for methods of effectively inhibiting RAS pathway signaling while minimizing or mitigating activation of resistance mechanisms.

Summary

The present disclosure provides methods for inhibiting RAS and for the treatment of cancer. The inventors observed that cancer cells treated with a RAS(OFF) inhibitor may develop resistance, e.g., through the acquisition of one or more mutations that render the RAS(OFF) inhibitor less effective or ineffective. The disclosure is based, at least in part, on the observation that some cancers resistant to treatment with a RAS(OFF) inhibitor remain responsive to treatment with a RAS(ON) inhibitor. Thus, administering a RAS(ON) inhibitor to a subject having cancer can slow or halt oncogenic signaling or disease progression where the cancer is resistant to treatment with a RAS(OFF) inhibitor. Additionally, administration of a RAS(ON) inhibitor, e.g., administered in combination with a RAS(OFF) inhibitor, may prevent the acquisition of one or more mutations in RAS that confer resistance to the RAS(OFF) inhibitor.

In one aspect, the present disclosue refers to use of a RAS(ON) inhibitor in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor, wherein the cancer comprises a mutation in RAS, the subject has been previously treated with a RAS(OFF) inhibitor, ~~and~~ the cancer is resistant to treatment with ~~a~~ the RAS(OFF) inhibitor, the subject's cancer progresses on the RAS(OFF) inhibitor, and wherein the RAS(ON) inhibitor is to be administered to the subject.

In another aspect, the present disclosue refers to use of a RAS(ON) inhibitor in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer comprises an amino acid substitution at RAS Y96, wherein the subject has been treated with a RAS(OFF) inhibitor, and the cancer is resistant to treatment with the RAS(OFF) inhibitor, the subject's cancer progresses on the RAS(OFF) inhibitor, and wherein the RAS(ON) inhibitor is to be administered to the subject.

Accordingly, in a first example, the disclosure provides a method of treating cancer in a subject in need thereof, wherein the cancer includes a mutation in RAS and the cancer is resistant to treatment with a RAS(OFF) inhibitor, the method including administering to the subject a RAS(ON) inhibitor. In some examples, the RAS mutation is an amino acid substitution at Y96. In some examples, the amino acid substitution is Y96D.

In another example, the disclosure provides a method of treating cancer in a subject in need thereof, wherein the cancer includes an amino acid substitution at RAS Y96, the method including administering to the subject a RAS(ON) inhibitor. In some examples, the amino acid substitution is Y96D.

In some examples, the method further includes administering to the subject a RAS(OFF) inhibitor (e.g., a RAS(OFF) inhibitor is administered to the subject in combination with the RAS(ON) inhibitor). The RAS(ON) inhibitor and the RAS(OFF) inhibitor may be administered simultaneously or sequentially. The RAS(ON) inhibitor and the RAS(OFF) inhibitor may administered as

a single formulation or in separate formulations. In some examples, the RAS(OFF) inhibitor is administered for a first period of time; and the RAS(ON) inhibitor is administered for a second period of time, wherein the first period of time and the second period of time do not overlap and the first period of time precedes the second period of time. In some examples, the RAS(OFF) inhibitor is administered for a first period of time; and the RAS(OFF) inhibitor and RAS(ON) inhibitor are administered for a second period of time, wherein the first period of time and the second period of time do not overlap and the first period of time precedes the second period of time. In some examples, the first period of time is a period of time sufficient to acquire a mutation (e.g., a RAS mutation) that confers resistance to treatment with the RAS(OFF) inhibitor. In some examples, the first period of time is between one week and one month, between one week and six months, between one week and one year, between one month and six months, between one month and one year, between one month and two years, between one month and

five years, at least one week, at least one month, at least six months, or at least one year. In some examples, the second period of time is between one week and one month, between one week and six months, between one week and one year, between one month and six months, between one month and one year, between one month and two years, between one month and five years, at least one week, at least one month, at least six months, or at least one year.

