. Publication No. 2016/0137654; 2015/0166564; 2015/0051222; 2015/0283132; and 2015/0306086; International Publication No. WO 2010/033941; WO 2010/048314; WO 2016/077841; WO 2011/146336; WO 2011/006074; WO 2010/033941; WO 2012/158413; WO 2014078454; WO 2014078417; WO 2014078408; WO 2014078378; WO 2014078372; WO 2014078331; WO 2014078328; WO 2014078325; WO 2014078323; WO 2014078322; WO 2015175788; WO 2009/013126; WO 2013/174876; WO 2015/124697; WO 2010/058006; WO 2015/017533; WO 2015/112806; WO 2013/183578; and WO 2013/074518, all of which are hereby incorporated by reference in their entireties.

[0449] Further examples of Trk inhibitors can be found in U.S. Pat. No. 8,637,516, International Publication No. WO

2012/034091, U.S. Pat. No. 9,102,671, International Publication No. WO 2012/116217, U.S. Publication No. 2010/0297115, International Publication No. WO 2009/053442, U.S. Pat. No. 8,642,035, International Publication No. WO 2009092049, U.S. Pat. No. 8,691,221, International Publication No. WO2006131952, all of which are incorporated by reference in their entireties herein. Exemplary Trk inhibitors include GNF-4256, described in *Cancer Chemother. Pharmacol.* 75(1):131-141, 2015; and GNF-5837 (N-[3-[[2,3-dihydro-2-oxo-3-(1H-pyrrol-2-ylmethylene)-1H-indol-6-yl]amino]-4-methylphenyl]-N'-[2-fluoro-5-(trifluoromethyl)phenyl]-urea), described in *ACS Med. Chem. Lett.* 3(2):140-145, 2012, each of which is incorporated by reference in its entirety herein.

[0450] Additional examples of Trk inhibitors include those disclosed in U.S. Publication No. 2010/0152219, U.S. Pat. No. 8,114,989, and International Publication No. WO 2006/123113, all of which are incorporated by reference in their entireties herein. Exemplary Trk inhibitors include AZ623, described in *Cancer* 117(6):1321-1391, 2011; AZD6918, described in *Cancer Biol. Ther.* 16(3):477-483, 2015; AZ64, described in *Cancer Chemother. Pharmacol.* 70:477-486, 2012; AZ-23 ((S)-5-Chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine), described in *Mol. Cancer Ther.* 8:1818-1827, 2009; and AZD7451; each of which is incorporated by reference in its entirety.

[0451] A Trk inhibitor can include those described in U.S. Pat. Nos. 7,615,383; 7,384,632; 6,153,189; 6,027,927; 6,025,166; 5,910,574; 5,877,016; and 5,844,092, each of which is incorporated by reference in its entirety.

[0452] Further examples of Trk inhibitors include CEP-751, described in *Int. J. Cancer* 72:672-679, 1997; CT327, described in *Acta Derm. Venereol.* 95:542-548, 2015; compounds described in International Publication No. WO 2012/034095; compounds described in U.S. Pat. No. 8,673,347 and International Publication No. WO 2007/022999; compounds described in U.S. Pat. No. 8,338,417; compounds described in International Publication No. WO 2016/027754; compounds described in U.S. Pat. No. 9,242,977; compounds described in U.S. Publication No. 2016/0000783; sunitinib (N-(2-diethylaminoethyl)-5-[(Z)-(5-fluoro-2-oxo-1H-indol-3-ylidene)methyl]-2,4-dimethyl-1H-pyrrole-3-carboxamide), as described in *PLoS One* 9:e95628, 2014; compounds described in International Publication No. WO 2011/133637; compounds described in U.S. Pat. No. 8,637,256; compounds described in *Expert. Opin. Ther. Pat.* 24(7):731-744, 2014; compounds described in *Expert Opin. Ther. Pat.* 19(3):305-319, 2009; (R)-2-phenylpyrrolidine substituted imidazopyridazines, e.g., GNF-8625, (R)-1-(6-(6-(2-(3-fluorophenyl)pyrrolidin-1-yl)imidazo[1,2-b]pyridazin-3-yl)-[2,4'-bipyridin]-2'-yl)piperidin-4-ol as described in *ACS Med. Chem. Lett.* 6(5):562-567, 2015; GTx-186 and others, as described in *PLoS One* 8(12):e83380, 2013; K252a ((9S-(9α,10β,12α))-2,3,9,10,11,12-hexahydro-10-hydroxy-10-(methoxycarbonyl)-9-methyl-9,12-epoxy-1H-diindolo[1,2,3-fg:3',2',1'-kl]pyrrolo[3,4-i][1,6]benzodiazocin-1-one), as described in *Mol. Cell Biochem.* 339(1-2):201-213, 2010; 4-aminopyrazolylpyrimidines, e.g., AZ-23 (((S)-5-chloro-N2-(1-(5-fluoropyridin-2-yl)ethyl)-N4-(5-isopropoxy-1H-pyrazol-3-yl)pyrimidine-2,4-diamine)), as described in *J. Med. Chem.* 51(15):4672-4684, 2008; PHA-739358 (danusertib), as described in *Mol. Cancer Ther.* 6:3158, 2007; Go 6976 (5,6,7,13-tetrahydro-13-methyl-5-oxo-12H-indolo[2,3-a]pyrrolo[3,4-c]carbazole-12-propanenitrile), as described in *J. Neurochem.* 72:919-924, 1999; GW441756 ((3Z)-3-[(1-methylindol-3-yl)methylidene]-1H-pyrrolo[3,2-b]pyridin-2-one), as described in *IJAE* 115:117, 2010; milciclib (PHA-848125AC), described in *J. Carcinog.* 12:22, 2013; AG-879 ((2E)-3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-2-cyano-2-propenethioamide); altiratinib (N-(4-((2-(cyclopropanecarboxamido)pyridin-4-yl)oxy)-2,5-difluorophenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); cabozantinib (N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); lestaurtinib ((5 S,6S,8R)-6-Hydroxy-6-(hydroxymethyl)-5-methyl-7,8,14,15-tetrahydro-5H-16-oxa-4b,8a,14-triaza-5,8-methanodibenzo[b,h]cycloocta[jkl]cyclopenta[e]-as-indacen-13(6H)-one); dovatinib (4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]quinolin-2(1H)-one mono 2-hydroxypropanoate hydrate); sitravatinib (N-(3-fluoro-4-((2-(5-(((2-methoxyethyl)amino)methyl)pyridin-2-yl)thieno[3,2-b]pyridin-7-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide); ONO-5390556; regorafenib (4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate); and VSR-902A; all of the references above are incorporated by reference in their entireties herein.

[0453] The ability of a Trk inhibitor to act as a TrkA, TrkB, and/or Trk C inhibitor may be tested using the assays described in Examples A and B in U.S. Pat. No. 8,513,263, which is incorporated herein by reference.

[0454] In some embodiments, signal transduction pathway inhibitors include Ras-Raf-MEK-ERK pathway inhibitors (e.g., binimetinib, selumetinib, encorafinib, sorafenib, trametinib, and vemurafenib), PI3K-Akt-mTOR-S6K pathway inhibitors (e.g. everolimus, rapamycin, perifosine, temsirolimus), and other kinase inhibitors, such as baricitinib, brigatinib, capmatinib, danusertib, ibrutinib, milciclib, quercetin, regorafenib, ruxolitinib, semaxanib, AP32788, BLU285, BLU554, INCB39110, INCB40093, INCB50465, INCB52793, INCB54828, MGCD265, NMS-088, NMS-1286937, PF 477736 ((R)-amino-N-[5,6-dihydro-2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-1Hpyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-cyclohexaneacetamide), PLX3397, PLX7486, PLX8394, PLX9486, PRN1008, PRN1371, RXDX103, RXDX106, RXDX108, and TG101209 (N-tert-butyl-3-(5-methyl-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)benzenesulfonamide).

[0455] Non-limiting examples of checkpoint inhibitors include ipilimumab, tremelimumab, nivolumab, pidilizumab, MPDL3208A, MEDI4736, MSB0010718C, BMS-936559, BMS-956559, BMS-935559 (MDX-1105), AMP-224, and pembrolizumab.

[0456] In some embodiments, cytotoxic chemotherapeutics are selected from arsenic trioxide, bleomycin, cabazitaxel, capecitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, irinotecan, lomustine, methotrexate, mitomycin C, oxaliplatin, paclitaxel, pemetrexed, temozolomide, and vincristine.

[0457] Non-limiting examples of angiogenesis-targeted therapies include aflibercept and bevacizumab.

[0458] The term "immunotherapy" refers to an agent that modulates the immune system. In some embodiments, an immunotherapy can increase the expression and/or activity

of a regulator of the immune system. In some embodiments, an immunotherapy can decrease the expression and/or activity of a regulator of the immune system. In some embodiments, an immunotherapy can recruit and/or enhance the activity of an immune cell.

[0459] In some embodiments, the immunotherapy is a cellular immunotherapy (e.g., adoptive T-cell therapy, dendritic cell therapy, natural killer cell therapy). In some embodiments, the cellular immunotherapy is sipuleucel-T (APC8015; Provenge™; Plosker (2011) *Drugs* 71(1): 101-108). In some embodiments, the cellular immunotherapy includes cells that express a chimeric antigen receptor (CAR). In some embodiments, the cellular immunotherapy is a CAR-T cell therapy. In some embodiments, the CAR-T cell therapy is tisagenlecleucel (Kymriah™).

[0460] In some embodiments, the immunotherapy is an antibody therapy (e.g., a monoclonal antibody, a conjugated antibody). In some embodiments, the antibody therapy is bevacizumab (Mvasti™, Avastin®), trastuzumab (Herceptin®), avelumab (Bavencio®), rituximab (MabThera™, Rituxan®), edrecolomab (Panorex), daratumuab (Darzalex®), olaratumab (Lartruvo™), ofatumumab (Arzerra®), alemtuzumab (Campath®), cetuximab (Erbitux®), oregovomab, pembrolizumab (Keytruda®), dinutiximab (Unituxin®), obinutuzumab (Gazyva®), tremelimumab (CP-675,206), ramucirumab (Cyramza®), ublituximab (TG-1101), panitumumab (Vectibix®), elotuzumab (Empliciti™), avelumab (Bavencio®), necitumumab (Portrazza™), cirmtuzumab (UC-961), ibritumomab (Zevalin®), isatuximab (SAR650984), nimotuzumab, fresolimumab (GC1008), lirilumab (INN), mogamulizumab (Poteligeo®), ficlatuzumab (AV-299), denosumab (Xgeva®), ganitumab, urelumab, pidilizumab or amatuximab.