In some examples, the subject's cancer progresses on the RAS(OFF) inhibitor (e.g., when the subject is administered the RAS(OFF) inhibitor in the absence of a RAS(ON) inhibitor).

In some examples, the subject has been treated with a RAS(OFF) inhibitor (e.g., the subject has been previously treated with a RAS(OFF) inhibitor, e.g., prior to administration of the RAS(ON) inhibitor). In some examples, the subject has acquired resistance to a RAS(OFF) inhibitor (e.g., has acquired a mutation that confers resistance to a RAS(OFF) inhibitor, e.g., prior to administration of the RAS(ON) inhibitor).

In another example, the disclosure provides a method of inhibiting RAS in a cell, wherein the RAS includes an amino acid substitution at Y96, the method including contacting the cell with a RAS(ON) inhibitor. In some examples, the amino acid substitution is Y96D.

In some examples, the RAS includes or further includes an amino acid substitution at G12, G13, Q61, or a combination thereof. In some examples, the amino acid substitution is selected from G12C, G12D, G12V, G13C, G13D, or Q61L. In some examples, the amino acid substitution is G12C.

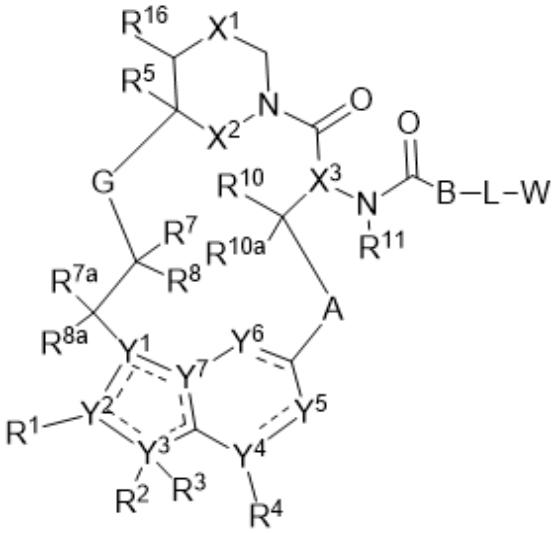
In some examples, the RAS is KRAS. In some examples, the KRAS includes or further includes an amino acid substitution at G12, G13, Q61, A146, K117, L19, Q22, V14, A59, or a combination thereof. In some examples, the KRAS amino acid substitution is selected from G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, G13V, or a combination thereof.

In some examples, the RAS is NRAS. In some examples, the NRAS includes or further includes an amino acid substitution at G12, G13, Q61, P185, A146, G60, A59, E132, E49, T50, or a combination thereof. In some examples, the NRAS amino acid substitution is selected from Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, A59T, or a combination thereof.

In some examples, the RAS is HRAS. In some examples, the HRAS includes or further includes an amino acid substitution at G12, G13, Q61, K117, A59, A18, D119, A66, A146, or a combination thereof. In some examples, the HRAS amino acid substitution is selected from Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, G12R, or a combination thereof.

In some examples, the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, G13D, or G12D. In some examples, the RAS(ON) inhibitor is a RAS(ON)^{MULTI} inhibitor.

In some examples, the RAS(ON) inhibitor is a compound described by Formula AI:



Formula AI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, S(O)$_2$R', optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or S(O)$_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form C=C$R^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

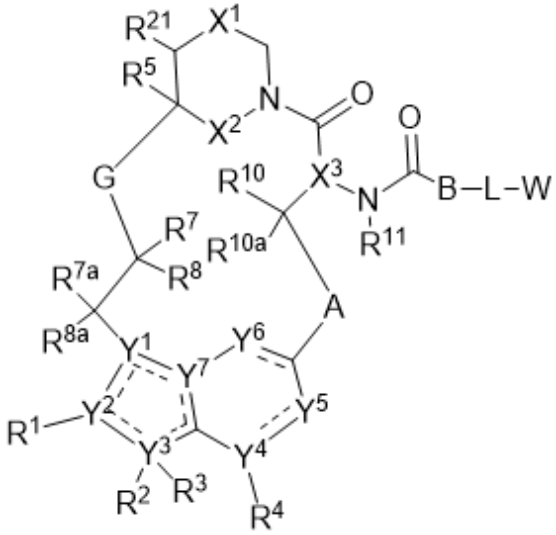
R^{11} is hydrogen or C_1-C_3 alkyl;

R^{16} is hydrogen or C_1-C_3 alkyl (e.g., methyl).

In some examples, the RAS(ON) inhibitor is a compound, or a pharmaceutically acceptable salt thereof, of any one of Formula AIa, Formula AIb, Formula AIc, Formula AId, Formula AIe, Formula AIf, Formula AIg, Formula AIh, or Formula AIi described herein.

In some examples, the RAS(ON) inhibitor is selected from a compound of Table A1 or Table A2, or a pharmaceutically acceptable salt thereof.

In some examples, the RAS(ON) inhibitor is a compound of Formula BI:



Formula BI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, a haloacetyl, or an alkynyl sulfone;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo;

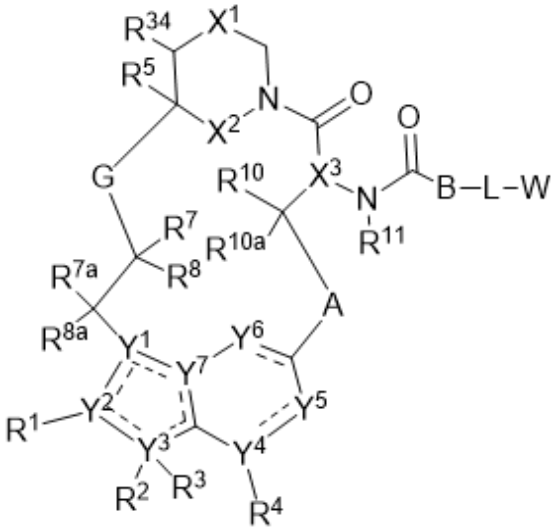
R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{21} is hydrogen or C_1-C_3 alkyl.

In some examples, the RAS(ON) inhibitor is a compound, or a pharmaceutically acceptable salt thereof, of any one of Formula BIa, Formula BIb, Formula BIc, Formula BId, Formula BIe, Formula BIf, Formula BIg, Formula BVI, Formula BVIa, Formula BVIb, or Formula BVIc described herein.

In some examples, the RAS(ON) inhibitor is selected from a compound of Table B1 or Table B2, or a pharmaceutically acceptable salt thereof.

In some examples, the RAS(ON) inhibitor is a compound described by Formula CI:



Formula CI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, an aziridine, a trifluoromethyl ketone, a boronic acid, a boronic ester, an *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), an iso-EEDQ or other EEDQ derivative, an epoxide, an oxazolium, or a glycal;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

R^{10a} is hydrogen or halo; and

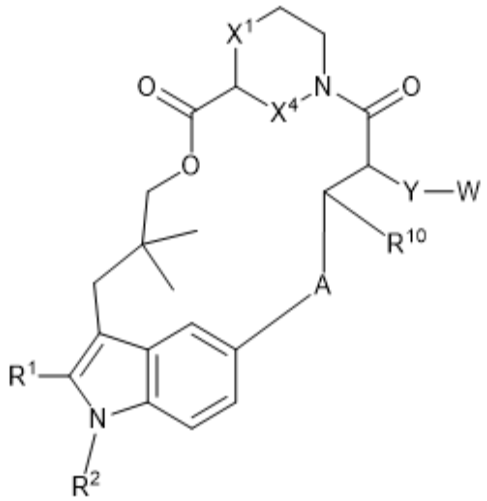
R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{34} is hydrogen or C_1-C_3 alkyl.