[0461] In some embodiments, the immunotherapy is an antibody-drug conjugate. In some embodiments, the antibody-drug conjugate is gemtuzumab ozogamicin (Mylotarg™), inotuzumab ozogamicin (Besponsa®), brentuximab vedotin (Adcetris®), ado-trastuzumab emtansine (TDM-1; Kadcyla®), mirvetuximab soravtansine (IMGN853) or anetumab ravtansine

[0462] In some embodiments, the immunotherapy includes blinatumomab (AMG103; Blincyto®) or midostaurin (Rydapt).

[0463] In some embodiments, the immunotherapy includes a toxin. In some embodiments, the immunotherapy is denileukin diftitox (Ontak®).

[0464] In some embodiments, the immunotherapy is a cytokine therapy. In some embodiments, the cytokine therapy is an interleukin 2 (IL-2) therapy, an interferon alpha (IFNα) therapy, a granulocyte colony stimulating factor (G-CSF) therapy, an interleukin 12 (IL-12) therapy, an interleukin 15 (IL-15) therapy, an interleukin 7 (IL-7) therapy or an erythropoietin-alpha (EPO) therapy. In some embodiments, the IL-2 therapy is aldesleukin (Proleukin®). In some embodiments, the IFNα therapy is IntronA® (Roferon-A®). In some embodiments, the G-CSF therapy is filgrastim (Neupogen®).

[0465] In some embodiments, the immunotherapy is an immune checkpoint inhibitor. In some embodiments, the immunotherapy includes one or more immune checkpoint inhibitors. In some embodiments, the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the CTLA-4 inhibitor is ipilimumab (Yervoy®) or tremelimumab (CP-675,206). In some embodiments, the PD-1 inhibitor is pembrolizumab (Keytruda®) or nivolumab (Opdivo®). In some embodiments, the PD-L1 inhibitor is atezolizumab (Tecentriq®), avelumab (Bavencio®) or durvalumab (Imfinzi™).

[0466] In some embodiments, the immunotherapy is mRNA-based immunotherapy. In some embodiments, the mRNA-based immunotherapy is CV9104 (see, e.g., Rausch et al. (2014) Human Vaccin Immunother 10(11): 3146-52; and Kubler et al. (2015) J. Immunother Cancer 3:26).

[0467] In some embodiments, the immunotherapy is *bacillus* Calmette-Guerin (BCG) therapy.

[0468] In some embodiments, the immunotherapy is an oncolytic virus therapy. In some embodiments, the oncolytic virus therapy is talimogene alherparepvec (T-VEC; Imlygic®).

[0469] In some embodiments, the immunotherapy is a cancer vaccine. In some embodiments, the cancer vaccine is a human papillomavirus (HPV) vaccine. In some embodiments, the HPV vaccine is Gardasil®, Gardasil9® or Cervarix®. In some embodiments, the cancer vaccine is a hepatitis B virus (HBV) vaccine. In some embodiments, the HBV vaccine is Engerix-B®, Recombivax HB® or GI-13020 (Tarmogen®). In some embodiments, the cancer vaccine is Twinrix® or Pediarix®. In some embodiments, the cancer vaccine is BiovaxID®, Oncophage®, GVAX, ADXS11-001, ALVAC-CEA, PROSTVAC®, Rindopepimut®, CimaVax-EGF, lapuleucel-T (APC8024; Neuvenge™), GRNVAC1, GRNVAC2, GRN-1201, hepcortespenlisimut-L (Hepko-V5), DCVAX®, SCIB1, BMT CTN 1401, PrCa VBIR, PANVAC, ProstAtak®, DPX-Survivac, or viagenpumatucel-L (HS-110).

[0470] In some embodiments, the immunotherapy is a peptide vaccine. In some embodiments, the peptide vaccine is nelipepimut-S(E75) (NeuVax™), IMA901, or SurVaxM (SVN53-67). In some embodiments, the cancer vaccine is an immunogenic personal neoantigen vaccine (see, e.g., Ott et al. (2017) *Nature* 547: 217-221; Sahin et al. (2017) *Nature* 547: 222-226). In some embodiments, the cancer vaccine is RGSH4K, or NEO-PV-01. In some embodiments, the cancer vaccine is a DNA-based vaccine. In some embodiments, the DNA-based vaccine is a mammaglobin-A DNA vaccine (see, e.g., Kim et al. (2016) Oncolmmunology 5(2): e1069940).

[0471] In some embodiments, immune-targeted agents are selected from aldesleukin, interferon alfa-2b, ipilimumab, lambrolizumab, nivolumab, prednisone, and sipuleucel-T.

[0472] Non-limiting examples of radiotherapy include radioiodide therapy, external-beam radiation, and radium 223 therapy.

[0473] Additional kinase inhibitors include those described in, for example, U.S. Pat. Nos. 7,514,446; 7,863,289; 8,026,247; 8,501,756; 8,552,002; 8,815,901; 8,912,204; 9,260,437; 9,273,051; U.S. Publication No. US 2015/0018336; International Publication No. WO 2007/002325; WO 2007/002433; WO 2008/080001; WO 2008/079906; WO 2008/079903; WO 2008/079909; WO 2008/080015; WO 2009/007748; WO 2009/012283; WO 2009/143018; WO 2009/143024; WO 2009/014637; 2009/152083; WO 2010/111527; WO 2012/109075; WO 2014/194127; WO 2015/112806; WO 2007/110344; WO 2009/071480; WO 2009/118411; WO 2010/031816; WO 2010/145998; WO 2011/092120; WO 2012/101032; WO 2012/139930; WO 2012/143248; WO 2012/152763; WO 2013/014039; WO

2013/102059; WO 2013/050448; WO 2013/050446; WO 2014/019908; WO 2014/072220; WO 2014/184069; and WO 2016/075224, all of which are hereby incorporated by reference in their entireties.

[0474] Further examples of kinase inhibitors include those described in, for example, WO 2016/081450; WO 2016/022569; WO 2016/011141; WO 2016/011144; WO 2016/011147; WO 2015/191667; WO 2012/101029; WO 2012/113774; WO 2015/191666; WO 2015/161277; WO 2015/161274; WO 2015/108992; WO 2015/061572; WO 2015/058129; WO 2015/057873; WO 2015/017528; WO/2015/017533; WO 2014/160521; and WO 2014/011900, each of which is hereby incorporated by reference in its entirety.

[0475] In some embodiments, a kinase inhibitor as provided herein may have activity against more than one kinase (i.e. may be a multikinase inhibitor). When more than one mechanism of action is recited in a method herein (e.g., ROS1, ALK, or TRK kinase inhibition), each of the compounds recited are structurally distinct from one another (e.g., the ROS1 inhibitor and the TRK inhibitor are not the same compound).

[0476] Accordingly, also provided herein is a method of treating cancer, comprising administering to a patient in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and the additional therapeutic agent are together effective in treating the cancer.

[0477] These additional therapeutic agents may be administered with one or more doses of the compound of Formula I, or a pharmaceutically acceptable salt or solvate thereof, or pharmaceutical composition thereof, as part of the same or separate dosage forms, via the same or different routes of administration, and/or on the same or different administration schedules according to standard pharmaceutical practice known to one skilled in the art.

[0478] Also provided herein is (i) a pharmaceutical combination for treating a cancer in a patient in need thereof, which comprises (a) a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, (b) at least one additional therapeutic agent (e.g., any of the exemplary additional therapeutic agents described herein or known in the art), and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or pharmaceutically acceptable salt or solvate thereof and of the additional therapeutic agent are together effective in treating the cancer; (ii) a pharmaceutical composition comprising such a combination; (iii) the use of such a combination for the preparation of a medicament for the treatment of cancer; and (iv) a commercial package or product comprising such a combination as a combined preparation for simultaneous, separate or sequential use; and to a method of treatment of cancer in a patient in need thereof. In some embodiments the patient is a human. In some embodiments, the cancer is a ROS1-associated cancer, e.g., a ROS1-associated cancer having one or more ROS1 inhibitor resistance mutations.

[0479] The term "pharmaceutical combination", as used herein, refers to a pharmaceutical therapy resulting from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term "fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., a chemotherapeutic agent), are both administered to a patient simultaneously in the form of a single composition or dosage. The term "non-fixed combination" means that a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof and at least one additional therapeutic agent (e.g., chemotherapeutic agent) are formulated as separate compositions or dosages such that they may be administered to a patient in need thereof simultaneously, concurrently or sequentially with variable intervening time limits (e.g., 1 hour, 1 day, 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months), wherein such administration provides effective levels of the two or more compounds in the body of the patient. These also apply to cocktail therapies, e.g. the administration of three or more active ingredients

[0480] Accordingly, also provided herein is a method of treating a cancer, comprising administering to a patient in need thereof a pharmaceutical combination for treating cancer which comprises (a) a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, (b) an additional therapeutic agent, and (c) optionally at least one pharmaceutically acceptable carrier for simultaneous, separate or sequential use for the treatment of cancer, wherein the amounts of the compound of Formula I or pharmaceutically acceptable salt or solvate thereof and the additional therapeutic agent are together effective in treating the cancer. In some embodiments, the compound of Formula I or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered simultaneously as separate dosages. In some embodiments, the compound of Formula I or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered as separate dosages sequentially in any order, in jointly therapeutically effective amounts, e.g. in daily or intermittently dosages. In some embodiments, the compound of Formula I or pharmaceutically acceptable salt or solvate thereof, and the additional therapeutic agent are administered simultaneously as a combined dosage. In some embodiments, the cancer is a ROS1-associated cancer. For example, a ROS1-associated cancer having one or more ROSlinhibitor resistance mutations.

[0481] Also provided herein is a method of treating a disease or disorder mediated by ROS1 in a patient in need of such treatment, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. In some embodiments, the disease or disorder mediated by ROS1 is a dysregulation of ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same. For example, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same includes one or more ROS1 inhibitor resistance mutations. A disease or disorder mediated by ROS1 can include any disease, disorder or condition that is directly or indirectly linked to expression or activity of ROS1, including overexpression and/or abnormal activity levels. In some embodiments, the disease is cancer

(e.g., a ROS1-associated cancer). In some embodiments, the cancer is any of the cancers or ROS1-associated cancers described herein.