In some examples, the RAS(ON) inhibitor is a compound, or a pharmaceutically acceptable salt thereof, of any one of Formula CIa, Formula CIb, Formula CIc, Formula CId, Formula CIe, Formula CIf, Formula CVI, Formula CVIa, CFormula VIb, or Formula CVII described herein.

In some examples, the RAS(ON) inhibitor is selected from a compound of Table C1 or Table C2, or a pharmaceutically acceptable salt thereof.

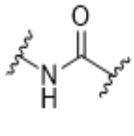
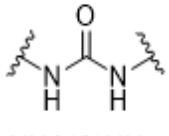
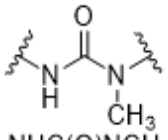
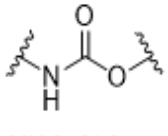
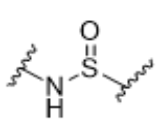
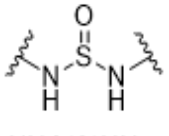
In some examples, the RAS(ON) inhibitor is a compound described by Formula DIa:

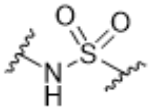
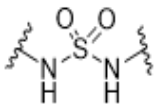


Formula DIa

or a pharmaceutically acceptable salt thereof,

wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, optionally substituted 5 to 6-membered heteroarylene, optionally substituted C_2-C_4 alkylene, or optionally substituted C_2-C_4 alkenylene;

Y is  -NHC(O)- ,  -NHC(O)NH- ,  -NHC(O)NCH$_3$- ,  -NHC(O)O- ,  -NHC(S)- ,  -NHC(S)NH- ,

 -NHS(O)$_2$- , or  -NHS(O)$_2$NH- ;

W is hydrogen, C_1-C_4 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

X^1 and X^4 are each, independently, CH_2 or NH;

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; and

R^{10} is hydrogen, hydroxy, optionally substituted C_1-C_3 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

In some examples, the RAS(ON) inhibitor is a compound, or a pharmaceutically acceptable salt thereof, of any one of Formula DII (e.g., Formula DII-1, DII-2, DII-3, DII-4, DII-5, DII-6, DII-7, DII-8, or DII-9), Formula DIII (e.g., Formula DIII-1, DIII-2, DIII-3, DIII-4, DIII-5, DIII-6, DIII-7, DIII-8, or DIII-9), Formula DIV (e.g., Formula DIV-1, DIV-2, DIV-3, DIV-4, DIV-5, DIV-6, DIV-7, DIV-8, or DIV-9), Formula DV (e.g., Formula DV-1, DV-2, DV-3, DV-4, or DV-5), Formula DVI (e.g., Formula DVI-1, DVI-2, DVI-3, DVI-4, or DVI-5), Formula DVII (e.g., Formula DVII-1, DVII-2, DVII-3, DVII-4, or DVII-5), Formula DVIII (e.g., Formula DVIII-1, DVIII-2, DVIII-3, DVIII-4, or DVIII-5), Formula DIX (e.g., Formula DIX-1, DIX-2, DIX-3, DIX-4, or DIX-5), or Formula DX (e.g., Formula DX-1, DX-2, DX-3, DX-4, or DX-5)

In some examples, the RAS(ON) inhibitor is selected from a compound of Table D1a or D1b, or a pharmaceutically acceptable salt thereof.

In some examples, the RAS(ON) inhibitor is a compound described by a Formula in WO 2020132597, such as a compound of Formula (I) therein, or a pharmaceutically acceptable salt thereof, or a compound of Figure 1 therein, or a pharmaceutically acceptable salt thereof.

In some examples, the RAS(OFF) inhibitor selectively targets RAS G12C. In some examples, the RAS(OFF) inhibitor selectively targets RAS G12D.