[0482] Although the genetic basis of tumorigenesis may vary between different cancer types, the cellular and molecular mechanisms required for metastasis appear to be similar for all solid tumor types. During a metastatic cascade, the cancer cells lose growth inhibitory responses, undergo alterations in adhesiveness and produce enzymes that can degrade extracellular matrix components. This leads to detachment of tumor cells from the original tumor, infiltration into the circulation through newly formed vasculature, migration and extravasation of the tumor cells at favorable distant sites where they may form colonies. A number of genes have been identified as being promoters or suppressors of metastasis.

[0483] Accordingly, also provided herein are methods for inhibiting, preventing, aiding in the prevention, or decreasing the symptoms of metastasis of a cancer in a patient in need thereof, the method comprising administering to the patient a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof or a pharmaceutical composition thereof. Such methods can be used in the treatment of one or more of the cancers described herein. See, e.g., US Publication No. 2013/0029925; International Publication No. WO 2014/083567; and U.S. Pat. No. 8,568,998. In some embodiments, the cancer is a ROS1-associated cancer. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is used in combination with an additional therapy or another therapeutic agent, including a chemotherapeutic agent, such as a kinase inhibitor, for example, a first or second ROS1 kinase inhibitor.

[0484] The term "metastasis" is an art known term and means the formation of an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient, where the additional tumor includes the same or similar cancer cells as the primary tumor.

[0485] Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a patient having a ROS1-associated cancer that include: selecting, identifying, or diagnosing a patient as having a ROS1-associated cancer, and administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to the patient selected, identified, or diagnosed as having a ROS1-associated cancer. Also provided are methods of decreasing the risk of developing a metastasis or an additional metastasis in a patient having a ROS1-associated cancer that includes administering a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvent thereof to a patient having a ROS1-associated cancer. The decrease in the risk of developing a metastasis or an additional metastasis in a patient having a ROS1-associated cancer can be compared to the risk of developing a metastasis or an additional metastasis in the patient prior to treatment, or as compared to a patient or a population of patients having a similar or the same ROS1-associated cancer that has received no treatment or a different treatment. In some embodiments, the ROS1-associated cancer is a ROS1-associated cancer having one or more ROSlinhibitor resistance mutations.

[0486] The phrase "risk of developing a metastasis" means the risk that a subject or patient having a primary tumor will develop an additional tumor (e.g., a solid tumor) at a site distant from a primary tumor in a subject or patient over a set period of time, where the additional tumor includes the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing a metastasis in a subject or patient having a cancer are described herein.

[0487] The phrase "risk of developing additional metastases" means the risk that a subject or patient having a primary tumor and one or more additional tumors at sites distant from the primary tumor (where the one or more additional tumors include the same or similar cancer cells as the primary tumor) will develop one or more further tumors distant from the primary tumor, where the further tumors include the same or similar cancer cells as the primary tumor. Methods for reducing the risk of developing additional metastasis are described herein.

[0488] In some embodiments, the presence of one or more ROS1 inhibitor resistance mutations in a tumor causes the tumor to be more resistant to treatment with a first ROS1 inhibitor. Methods useful when a ROS1 inhibitor resistance mutation causes the tumor to be more resistant to treatment with a first ROS1 inhibitor are described below. For example, provided herein are methods of treating a subject having a cancer that include: identifying a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations; and administering to the identified subject a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with the first ROS1 inhibitor. Also provided are methods of treating a subject identified as having a cancer cell that has one or more ROS1 inhibitor resistance mutations that include administering to the subject a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N.

[0489] For example, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a compound of Formula I, or a pharmaceutically acceptable salt of solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance muta-

tions. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 2 and/or one or more ROS1 kinase protein point mutations, insertions, and/or deletions (e.g., one or more point mutations of Table 3 or Table 3a) in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations of Table 4; and (d) administering a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more of the fusion proteins SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROS1 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more of the ROS1 inhibitor resistance mutations L2026M, G2032R, or D2033N; and (d) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof selected from the group consisting of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0490] For example, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor, wherein the first ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a compound of Formula I, or a pharmaceutically acceptable salt of solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor, wherein the first ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 2 and/or one or more ROS1 kinase protein point mutations, insertions, and/or deletions (e.g., one or more point mutations of Table 3 or Table 3a) in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor, wherein the first ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations of Table 4; and (d) administering a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance

mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more of the fusion proteins SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROSlin a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a first ROS1 inhibitor, wherein the first ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more of the ROS1 inhibitor resistance mutations L2026M, G2032R, or D2033N; and (d) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof selected from the group consisting of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0491] As another example, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a second ROS1 inhibitor, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a second ROS1 inhibitor, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the first ROS1 inhibitor of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more of the fusion proteins SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROS1 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more of the ROS1 inhibitor resistance mutations L2026M, G2032R, or D2033N; and (d) administering a second ROS1 inhibitor, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0492] In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt of solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a second ROS1 inhibitor, wherein the second ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and meses-

tinib, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering a second ROS1 inhibitor, wherein the second ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more fusion proteins of Table 2 and/or one or more ROS1 kinase protein point mutations, insertions, and/or deletions (e.g., one or more of the point mutations of Table 3 or Table 3a) in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations of Table 4; and (d) administering a second ROS1 inhibitor, wherein the second ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more of the fusion proteins SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROS1 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more of the ROS1 inhibitor resistance mutations L2026M, G2032R, or D2033N; and (d) administering a second ROS1 inhibitor, wherein the second ROS1 inhibitor is selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib, as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (e) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations.

[0493] Also, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second ROS1 inhibitor, a second compound of Formula I, an ALK inhibitor, a TRK inhibitor, or a pharmaceutically acceptable salt thereof) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations. In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting a dysregulation of a ROS1 gene, a ROS1 kinase, or the expression or activity or level of any of the same in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second ROS1 inhibitor, a second compound of Formula I, an ALK inhibitor, a TRK inhibitor, or a pharmaceutically acceptable salt thereof) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations.

[0494] In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more ROS1 fusion proteins of Table 2 and/or one or more ROS1 kinase protein point mutations, insertions, and/or deletions (e.g., one or more of the point mutations of

Table 3 or Table 3a) in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof selected from the group consisting of a compound of Formula I selected from Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations of Table 4; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second ROS1 inhibitor, a second compound of Formula I, an ALK inhibitor, a TRK inhibitor, or a pharmaceutically acceptable salt thereof) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations. In some embodiments, a second ROS1 inhibitor selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib is administered in step (d). In some embodiments, provided herein are methods for treating a ROS1-associated cancer in a subject in need of such treatment, the method comprising (a) detecting one or more of the fusion proteins SLC34A2-ROS1, CD74-ROS1, EZR-ROS1, TPM3-ROS1, or SDC4-ROS1 in a sample from the subject; and (b) administering to the subject a therapeutically effective amount of a compound of Formula I selected Example No. 2, 3, 7, 9, 14, 19, 20, 22, 33-A, 33-B, 35, 36, and 45, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the methods further comprise (after (b)) (c) determining whether a cancer cell in a sample obtained from the subject has one or more of the ROS1 inhibitor resistance mutations L2026M, G2032R, or D2033N; and (d) administering additional doses of the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof of step (b) to the subject as a monotherapy or in conjunction with another anticancer agent (e.g., a second ROS1 inhibitor, a second compound of Formula I, an ALK inhibitor, a TRK inhibitor, or a pharmaceutically acceptable salt thereof) or anticancer therapy (e.g., surgery or radiation) if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations. In some embodiments, a second ROS1 inhibitor selected from the group consisting of alectinib, brigatinib, cabozantinib, ceritinib, crizotinib, entrectinib, foretinib, lorlatinib, and mesestinib is administered in step (d).

[0495] Also provided are methods of selecting a treatment for a subject having a cancer that include: identifying a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations; and selecting a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with a first ROS1 inhibitor. In some embodiments, the compound of Formula I or a pharmaceutically acceptable salt or solvate thereof is administered in combination with the first ROS1 inhibitor. Also provided are methods of selecting a treatment for a subject having a cancer that include: selecting a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof for a subject identified as having a cancer cell that has one or more ROS1 inhibitor resistance mutations. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a first ROS1 inhibitor as a monotherapy that include: identifying a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations; and selecting the identified subject for a treatment that includes a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. Also provided are methods of selecting a subject having a cancer for a treatment that does not include a first ROS1 inhibitor as a monotherapy that include: selecting a subject identified as having a cancer cell that has one or more ROS1 inhibitor resistance mutations for a treatment that includes administration of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. In some embodiments, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N.

[0496] Also provided are methods of determining the likelihood that a subject having a cancer (e.g., a ROS1-associated cancer) will have a positive response to treatment with a first ROS1 inhibitor as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and determining that a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations has a decreased likelihood of having a positive response (i.e. an increased likelihood of having a negative response) to treatment with a first ROS1 inhibitor as a monotherapy. Also provided are methods of determining the likelihood that a subject having a cancer (e.g., a ROS1-associated cancer) will have a positive response to treatment with a first ROS1 inhibitor as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and determining that a subject not having a cancer cell that has one or more ROS1 inhibitor resistance mutations has an increased likelihood of having a positive response to treatment with a first ROS1 inhibitor as a monotherapy as compared to a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a first ROS1 inhibitor as a monotherapy in a subject having cancer that include: determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and determining that treatment with a first ROS1 inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more ROS1 inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a first ROS1 inhibitor as a monotherapy in a subject having cancer that include: determining that treatment with a first ROS1 inhibitor as a monotherapy is less likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more ROS1 inhibitor resistance mutations. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1

inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N.

[0497] Also provided are methods of treating a subject having a cancer that include: (a) administering a first ROS1 inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (d) administering additional doses of the first ROS1 inhibitor of step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ROS1 inhibitor of step (a), the subject can also be administered another anticancer agent (e.g., a second ROS1 inhibitor, an ALK inhibitor, a TRK inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor (e.g., a second ROS1 inhibitor). In some embodiments of step (c), another anticancer agent can be the first ROS1 inhibitor administered in step (a). In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2032, e.g., L2026M, G2032R, or D2033N.

[0498] Also provided are methods of treating a subject having a cancer that include: (a) administering a first ALK inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has one or more ROS1 inhibitor resistance mutations; or (d) administering additional doses of the first ALK inhibitor of step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ALK inhibitor of step (a), the subject can also be administered another anticancer agent (e.g., a second ALK inhibitor, a first ROS1 inhibitor, a TRK inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ALK inhibitor (e.g., a second ALK inhibitor). In some embodiments of step (c), another anticancer agent can be the first ALK inhibitor administered in step (a). In some embodiments of step (c), another anticancer agent can be another ROS1 inhibitor. In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N.

[0499] Also provided are methods of treating a subject having a cancer that include: (a) administering a first TRK inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has one or more ROS1 inhibitor resistance mutations; or (d) administering additional doses of the first TRK inhibitor of step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first TRK inhibitor of step (a), the subject can also be administered another anticancer agent (e.g., a second TRK inhibitor, a first ROS1 inhibitor, an ALK inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another TRK inhibitor (e.g., a second TRK inhibitor). In some embodiments of step (c), another anticancer agent can be the first TRK inhibitor administered in step (a). In some embodiments of step (c), another anticancer agent can be another ROS1 inhibitor. In some embodiments, the dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same confers increased resistance to a cancer cell or tumor to treatment with the first TRK inhibitor. In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N.

[0500] Also provided are methods of treating a subject having a cancer that include: (a) administering a first ROS1 inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) administering a second ROS1 inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (d) administering additional doses of the first ROS1 inhibitor step (a) to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ROS1 inhibitor of step (a), the subject can also be administered another anticancer agent. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance

mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof).

[0501] Also provided are methods of treating a subject having a cancer (e.g., a ROS1-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ROS1 inhibitor, has one or more ROS1 inhibitor resistance mutations; and (b) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) administering additional doses of the first ROS1 inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ROS1 inhibitor previously administered to the subject, the subject can also be administered another anticancer agent (e.g., a second ROS1 inhibitor, an ALK inhibitor, a TRK inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor (e.g., a second ROS1 inhibitor). In some embodiments of step (b), another anticancer agent can be the first ROS1 inhibitor administered in step (a).

[0502] Also provided are methods of treating a subject having a cancer (e.g., a ROS1-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ALK inhibitor has one or more ROS1 inhibitor resistance mutations; and (b) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell having one or more ROS1 inhibitor resistance mutations; or (c) administering additional doses of the first ALK inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ALK inhibitor previously administered to the subject, the subject can also be administered another anticancer agent (e.g., a second ALK inhibitor, a TRK inhibitor, a first ROS1 inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiment, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is can be another ALK inhibitor (e.g., a second ALK inhibitor). In some embodiments of step (b), another anticancer agent can be the first ALK inhibitor administered in step (a). In some embodiments of step (b), another anticancer agent can be another ROS1 inhibitor.

[0503] Also provided are methods of treating a subject having a cancer (e.g., a ROS1-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first TRK inhibitor is associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same; and (b) administering a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) administering additional doses of the first TRK inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first TRK inhibitor previously administered to the subject, the subject can also be administered another anticancer agent (e.g., a second TRK inhibitor, an ALK inhibitor, a first ROS1 inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is can be another TRK inhibitor (e.g., a second TRK inhibitor). In some embodiments of step (b), another anticancer agent can be the first TRK inhibitor administered in step (a). In some embodiments of step (b), another anticancer agent can be another ROS1 inhibitor.

[0504] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ROS1 inhibitor has one or more ROS1 inhibitor resistance mutations; and (b) administering a second ROS1 inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) administering additional doses of the first ROS1 inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ROS1 inhibitor previously administered to the subject, the subject can also be administered another anticancer agent. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations

include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments of (b), another anticancer agent can be the first ROS1 inhibitor administered in step (a).

[0505] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ALK inhibitor has one or more ROS1 inhibitor resistance mutations; and (b) administering a ROS1 inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) administering additional doses of the first ALK inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first ALK inhibitor previously administered to the subject, the subject can also be administered another anticancer agent. In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be a ROS1 inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments of (b), another anticancer agent can be the first ALK inhibitor administered in step (a).

[0506] Also provided are methods of treating a subject having a cancer that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first TRK inhibitor is associated with a dysregulation of a ROS1 gene, a ROS1 kinase, or expression or activity or level of any of the same; and (b) administering a ROS1 inhibitor as a monotherapy or in conjunction with another anticancer agent to the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) administering additional doses of the first TRK inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where the subject is administered additional doses of the first TRK inhibitor previously administered to the subject, the subject can also be administered another anticancer agent. In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be a ROS1 inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments of (b), another anticancer agent can be the first TRK inhibitor administered in step (a).

[0507] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering a first ROS1 inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (d) selecting additional doses of the first ROS1 inhibitor of step (a) for the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, when additional doses of the first ROS1 inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor (e.g., a second ROS1 inhibitor). In some embodiments of step (c), another ROS1 inhibitor can be the first ROS1 inhibitor administered in step (a).

[0508] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering a first ALK inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (d) selecting additional doses of the first ALK inhibitor of step (a) for the subject if the subject has a cancer cell that does not have has one or more ROS1 inhibitor resistance mutations. In some embodiments, when additional doses of the first ALK inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments of step (c), another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor. In some embodiments of step (c), another anticancer agent is the first ALK inhibitor administered in step (a).

[0509] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering

one or more doses of a first TRK inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (d) selecting additional doses of the first TRK inhibitor of step (a) for the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, when additional doses of the first TRK inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments of step (c), another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent can be another ROS1 inhibitor. In some embodiments of step (c), another anticancer agent is the first TRK inhibitor administered in step (a).

[0510] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) administering a first ROS1 inhibitor to the subject for a period of time (e.g., 1 month, 2 months, 3 months, 6 months, 9 months, 1 year); (b) after (a), determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and (c) selecting a second ROS1 inhibitor as a monotherapy or in conjunction with another anticancer agent if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (d) selecting additional doses of the first ROS1 inhibitor of step (a) for the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, when additional doses of the first ROS1 inhibitor of step (a) are selected for the subject, the method can further include selecting doses of another anticancer agent for the subject. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is another ROS1 inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, another ROS1 can be the first ROS1 inhibitor administered in step (a).

[0511] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ROS1 inhibitor has one or more ROS1 inhibitor resistance mutations; (b) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) selecting additional doses of the first ROS1 inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, when additional doses of the first ROS1 inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof) for the subject. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is another ROS1 inhibitor (e.g., a second ROS1 inhibitor). In some embodiments of step (c), another ROS1 inhibitor can be the first ROS1 inhibitor administered in step (a).

[0512] Also provided are methods of selecting a treatment for a subject having a cancer (e.g., a ROS1-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ALK inhibitor has one or more ROS1 inhibitor resistance mutations; and (b) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) selecting additional doses of the first ALK inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where additional doses of the first ALK inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a second ALK inhibitor, a TRK inhibitor, a first ROS1 inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is can be another ALK inhibitor (e.g., a second ALK inhibitor). In some embodiments of step (b), another anticancer agent can be the first ALK inhibitor administered in step (a). In some embodiments of step (b), another anticancer agent can be another ROS1 inhibitor.

[0513] Also provided are methods of selecting a treatment for a subject having a cancer (e.g., a ROS1-associated cancer) that include: (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first TRK inhibitor has one or

more ROS1 inhibitor resistance mutations; and (b) selecting a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) selecting additional doses of the first TRK inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, where additional doses of the first TRK inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a second TRK inhibitor, an ALK inhibitor, a first ROS1 inhibitor, or a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, the ROS1 inhibitor resistance mutation includes one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, a ROS1 inhibitor resistance mutation can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is can be another TRK inhibitor (e.g., a second TRK inhibitor). In some embodiments of step (b), another anticancer agent can be the first TRK inhibitor administered in step (a). In some embodiments of step (b), another anticancer agent can be another ROS1 inhibitor.

[0514] Also provided are methods of selecting a treatment for a subject having a cancer that include (a) determining whether a cancer cell in a sample obtained from a subject having a cancer and previously administered a first ROS1 inhibitor has one or more ROS1 inhibitor resistance mutations; (b) selecting a second ROS1 inhibitor as a monotherapy or in conjunction with another anticancer agent for the subject if the subject has a cancer cell that has one or more ROS1 inhibitor resistance mutations; or (c) selecting additional doses of the first ROS1 inhibitor previously administered to the subject if the subject has a cancer cell that does not have one or more ROS1 inhibitor resistance mutations. In some embodiments, when additional doses of the first ROS1 inhibitor previously administered to the subject are selected for the subject, the method can further include selecting doses of another anticancer agent (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof) for the subject. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N. In some embodiments, another anticancer agent is any anticancer agent known in the art. For example, another anticancer agent is another ROS1 inhibitor (e.g., a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof). In some embodiments, another ROS1 can be the first ROS1 inhibitor administered in step (a).

[0515] Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a first ROS1 inhibitor that include: determining whether a cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and identifying a subject having a cell that has one or more ROS1 inhibitor resistance mutations as having an increased likelihood of developing a cancer that has some resistance to the first ROS1 inhibitor. Also provided are methods of determining a subject's risk for developing a cancer that has some resistance to a first ROS1 inhibitor that include: identifying a subject having a cell that has one or more ROS1 inhibitor resistance mutations as having an increased likelihood of developing a cancer that has some resistance to the first ROS1 inhibitor. Also provided are methods of determining the presence of a cancer that has some resistance to a first ROS1 inhibitor that include: determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and determining that the subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations has a cancer that has some resistance to the first ROS1 inhibitor. Also provided are methods of determining the presence of a cancer that has some resistance to a first ROS1 inhibitor in a subject that include: determining that a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations has a cancer that has some resistance to the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations confer increased resistance to a cancer cell or tumor to treatment with the first ROS1 inhibitor. In some embodiments, the one or more ROS1 inhibitor resistance mutations include one or more ROS1 inhibitor resistance mutations listed in Table 4. For example, the one or more ROS1 inhibitor resistance mutations can include a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N.

[0516] In some embodiments of any of the methods described herein, a ROS1 inhibitor resistance mutation that confers increased resistance to a cancer cell or tumor to treatment with a first ROS1 inhibitor can be any of the ROS1 inhibitor resistance mutations listed in Table 4 (e.g., a substitution at one or more of amino acid positions 2026, 2032, or 2033, e.g., L2026M, G2032R, or D2033N).