In some examples, the RAS(OFF) inhibitor is selected from AMG 510 (sotorasib), MRTX849 (adagrasib), MRTX1257, JNJ-74699157 (ARS-3248), LY3537982, LY3499446, ARS-853, ARS-1620, GDC-6036, JDQ443, BPI-421286, and JAB-21000. In some examples, the RAS(OFF) inhibitor is an inhibitor of K-Ras G12D, such as MRTX1133 or JAB-22000. In some examples, the RAS(OFF) inhibitor is a K-Ras G12V inhibitor, such as JAB-23000.

In some examples, the RAS(OFF) inhibitor is a compound disclosed in any one of the following patent publications: WO 2022052895, WO 2022048545, WO 2022047093, WO 2022042630, WO 2022040469, WO 2022037631, WO 2022037560, WO 2022031678, WO 2022028492, WO 2022028346, WO 2022026726, WO 2022026723, WO 2022015375, WO 2022002102, WO 2022002018, WO 2021259331, WO 2021257828, WO 2021252339, WO 2021248095, WO 2021248090, WO 2021248083, WO 2021248082, WO 2021248079, WO 2021248055, WO 2021245051, WO 2021244603, WO 2021239058, WO 2021231526, WO 2021228161, WO 2021219090, WO 2021219090, WO 2021219072, WO 2021218939, WO 2021217019, WO 2021216770, WO 2021215545, WO 2021215544, WO 2021211864, WO 2021190467, WO 2021185233, WO 2021180181, WO 2021175199, 2021173923, WO 2021169990, WO 2021169963, WO 2021168193, WO 2021158071, WO 2021155716, WO 2021152149, WO 2021150613, WO 2021147967, WO 2021147965, WO 2021143693, WO 2021142252, WO 2021141628, WO 2021139748, WO 2021139678, WO 2021129824, WO 2021129820, WO 2021127404, WO 2021126816, WO 2021126799, WO 2021124222, WO 2021121371, WO 2021121367, WO 2021121330, WO 2021055728, WO 2021031952, WO 2021027911, WO 2021023247, WO 2020259513, WO 2020259432, WO 2020234103, WO 2020233592, WO 2020216190, WO 2020178282, WO 2020146613, WO 2020118066, WO 2020113071, WO 2020106647, WO 2020102730, WO 2020101736, WO 2020097537, WO 2020086739, WO 2020081282, WO 2020050890, WO 2020047192, WO 2020035031, WO 2020028706, WO 2019241157, WO 2019232419, WO 2019217691, WO 2019217307, WO 2019215203, WO 2019213526, WO 2019213516, WO 2019155399, WO 2019150305, WO 2019110751, WO 2019099524, WO 2019051291, WO 2018218070, WO 2018218071, WO 2018218069, WO 2018217651, WO 2018206539, WO 2018143315, WO 2018140600, WO 2018140599, WO 2018140598, WO 2018140514, WO 2018140513, WO 2018140512, WO 2018119183, WO 2018112420, WO 2018068017, WO 2018064510, WO 2017201161, WO 2017172979, WO 2017100546, WO 2017087528, WO 2017058807, WO 2017058805, WO 2017058728, WO 2017058902, WO 2017058792, WO 2017058768, WO 2017058915, WO 2017015562, WO 2016168540, WO 2016164675, WO 2016049568, WO 2016049524, WO 2015054572, WO 2014152588, WO 2014143659, WO 2013155223, CN 114195788, CN 114057776, CN 114057744, CN 114057743, CN 113999226, CN

113980032, CN 113980014, CN 113960193, CN 113929676, CN 113754653, CN 113683616, CN 113563323, CN 113527299, CN 113527294, CN 113527293, CN 113493440, CN 113429405, CN 113248521, CN 113087700, CN 113024544, CN 113004269, CN 112920183, CN 112390818, CN 112390788, CN 112300194, CN 112300173, CN 112225734, CN 112142735, CN 112110918, CN 112094269, CN 112047937, and CN 109574871, each of which is incorporated herein by reference in its entirety.