[0517] Also provided are methods of determining the likelihood that a subject having a cancer will have a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy that include: determining whether a cancer cell in a sample obtained from the subject has one or more ROS1 inhibitor resistance mutations; and determining that the subject having the cancer cell that has one or more ROS1 inhibitor resistance mutations has an increased likelihood of having a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy. Also provided are methods of determining the likelihood that a subject having cancer will have a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy that include: determining that a subject having a cancer cell that has one or more ROS1 inhibitor resistance mutations has an increased likelihood of having a positive response to treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy. Also provided are methods of predicting the efficacy of treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy in a subject having cancer that include: determining whether a cancer cell in a sample

obtained from the subject has one or more ROS1 inhibitor resistance mutations; and determining that treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy is likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more ROS1 inhibitor resistance mutations. Also provided are methods of predicting the efficacy of treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy in a subject having cancer that include: determining that treatment with a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof as a monotherapy is likely to be effective in a subject having a cancer cell in a sample obtained from the subject that has one or more ROS1 inhibitor resistance mutations.

[0518] Methods of determining the level of resistance of a cancer cell or a tumor to a ROS1 inhibitor (e.g., any of the ROS1 inhibitors described herein or known in the art) can be determined using methods known in the art. For example, the level of resistance of a cancer cell to a ROS1 inhibitor can be assessed by determining the IC_{50} of a ROS1 inhibitor (e.g., any of the ROS1 inhibitors described herein or known in the art) on the viability of a cancer cell. In other examples, the level of resistance of a cancer cell to a ROS1 inhibitor can be assessed by determining the growth rate of the cancer cell in the presence of a ROS1 inhibitor (e.g., any of the ROS1 inhibitors described herein). In other examples, the level of resistance of a tumor to a ROS1 inhibitor can be assessed by determining the mass or size of one or more tumors in a subject over time during treatment with a ROS1 inhibitor (e.g., any of the ROS1 inhibitors described herein). In other examples, the level of resistance of a cancer cell or a tumor to a ROS1 inhibitor can be indirectly assessed by determining the activity of a ROS1 kinase including one or more of the ROS1 inhibitor resistance mutations (i.e., the same ROS1 kinase expressed in a cancer cell or a tumor in a subject). The level of resistance of a cancer cell or tumor having one or more ROS1 inhibitor resistance mutations to a ROS1 inhibitor is relative to the level of resistance in a cancer cell or tumor that does not have one or more ROS1 inhibitor resistance mutations (e.g., a cancer cell or tumor that does not have the same ROS1 inhibitor resistance mutations, a cancer cell or a tumor that does not have any ROS1 inhibitor resistance mutations, or a cancer cell or a tumor that expresses a wildtype ROS1 protein). For example, the determined level of resistance of a cancer cell or a tumor having one or more ROS1 inhibitor resistance mutations can be greater than about 1%, greater than about 2%, greater than about 3%,greater than about 4%, greater than about 5%, greater than about 6%, greater than about 7%, greater than about 8%, greater than about 9%, greater than about 10%, greater than about 11%, greater than about 12%, greater than about 13%, greater than about 14%, greater than about 15%, greater than about 20%, greater than about 25%, greater than about 30%, greater than about 35%, greater than about 40%, greater than about 45%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, greater than about 150%, greater than about 160%, greater than about 170%, greater than about 180%, greater than about 190%, greater than about 200%, greater than about 210%, greater than about 220%, greater than about 230%, greater than about 240%, greater than about 250%, greater than about 260%, greater than about 270%, greater than about 280%, greater than about 290%, or greater than about 300% of the level of resistance in a cancer cell or tumor that does not have one or more ROS1 inhibitor resistance mutations (e.g., a cancer cell or tumor that does not have the same ROS1 inhibitor resistance mutations, a cancer cell or a tumor that does not have any ROS1 inhibitor resistance mutations, or a cancer cell or a tumor that expresses a wildtype ROS1 protein).

[0519] Also provided is a method for inhibiting ROS1 kinase activity in a cell, comprising contacting the cell with a compound of Formula I. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to a subject having a cell having ROS1 kinase activity. In some embodiments, the cell is a cancer cell. In some embodiments, the cancer cell is any cancer as described herein. In some embodiments, the cancer cell is a ROS1-associated cancer cell.

[0520] Also provided is a method for inhibiting ROS1 kinase activity in a mammalian cell, comprising contacting the cell with a compound of Formula I. In some embodiments, the contacting is in vitro. In some embodiments, the contacting is in vivo. In some embodiments, the contacting is in vivo, wherein the method comprises administering an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof to a mammal having a cell having ROSlkinase activity. In some embodiments, the mammalian cell is a mammalian cancer cell. In some embodiments, the mammalian cancer cell is any cancer as described herein. In some embodiments, the mammalian cancer cell is a ROS1-associated cancer cell.

[0521] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an in vitro system or an in vivo system. For example, "contacting" a ROS1 kinase with a compound provided herein includes the administration of a compound provided herein to an individual or patient, such as a human, having a ROS1 kinase, as well as, for example, introducing a compound provided herein into a sample containing a cellular or purified preparation containing the ROS1 kinase.

[0522] Also provided herein is a method of inhibiting cell proliferation, in vitro or in vivo, the method comprising contacting a cell with an effective amount of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition thereof as defined herein

[0523] The phrase "effective amount" means an amount of compound that, when administered to a patient in need of such treatment, is sufficient to (i) treat a ROS1 kinase-associated disease or disorder, (ii) attenuate, ameliorate, or eliminate one or more symptoms of the particular disease, condition, or disorder, or (iii) delay the onset of one or more symptoms of the particular disease, condition, or disorder described herein. The amount of a compound of Formula I that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the patient in need of treatment, but can nevertheless be routinely determined by one skilled in the art.

[0524] When employed as pharmaceuticals, the compounds of Formula I can be administered in the form of pharmaceutical compositions. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery), pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Oral administration can include a dosage form formulated for once-daily or twice-daily (BID) administration. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable

[0525] Also provided herein are pharmaceutical compositions which contain, as the active ingredient, a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, in combination with one or more pharmaceutically acceptable carriers (excipients). In some embodiments, the composition is suitable for topical administration. In making the compositions provided herein, the active ingredient is typically mixed with an excipient, diluted by an excipient or enclosed within such a carrier in the form of, for example, a capsule, sachet, paper, or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders. In some embodiments, the composition is formulated for oral administration. In some embodiments, the composition is formulated as a tablet or capsule.

[0526] The compositions comprising a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof can be formulated in a unit dosage form, each dosage containing from about 5 to about 1,000 mg (1 g), more usually about 100 mg to about 500 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other patients, each unit containing a predetermined quantity of active material (i.e., a compound for Formula I as provided herein) calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0527] In some embodiments, the compositions provided herein contain from about 5 mg to about 50 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 5 mg to about 10 mg, about 10 mg to about 15 mg, about 15 mg to about 20 mg, about 20 mg to about 25 mg, about 25 mg to about 30 mg, about 30 mg to about 35 mg, about 35 mg to about 40 mg, about 40 mg to about 45 mg, or about 45 mg to about 50 mg of the active ingredient.

[0528] In some embodiments, the compositions provided herein contain from about 50 mg to about 500 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 50 mg to about 100 mg, about 100 mg to about 150 mg, about 150 mg to about 200 mg, about 200 mg to about 250 mg, about 250 mg to about 300 mg, about 350 mg to about 400 mg, or about 450 mg to about 500 mg of the active ingredient.

[0529] In some embodiments, the compositions provided herein contain from about 500 mg to about 1,000 mg of the active ingredient. One having ordinary skill in the art will appreciate that this embodies compounds or compositions containing about 500 mg to about 550 mg, about 550 mg to about 600 mg, about 600 mg to about 650 mg, about 650 mg to about 700 mg, about 700 mg to about 750 mg, about 750 mg to about 800 mg, about 800 mg to about 850 mg, about 850 mg to about 900 mg, about 900 mg to about 950 mg, or about 950 mg to about 1,000 mg of the active ingredient.

[0530] The active compound may be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0531] Provided herein are pharmaceutical kits useful, for example, in the treatment of RET-associated diseases or disorders, such as cancer or irritable bowel syndrome (IBS), which include one or more containers containing a pharmaceutical composition comprising a therapeutically effective amount of a compound provided herein. Such kits can further include, if desired, one or more of various conventional pharmaceutical kit components, such as, for example, containers with one or more pharmaceutically acceptable carriers, additional containers, etc., as will be readily apparent to those skilled in the art. Instructions, either as inserts or as labels, indicating quantities of the components to be administered, guidelines for administration, and/or guidelines for mixing the components, can also be included in the kit.

[0532] One skilled in the art will recognize that, both in vivo and in vitro trials using suitable, known and generally accepted cell and/or animal models are predictive of the ability of a test compound to treat or prevent a given disorder.

[0533] One skilled in the art will further recognize that human clinical trials including first-in-human, dose ranging and efficacy trials, in healthy patients and/or those suffering from a given disorder, may be completed according to methods well known in the clinical and medical arts.

EXAMPLES

Example A. Inhibition of ROS1 Kinase

[0534] The potency of a compound inhibiting wild type and exemplary mutant ROS1 kinases was determined using CisBio's HTRF Kinease-TK assay technology. The assays

contained 5 nM wild type ROS1 (SignalChem—Cat. No. R14-11G), 5 nM G2032R ROS1 (SignalChem—Cat. No. R14-12BG), 5 nM L2026M ROS1 (Array Biopharma, p 1965), or 5 nM D2033N ROS1 (Array Biopharma, p 1994). Each kinase is incubated with 250 nM TK-substrate biotin (CisBio, Cat. No. 62TKOPEC) and 1 mM ATP along with test compound in a buffer consisting of 25 mM MOPS [pH 7.4], 5 mM $MgCl_2$, 0.005% Triton X-100, and 2% DMSO in a volume of 8 μL. Compounds were prepared in a four-fold serial dilution in DMSO and added to the assay to give the appropriate final concentration. After a 120-minute incubation at 22° C., the reaction was quenched by adding 8 μL of quench solution containing 31.3 nM Sa-XL665 and 1×TK-Ab-Cryptate in HTRF detection buffer (CisBio, Cat. No. 62TKOPEC). After a 1 hour incubation at 22° C., the extent of reaction was determined using a PerkinElmer EnVision multimode plate reader via HTRF dual wavelength detection, and the percent of control (POC) was calculated using a ratiometric emission factor. 100 POC is determined using no test compound and 0 POC is determined in the absence of enzyme. The POC values are fit to a 4-parameter logistic curve and the IC_{50} value is calculated based on the point at which the curve crosses 50 POC.

[0535] Table 9 provides averaged IC_{50} values for compounds tested in this assay.