In any example herein regarding a RAS(OFF) inhibitor, the RAS(OFF) inhibitor may be substituted by a RAS inhibitor disclosed in the following patent publication: WO 2021041671, which is incorporated herein by reference in its entirety. In some examples, such a substituted RAS inhibitor is MRTX1133.

In some examples, the cancer is selected from colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, appendiceal cancer, endometrial cancer, and melanoma. In some examples, the cancer is non-small cell lung cancer. In some examples, the cancer is pancreatic cancer.

It is specifically contemplated that any limitation discussed with respect to one example of the disclosure may apply to any other example of the disclosure. Furthermore, any compound or composition of the disclosure may be used in any method of the disclosure, and any method of the disclosure may be used to produce or to utilize any compound or composition of the disclosure.

Brief Description of the Figures

FIG. 1A is a series of computed tomography (CT) images of a subject's axillary lymph node metastasis at baseline, during response to a RAS(OFF) inhibitor, MRTX849, and at progression on MRTX849.

FIG. 1B is a western blot analysis of MIA PaCa-2 cells (stably expressing BRAF (V600E)-V5) that were treated with a RAS(OFF) inhibitor, MRTX849, at the indicated concentrations for 4 hours.

FIG. 1C is a diagram illustrating alterations detected in post-MRTX849 cfDNA that include acquired mutations in KRAS as well as multiple components of the MAPK signaling cascade.

FIG. 2A is a sequence read pile-up of $KRAS^{G13D}$ occurring *in trans* to $KRAS^{G12C}$.

FIG. 2B is a sequence read pile-up of $KRAS^{G12V}$ occurring *in cis* to $KRAS^{G12C}$.

FIG. 3 is a series of modeled crystal structures of RAS(OFF) inhibitors MRTX849 (6UT0), AMG 510 (6OIM), and ARS-1620 (5V9U) bound to $KRAS^{G12C}$ (top panels) and $KRAS^{G12C/Y96D}$ (bottom panels).

FIG. 4A are a series of plots of cell viability assays performed with NCI-H358, MIA PaCa-2 and Ba/F3 cells infected with retrovirus packaging *KRAS* (G12C or G12C/Y96D) in the presence of RAS(OFF) inhibitors.

Claims

1. Use of a RAS(ON) inhibitor in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor, wherein the cancer comprises a mutation in RAS, the subject has been previously treated with a RAS(OFF) inhibitor, ~~and~~ the cancer is resistant to treatment with ~~a~~ the RAS(OFF) inhibitor, the subject's cancer progresses on the RAS(OFF) inhibitor, and wherein the RAS(ON) inhibitor is to be administered to the subject.

2. The use of claim 1, wherein a RAS(OFF) inhibitor is to be further administered to the subject.

3. The use of claim 2, wherein the RAS(ON) inhibitor and the RAS(OFF) inhibitor are to be administered simultaneously or sequentially.

4. The use of claim 2 or 3 wherein the RAS(ON) inhibitor and the RAS(OFF) inhibitor are to be administered as a single formulation or in separate formulations.

5. The use of claim 3, wherein:

the RAS(OFF) inhibitor is to be administered for a first period of time; and

the RAS(ON) inhibitor is to be administered for a second period of time,

wherein the first period of time and the second period of time do not overlap and the first period of time precedes the second period of time.

6. The use of claim 3, wherein:

the RAS(OFF) inhibitor is to be administered for a first period of time; and

the RAS(OFF) inhibitor and RAS(ON) inhibitor are to be administered for a second period of time,

wherein the first period of time and the second period of time do not overlap and the first period of time precedes the second period of time.

7. The use of claim 1, wherein the RAS further comprises an amino acid substitution at Y96.

8. The use of claim 7, wherein the amino acid substitution is Y96D.

9. Use of a RAS(ON) inhibitor in the manufacture of a medicament for treating cancer in a subject in need thereof, wherein the cancer comprises an amino acid substitution at RAS Y96, wherein the subject has been treated with a RAS(OFF) inhibitor, and the cancer is resistant to treatment with the RAS(OFF)

inhibitor, the subject's cancer progresses on the RAS(OFF) inhibitor, and wherein the RAS(ON) inhibitor is to be administered to the subject.

10. The use of claim 9, wherein the amino acid substitution is Y96D.

11. The use of any one of claims 1-10, wherein the RAS comprises or further comprises an amino acid substitution at G12, G13, Q61, or a combination thereof.

12. The use of claim 11, wherein the amino acid substitution is selected from G12C, G12D, G12V, G13C, G13D, or Q61L.

13. The use of claim 12, wherein the amino acid substitution is G12C.

14. The use of any one of claims 1-10, wherein the RAS is KRAS.

15. The use of claim 14, wherein the KRAS comprises or further comprises an amino acid substitution at G12, G13, Q61, A146, K117, L19, Q22, V14, A59, or a combination thereof.

16. The use of claim 15, wherein the KRAS amino acid substitution is selected from G12D, G12V, G12C, G13D, G12R, G12A, Q61H, G12S, A146T, G13C, Q61L, Q61R, K117N, A146V, G12F, Q61K, L19F, Q22K, V14I, A59T, A146P, G13R, G12L, G13V, or a combination thereof.

17. The use of any one of claim 1-10, wherein the RAS is NRAS.

18. The use of claim 17, wherein the NRAS comprises or further comprises an amino acid substitution at G12, G13, Q61, P185, A146, G60, A59, E132, E49, T50, or a combination thereof.

19. The use of claim 18, wherein the NRAS amino acid substitution is selected from Q61R, Q61K, G12D, Q61L, Q61H, G13R, G13D, G12S, G12C, G12V, G12A, G13V, G12R, P185S, G13C, A146T, G60E, Q61P, A59D, E132K, E49K, T50I, A146V, A59T, or a combination thereof.

20. The use of any one of claim 1-10, wherein the RAS is HRAS.

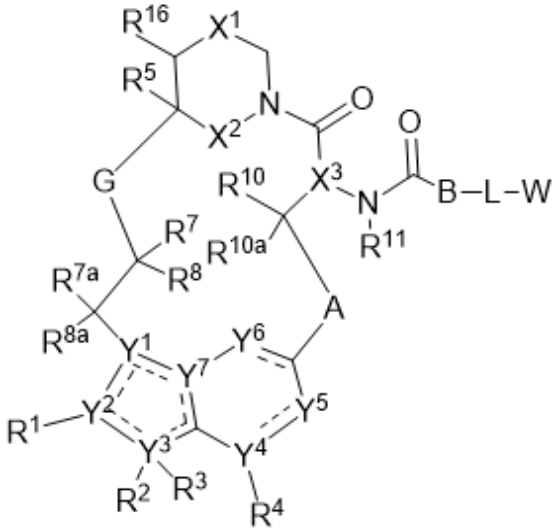
21. The use of claim 20, wherein the HRAS comprises or further comprises an amino acid substitution at G12, G13, Q61, K117, A59, A18, D119, A66, A146, or a combination thereof.

22. The use of claim 21, wherein the HRAS amino acid substitution is selected from Q61R, G13R, Q61K, G12S, Q61L, G12D, G13V, G13D, G12C, K117N, A59T, G12V, G13C, Q61H, G13S, A18V, D119N, G13N, A146T, A66T, G12A, A146V, G12N, G12R, or a combination thereof.