TABLE 9

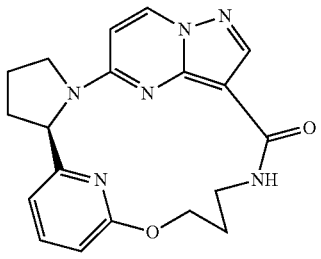
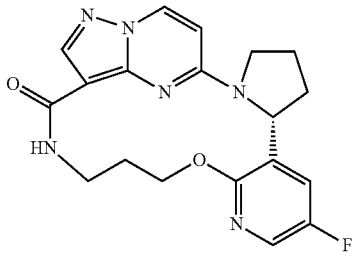
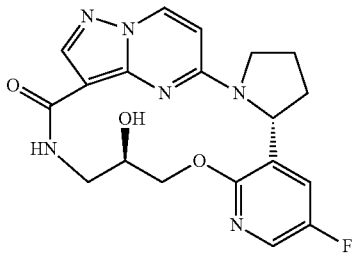
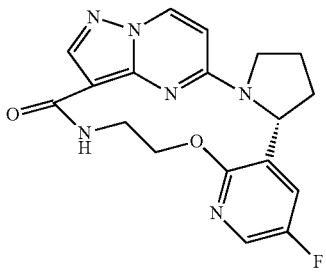
Compound No.	Structure	ROS1 wT IC_{50} (nM)	ROS1 G2032R IC_{50} (nM)	ROS1 L2026M IC_{50} (nM)	ROS1 D2033N IC_{50} (nM)
2		80.3	1062.2	67.0	11.9
3		1.2	9.4	1.2	0.3
7		3.1	29.2	2.9	0.6
9		9.2	98.6	10.2	1.7

TABLE 9-continued

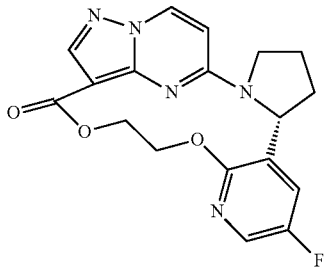
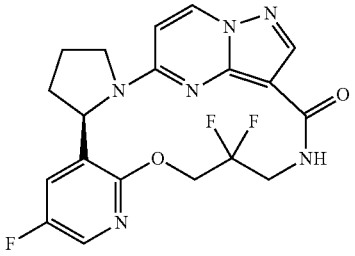
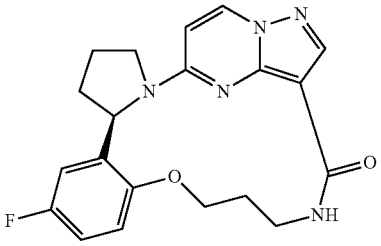
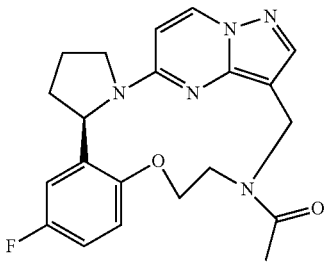
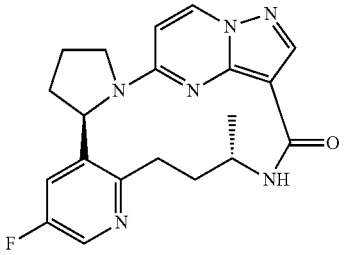
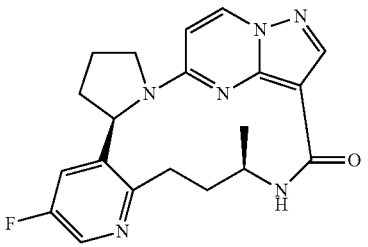
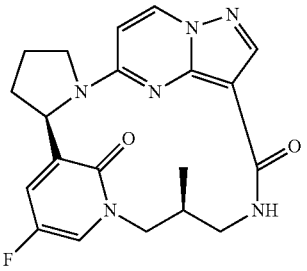
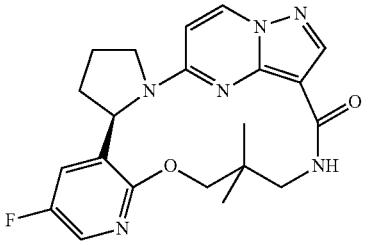
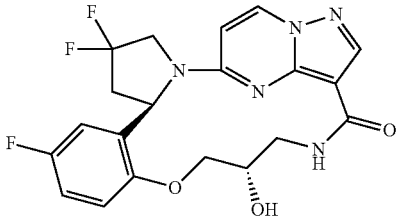
Compound No.	Structure	ROS1 wT IC_{50} (nM)	ROS1 G2032R IC_{50} (nM)	ROS1 L2026M IC_{50} (nM)	ROS1 D2033N IC_{50} (nM)
14		28.9	107.3	30.3	7.6
19		2.4	14.4	2.4	1.2
20		2.5	21.6	2.2	2.8
22		330.6	3980.2	712.9	396.9
33-A		19.2	157.1	19.6	14.3

TABLE 9-continued

Compound No.	Structure	ROS1 wT IC_{50} (nM)	ROS1 G2032R IC_{50} (nM)	ROS1 L2026M IC_{50} (nM)	ROS1 D2033N IC_{50} (nM)
33-B		2.7	20.4	3.6	0.5
35		779.1	4931.9	589.3	260.1
36		0.7	6.5	0.5	0.2
45		6.1	113.6	4.6	16.8

Other Embodiments

[0536] It is to be understood that while the disclosure has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

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            20                  25                  30

Cys Leu Lys Ser Cys Val Thr Asn Leu Gly Gln Gln Leu Asp Leu Gly
        35                  40                  45

Thr Pro His Asn Leu Ser Glu Pro Cys Ile Gln Gly Cys His Phe Trp
    50                  55                  60

Asn Ser Val Asp Gln Lys Asn Cys Ala Leu Lys Cys Arg Glu Ser Cys
65                  70                  75                  80

Glu Val Gly Cys Ser Ser Ala Glu Gly Ala Tyr Glu Glu Glu Val Leu
                85                  90                  95

Glu Asn Ala Asp Leu Pro Thr Ala Pro Phe Ala Ser Ser Ile Gly Ser
            100                 105                 110

His Asn Met Thr Leu Arg Trp Lys Ser Ala Asn Phe Ser Gly Val Lys
        115                 120                 125

Tyr Ile Ile Gln Trp Lys Tyr Ala Gln Leu Leu Gly Ser Trp Thr Tyr
    130                 135                 140

Thr Lys Thr Val Ser Arg Pro Ser Tyr Val Val Lys Pro Leu His Pro
145                 150                 155                 160

Phe Thr Glu Tyr Ile Phe Arg Val Val Trp Ile Phe Thr Ala Gln Leu
                165                 170                 175

Gln Leu Tyr Ser Pro Pro Ser Pro Ser Tyr Arg Thr His Pro His Gly
            180                 185                 190

Val Pro Glu Thr Ala Pro Leu Ile Arg Asn Ile Glu Ser Ser Ser Pro
        195                 200                 205

Asp Thr Val Glu Val Ser Trp Asp Pro Pro Gln Phe Pro Gly Gly Pro
    210                 215                 220

Ile Leu Gly Tyr Asn Leu Arg Leu Ile Ser Lys Asn Gln Lys Leu Asp
225                 230                 235                 240

Ala Gly Thr Gln Arg Thr Ser Phe Gln Phe Tyr Ser Thr Leu Pro Asn
                245                 250                 255

Thr Ile Tyr Arg Phe Ser Ile Ala Ala Val Asn Glu Val Gly Glu Gly
            260                 265                 270

Pro Glu Ala Glu Ser Ser Ile Thr Thr Ser Ser Ser Ala Val Gln Gln
        275                 280                 285

Glu Glu Gln Trp Leu Phe Leu Ser Arg Lys Thr Ser Leu Arg Lys Arg
    290                 295                 300

Ser Leu Lys His Leu Val Asp Glu Ala His Cys Leu Arg Leu Asp Ala
305                 310                 315                 320

Ile Tyr His Asn Ile Thr Gly Ile Ser Val Asp Val His Gln Gln Ile
                325                 330                 335

Val Tyr Phe Ser Glu Gly Thr Leu Ile Trp Ala Lys Lys Ala Ala Asn
            340                 345                 350

Met Ser Asp Val Ser Asp Leu Arg Ile Phe Tyr Arg Gly Ser Gly Leu
        355                 360                 365

Ile Ser Ser Ile Ser Ile Asp Trp Leu Tyr Gln Arg Met Tyr Phe Ile
    370                 375                 380

Met Asp Glu Leu Val Cys Val Cys Asp Leu Glu Asn Cys Ser Asn Ile
385                 390                 395                 400

Glu Glu Ile Thr Pro Pro Ser Ile Ser Ala Pro Gln Lys Ile Val Ala
                405                 410                 415
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Asp Ser Tyr Asn Gly Tyr Val Phe Tyr Leu Leu Arg Asp Gly Ile Tyr
            420                 425                 430

Arg Ala Asp Leu Pro Val Pro Ser Gly Arg Cys Ala Glu Ala Val Arg
        435                 440                 445

Ile Val Glu Ser Cys Thr Leu Lys Asp Phe Ala Ile Lys Pro Gln Ala
    450                 455                 460

Lys Arg Ile Ile Tyr Phe Asn Asp Thr Ala Gln Val Phe Met Ser Thr
465                 470                 475                 480

Phe Leu Asp Gly Ser Ala Ser His Leu Ile Leu Pro Arg Ile Pro Phe
                485                 490                 495

Ala Asp Val Lys Ser Phe Ala Cys Glu Asn Asn Asp Phe Leu Val Thr
            500                 505                 510

Asp Gly Lys Val Ile Phe Gln Gln Asp Ala Leu Ser Phe Asn Glu Phe
        515                 520                 525

Ile Val Gly Cys Asp Leu Ser His Ile Glu Glu Phe Gly Phe Gly Asn
    530                 535                 540

Leu Val Ile Phe Gly Ser Ser Ser Gln Leu His Pro Leu Pro Gly Arg
545                 550                 555                 560

Pro Gln Glu Leu Ser Val Leu Phe Gly Ser His Gln Ala Leu Val Gln
                565                 570                 575

Trp Lys Pro Pro Ala Leu Ala Ile Gly Ala Asn Val Ile Leu Ile Ser
            580                 585                 590

Asp Ile Ile Glu Leu Phe Glu Leu Gly Pro Ser Ala Trp Gln Asn Trp
        595                 600                 605

Thr Tyr Glu Val Lys Val Ser Thr Gln Asp Pro Pro Glu Val Thr His
    610                 615                 620

Ile Phe Leu Asn Ile Ser Gly Thr Met Leu Asn Val Pro Glu Leu Gln
625                 630                 635                 640

Ser Ala Met Lys Tyr Lys Val Ser Val Arg Ala Ser Ser Pro Lys Arg
                645                 650                 655

Pro Gly Pro Trp Ser Glu Pro Ser Val Gly Thr Thr Leu Val Pro Ala
            660                 665                 670

Ser Glu Pro Pro Phe Ile Met Ala Val Lys Glu Asp Gly Leu Trp Ser
        675                 680                 685

Lys Pro Leu Asn Ser Phe Gly Pro Gly Glu Phe Leu Ser Ser Asp Ile
    690                 695                 700

Gly Asn Val Ser Asp Met Asp Trp Tyr Asn Asn Ser Leu Tyr Tyr Ser
705                 710                 715                 720

Asp Thr Lys Gly Asp Val Phe Val Trp Leu Leu Asn Gly Thr Asp Ile
                725                 730                 735

Ser Glu Asn Tyr His Leu Pro Ser Ile Ala Gly Ala Gly Ala Leu Ala
            740                 745                 750

Phe Glu Trp Leu Gly His Phe Leu Tyr Trp Ala Gly Lys Thr Tyr Val
        755                 760                 765

Ile Gln Arg Gln Ser Val Leu Thr Gly His Thr Asp Ile Val Thr His
    770                 775                 780

Val Lys Leu Leu Val Asn Asp Met Val Val Asp Ser Val Gly Gly Tyr
785                 790                 795                 800

Leu Tyr Trp Thr Thr Leu Tyr Ser Val Glu Ser Thr Arg Leu Asn Gly
                805                 810                 815
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Glu Ser Ser Leu Val Leu Gln Thr Gln Pro Trp Phe Ser Gly Lys Lys
            820                 825                 830

Val Ile Ala Leu Thr Leu Asp Leu Ser Asp Gly Leu Leu Tyr Trp Leu
        835                 840                 845

Val Gln Asp Ser Gln Cys Ile His Leu Tyr Thr Ala Val Leu Arg Gly
    850                 855                 860

Gln Ser Thr Gly Asp Thr Thr Ile Thr Glu Phe Ala Ala Trp Ser Thr
865                 870                 875                 880

Ser Glu Ile Ser Gln Asn Ala Leu Met Tyr Tyr Ser Gly Arg Leu Phe
                885                 890                 895

Trp Ile Asn Gly Phe Arg Ile Ile Thr Thr Gln Glu Ile Gly Gln Lys
            900                 905                 910

Thr Ser Val Ser Val Leu Glu Pro Ala Arg Phe Asn Gln Phe Thr Ile
        915                 920                 925

Ile Gln Thr Ser Leu Lys Pro Leu Pro Gly Asn Phe Ser Phe Thr Pro
    930                 935                 940

Lys Val Ile Pro Asp Ser Val Gln Glu Ser Ser Phe Arg Ile Glu Gly
945                 950                 955                 960

Asn Ala Ser Ser Phe Gln Ile Leu Trp Asn Gly Pro Pro Ala Val Asp
                965                 970                 975

Trp Gly Val Val Phe Tyr Ser Val Glu Phe Ser Ala His Ser Lys Phe
            980                 985                 990

Leu Ala Ser Glu Gln His Ser Leu  Pro Val Phe Thr Val  Glu Gly Leu
        995                 1000                1005

Glu Pro  Tyr Ala Leu Phe Asn  Leu Ser Val Thr Pro  Tyr Thr Tyr
    1010                1015                1020

Trp Gly  Lys Gly Pro Lys Thr  Ser Leu Ser Leu Arg  Ala Pro Glu
    1025                1030                1035

Thr Val  Pro Ser Ala Pro Glu  Asn Pro Arg Ile Phe  Ile Leu Pro
    1040                1045                1050

Ser Gly  Lys Cys Cys Asn Lys  Asn Glu Val Val Val  Glu Phe Arg
    1055                1060                1065

Trp Asn  Lys Pro Lys His Glu  Asn Gly Val Leu Thr  Lys Phe Glu
    1070                1075                1080

Ile Phe  Tyr Asn Ile Ser Asn  Gln Ser Ile Thr Asn  Lys Thr Cys
    1085                1090                1095

Glu Asp  Trp Ile Ala Val Asn  Val Thr Pro Ser Val  Met Ser Phe
    1100                1105                1110

Gln Leu  Glu Gly Met Ser Pro  Arg Cys Phe Ile Ala  Phe Gln Val
    1115                1120                1125

Arg Ala  Phe Thr Ser Lys Gly  Pro Gly Pro Tyr Ala  Asp Val Val
    1130                1135                1140

Lys Ser  Thr Thr Ser Glu Ile  Asn Pro Phe Pro His  Leu Ile Thr
    1145                1150                1155

Leu Leu  Gly Asn Lys Ile Val  Phe Leu Asp Met Asp  Gln Asn Gln
    1160                1165                1170

Val Val  Trp Thr Phe Ser Ala  Glu Arg Val Ile Ser  Ala Val Cys
    1175                1180                1185

Tyr Thr  Ala Asp Asn Glu Met  Gly Tyr Tyr Ala Glu  Gly Asp Ser
    1190                1195                1200

Leu Phe  Leu Leu His Leu His  Asn Arg Ser Ser Ser  Glu Leu Phe
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    1205                1210                1215

Gln Asp  Ser Leu Val Phe Asp  Ile Thr Val Ile Thr  Ile Asp Trp
    1220                1225                1230

Ile Ser  Arg His Leu Tyr Phe  Ala Leu Lys Glu Ser  Gln Asn Gly
    1235                1240                1245

Met Gln  Val Phe Asp Val Asp  Leu Glu His Lys Val  Lys Tyr Pro
    1250                1255                1260

Arg Glu  Val Lys Ile His Asn  Arg Asn Ser Thr Ile  Ile Ser Phe
    1265                1270                1275

Ser Val  Tyr Pro Leu Leu Ser  Arg Leu Tyr Trp Thr  Glu Val Ser
    1280                1285                1290

Asn Phe  Gly Tyr Gln Met Phe  Tyr Tyr Ser Ile Ile  Ser His Thr
    1295                1300                1305

Leu His  Arg Ile Leu Gln Pro  Thr Ala Thr Asn Gln  Gln Asn Lys
    1310                1315                1320

Arg Asn  Gln Cys Ser Cys Asn  Val Thr Glu Phe Glu  Leu Ser Gly
    1325                1330                1335

Ala Met  Ala Ile Asp Thr Ser  Asn Leu Glu Lys Pro  Leu Ile Tyr
    1340                1345                1350

Phe Ala  Lys Ala Gln Glu Ile  Trp Ala Met Asp Leu  Glu Gly Cys
    1355                1360                1365

Gln Cys  Trp Arg Val Ile Thr  Val Pro Ala Met Leu  Ala Gly Lys
    1370                1375                1380

Thr Leu  Val Ser Leu Thr Val  Asp Gly Asp Leu Ile  Tyr Trp Ile
    1385                1390                1395

Ile Thr  Ala Lys Asp Ser Thr  Gln Ile Tyr Gln Ala  Lys Lys Gly
    1400                1405                1410

Asn Gly  Ala Ile Val Ser Gln  Val Lys Ala Leu Arg  Ser Arg His
    1415                1420                1425

Ile Leu  Ala Tyr Ser Ser Val  Met Gln Pro Phe Pro  Asp Lys Ala
    1430                1435                1440

Phe Leu  Ser Leu Ala Ser Asp  Thr Val Glu Pro Thr  Ile Leu Asn
    1445                1450                1455

Ala Thr  Asn Thr Ser Leu Thr  Ile Arg Leu Pro Leu  Ala Lys Thr
    1460                1465                1470

Asn Leu  Thr Trp Tyr Gly Ile  Thr Ser Pro Thr Pro  Thr Tyr Leu
    1475                1480                1485

Val Tyr  Tyr Ala Glu Val Asn  Asp Arg Lys Asn Ser  Ser Asp Leu
    1490                1495                1500

Lys Tyr  Arg Ile Leu Glu Phe  Gln Asp Ser Ile Ala  Leu Ile Glu
    1505                1510                1515

Asp Leu  Gln Pro Phe Ser Thr  Tyr Met Ile Gln Ile  Ala Val Lys
    1520                1525                1530

Asn Tyr  Tyr Ser Asp Pro Leu  Glu His Leu Pro Pro  Gly Lys Glu
    1535                1540                1545

Ile Trp  Gly Lys Thr Lys Asn  Gly Val Pro Glu Ala  Val Gln Leu
    1550                1555                1560

Ile Asn  Thr Thr Val Arg Ser  Asp Thr Ser Leu Ile  Ile Ser Trp
    1565                1570                1575

Arg Glu  Ser His Lys Pro Asn  Gly Pro Lys Glu Ser  Val Arg Tyr
    1580                1585                1590
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Gln Leu  Ala Ile Ser His Leu  Ala Leu Ile Pro Glu  Thr Pro Leu
    1595                1600                1605

Arg Gln  Ser Glu Phe Pro Asn  Gly Arg Leu Thr Leu  Leu Val Thr
    1610                1615                1620

Arg Leu  Ser Gly Gly Asn Ile  Tyr Val Leu Lys Val  Leu Ala Cys
    1625                1630                1635

His Ser  Glu Glu Met Trp Cys  Thr Glu Ser His Pro  Val Thr Val
    1640                1645                1650

Glu Met  Phe Asn Thr Pro Glu  Lys Pro Tyr Ser Leu  Val Pro Glu
    1655                1660                1665

Asn Thr  Ser Leu Gln Phe Asn  Trp Lys Ala Pro Leu  Asn Val Asn
    1670                1675                1680

Leu Ile  Arg Phe Trp Val Glu  Leu Gln Lys Trp Lys  Tyr Asn Glu
    1685                1690                1695

Phe Tyr  His Val Lys Thr Ser  Cys Ser Gln Gly Pro  Ala Tyr Val
    1700                1705                1710

Cys Asn  Ile Thr Asn Leu Gln  Pro Tyr Thr Ser Tyr  Asn Val Arg
    1715                1720                1725

Val Val  Val Val Tyr Lys Thr  Gly Glu Asn Ser Thr  Ser Leu Pro
    1730                1735                1740

Glu Ser  Phe Lys Thr Lys Ala  Gly Val Pro Asn Lys  Pro Gly Ile
    1745                1750                1755

Pro Lys  Leu Leu Glu Gly Ser  Lys Asn Ser Ile Gln  Trp Glu Lys
    1760                1765                1770

Ala Glu  Asp Asn Gly Cys Arg  Ile Thr Tyr Tyr Ile  Leu Glu Ile
    1775                1780                1785

Arg Lys  Ser Thr Ser Asn Asn  Leu Gln Asn Gln Asn  Leu Arg Trp
    1790                1795                1800

Lys Met  Thr Phe Asn Gly Ser  Cys Ser Ser Val Cys  Thr Trp Lys
    1805                1810                1815

Ser Lys  Asn Leu Lys Gly Ile  Phe Gln Phe Arg Val  Val Ala Ala
    1820                1825                1830

Asn Asn  Leu Gly Phe Gly Glu  Tyr Ser Gly Ile Ser  Glu Asn Ile
    1835                1840                1845

Ile Leu  Val Gly Asp Asp Phe  Trp Ile Pro Glu Thr  Ser Phe Ile
    1850                1855                1860

Leu Thr  Ile Ile Val Gly Ile  Phe Leu Val Val Thr  Ile Pro Leu
    1865                1870                1875

Thr Phe  Val Trp His Arg Arg  Leu Lys Asn Gln Lys  Ser Ala Lys
    1880                1885                1890

Glu Gly  Val Thr Val Leu Ile  Asn Glu Asp Lys Glu  Leu Ala Glu
    1895                1900                1905

Leu Arg  Gly Leu Ala Ala Gly  Val Gly Leu Ala Asn  Ala Cys Tyr
    1910                1915                1920

Ala Ile  His Thr Leu Pro Thr  Gln Glu Glu Ile Glu  Asn Leu Pro
    1925                1930                1935

Ala Phe  Pro Arg Glu Lys Leu  Thr Leu Arg Leu Leu  Leu Gly Ser
    1940                1945                1950

Gly Ala  Phe Gly Glu Val Tyr  Glu Gly Thr Ala Val  Asp Ile Leu
    1955                1960                1965
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Gly Val  Gly Ser Gly Glu Ile  Lys Val Ala Val Lys  Thr Leu Lys
    1970                 1975                 1980

Lys Gly  Ser Thr Asp Gln Glu  Lys Ile Glu Phe Leu  Lys Glu Ala
    1985                 1990                 1995

His Leu  Met Ser Lys Phe Asn  His Pro Asn Ile Leu  Lys Gln Leu
    2000                 2005                 2010

Gly Val  Cys Leu Leu Asn Glu  Pro Gln Tyr Ile Ile  Leu Glu Leu
    2015                 2020                 2025

Met Glu  Gly Gly Asp Leu Leu  Thr Tyr Leu Arg Lys  Ala Arg Met
    2030                 2035                 2040

Ala Thr  Phe Tyr Gly Pro Leu  Leu Thr Leu Val Asp  Leu Val Asp
    2045                 2050                 2055

Leu Cys  Val Asp Ile Ser Lys  Gly Cys Val Tyr Leu  Glu Arg Met
    2060                 2065                 2070

His Phe  Ile His Arg Asp Leu  Ala Ala Arg Asn Cys  Leu Val Ser
    2075                 2080                 2085

Val Lys  Asp Tyr Thr Ser Pro  Arg Ile Val Lys Ile  Gly Asp Phe
    2090                 2095                 2100

Gly Leu  Ala Arg Asp Ile Tyr  Lys Asn Asp Tyr Tyr  Arg Lys Arg
    2105                 2110                 2115

Gly Glu  Gly Leu Leu Pro Val  Arg Trp Met Ala Pro  Glu Ser Leu
    2120                 2125                 2130

Met Asp  Gly Ile Phe Thr Thr  Gln Ser Asp Val Trp  Ser Phe Gly
    2135                 2140                 2145

Ile Leu  Ile Trp Glu Ile Leu  Thr Leu Gly His Gln  Pro Tyr Pro
    2150                 2155                 2160

Ala His  Ser Asn Leu Asp Val  Leu Asn Tyr Val Gln  Thr Gly Gly
    2165                 2170                 2175

Arg Leu  Glu Pro Pro Arg Asn  Cys Pro Asp Asp Leu  Trp Asn Leu
    2180                 2185                 2190

Met Thr  Gln Cys Trp Ala Gln  Glu Pro Asp Gln Arg  Pro Thr Phe
    2195                 2200                 2205

His Arg  Ile Gln Asp Gln Leu  Gln Leu Phe Arg Asn  Phe Phe Leu
    2210                 2215                 2220

Asn Ser  Ile Tyr Lys Ser Arg  Asp Glu Ala Asn Asn  Ser Gly Val
    2225                 2230                 2235

Ile Asn  Glu Ser Phe Glu Gly  Glu Asp Gly Asp Val  Ile Cys Leu
    2240                 2245                 2250

Asn Ser  Asp Asp Ile Met Pro  Val Ala Leu Met Glu  Thr Lys Asn
    2255                 2260                 2265

Arg Glu  Gly Leu Asn Tyr Met  Val Leu Ala Thr Glu  Cys Gly Gln
    2270                 2275                 2280

Gly Glu  Glu Lys Ser Glu Gly  Pro Leu Gly Ser Gln  Glu Ser Glu
    2285                 2290                 2295

Ser Cys  Gly Leu Arg Lys Glu  Glu Lys Glu Pro His  Ala Asp Lys
    2300                 2305                 2310

Asp Phe  Cys Gln Glu Lys Gln  Val Ala Tyr Cys Pro  Ser Gly Lys
    2315                 2320                 2325
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Pro Glu  Gly Leu Asn Tyr Ala  Cys Leu Thr His Ser  Gly Tyr Gly
    2330                2335                2340

Asp Gly  Ser Asp
    2345
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1. A method for treating a ROS1-associated cancer in a subject in need thereof, wherein the cancer has a fusion selected from the group consisting of: TPD52L1-ROS1, CCDC30-ROS1, FYN-ROS1, MKX-ROS1, and LIMA1-ROS1, the method comprising administering a compound selected from the group consisting of:

(6R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.02,6.07,12.022,26] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.02,6.07,12.022,26] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-13-oxa-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7, 9,11, 18(25), 19,22-heptaen-17-one;

(6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo[18.5.2.02,6.07,12.023,27]heptacosa-1(26),7,9,11, 20(27),21,24-heptaen-19-one;

(6R)-9-fluoro-2,11,13,16,20,21,24-heptaazapentacyclo [16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18 (25),19,22-heptaen-17-one;

(6R)-9-fluoro-2,11,13,17,21,22,25-heptaazapentacyclo [17.5.2.02,6.07,12.022,26]hexacosa-1(25),7,9,11,19 (26),20,23-heptaen-18-one;

(6R)-9-fluoro-17-methyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.02,6.07,12.022,26] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one;

(6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.02,6.07,12.022,26]hexacosa-1(25), 7,9,11,19(26),20,23-heptaen-18-one;

(6R)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18(25),19, 22-heptaen-17-one;

(6R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9, 11,18(25),19,22-heptaen-17-one;

(6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24), 7,9,11,18(25),19,22-heptaen-17-one;

(6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo [17.5.2.02,6.07,12.022,26] hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one; and

(6R)-9-fluoro-15,15-dimethyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24), 7,9,11,18(25),19,22-heptaen-17-one;

TPX-0005;

brigatinib; and

crizotinib;

or a pharmaceutically acceptable salt thereof.

2. The method of claim 1, wherein the compound is (6R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.02,6.07,12.022,26] hexacosa-1 (25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

3. The method of claim 1, wherein the compound is (6R,15R)-9-fluoro-15-hydroxy-13-oxa-2,11,17,21,22,25-hexaazapentacyclo-[17.5.2.02,6.07,12.022,26] hexacosa-1 (25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

4. The method of claim 1, wherein the compound is (6R)-9-fluoro-13-oxa-2,11,16,20,21,24-hexaazapentacyclo [16.5.2.02,6.07,12.021,25]pentacosa-1(24),7, 9,11,18(25), 19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

5. The method of claim 1, wherein the compound is (6R)-9-fluoro-13-oxa-2,11,18,22,23,26-hexaazapentacyclo [18.5.2.02,6.07,12.023,27]heptacosa-1(26),7,9,11,20(27), 21,24-heptaen-19-one, or a pharmaceutically acceptable salt thereof.

6. The method of claim 1, wherein the compound is (6R)-9-fluoro-2,11,13,16,20,21,24-heptaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18(25), 19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

7. The method of claim 1, wherein the compound is (6R)-9-fluoro-2,11,13,17,21,22,25-heptaazapentacyclo[17.5.2.02,6.07,12.022,26]hexacosa-1(25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

8. The method of claim 1, wherein the compound is (6R)-9-fluoro-17-methyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.02,6.07,12.022,26] hexacosa-1(25),7,9, 11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

9. The method of claim 1, wherein the compound is (6R)-9,15,15-trifluoro-13-oxa-2,11,17,21,22,25-hexaazapentacyclo[17.5.2.02,6.07,12.022,26]hexacosa-1(25),7,9, 11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

10. The method of claim 1, wherein the compound is (6R)-9-fluoro-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18(25), 19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

11. The method of claim 1, wherein the compound is (6R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18 (25), 19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

12. The method of claim 1, wherein the compound is (6R,15R)-9-fluoro-15-methyl-2,11,16,20,21,24-hexaazapentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9, 11,18(25), 19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

13. The method of claim 1, wherein the compound is (6R)-9-fluoro-15,15-dimethyl-13-oxa-2,11,17,21,22,25-hexaazapentacyclo [17.5.2.02,6.07,12.022,26] hexacosa-1 (25),7,9,11,19(26),20,23-heptaen-18-one, or a pharmaceutically acceptable salt thereof.

14. The method of claim **1**, wherein the compound is (6R)-9-fluoro-15,15-dimethyl-2,11,16,20,21,24-hexaaza-pentacyclo[16.5.2.02,6.07,12.021,25]pentacosa-1(24),7,9,11,18(25), 19,22-heptaen-17-one, or a pharmaceutically acceptable salt thereof.

15. The method of claim **1**, wherein the compound is TPX-0005, or a pharmaceutically acceptable salt thereof.

16. The method of claim **1**, wherein the ROS1-associated cancer is one or more of non-small-cell lung cancer and papillary thyroid carcinoma.

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