23. The use of any one of claims 1-22, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, G13D, or G12D.

24. The use of any one of claims 1-22, wherein the RAS(ON) inhibitor is a RAS(ON)^{MULTI} inhibitor.

25. The use of any one of claims 1-24, wherein the RAS(ON) inhibitor is a compound of Formula AI:



Formula AI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)-

where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is hydrogen, cyano, $S(O)_2R'$, optionally substituted amino, optionally substituted amido, optionally substituted C_1-C_4 alkoxy, optionally substituted C_1-C_4 hydroxyalkyl, optionally substituted C_1-C_4 aminoalkyl, optionally substituted C_1-C_4 haloalkyl, optionally substituted C_1-C_4 alkyl, optionally substituted C_1-C_4 guanidinoalkyl, C_0-C_4 alkyl optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', $C(O)N(R')_2$, S(O)R', $S(O)_2R'$, or $S(O)_2N(R')_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl;

R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

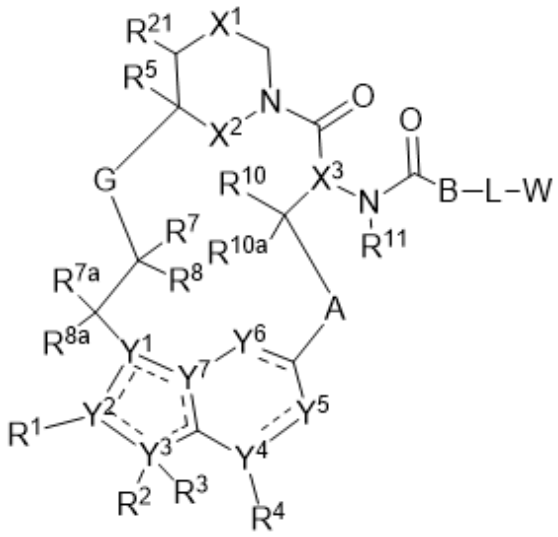
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl;

R^{16} is hydrogen or C_1-C_3 alkyl.

26. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is selected from a compound of Table A1 or Table A2, or a pharmaceutically acceptable salt thereof.

27. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is a compound of Formula BI:



Formula BI

or a pharmaceutically acceptable salt thereof,

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is absent, -CH(R^9)-, >C=C$R^9R^{9'}$, or >C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a vinyl ketone, a vinyl sulfone, an ynone, a haloacetyl, or an alkynyl sulfone;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or $S(O)_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', $S(O)_2$R', or $S(O)_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxy, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is H, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl; or

R^9 and $R^{9'}$, combined with the atoms to which they are attached, form a 3 to 6-membered cycloalkyl or a 3 to 6-membered heterocycloalkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

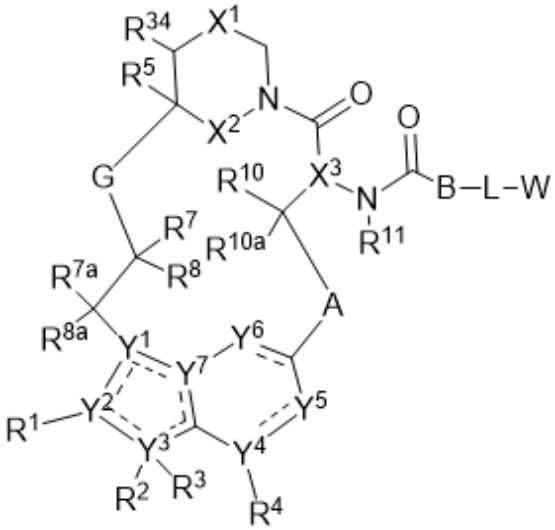
R^{10a} is hydrogen or halo;

R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{21} is hydrogen or C_1-C_3 alkyl.

28. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is selected from a compound of Table B1 or Table B2, or a pharmaceutically acceptable salt thereof.

29. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is a compound of Formula CI, or a pharmaceutically acceptable salt thereof.



Formula CI

wherein the dotted lines represent zero, one, two, three, or four non-adjacent double bonds;

A is -N(H or CH_3)C(O)-(CH_2)- where the amino nitrogen is bound to the carbon atom of -CH(R^{10})-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

B is -CH(R^9)- or >C=C$R^9R^{9'}$ where the carbon is bound to the carbonyl carbon of -N(R^{11})C(O)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or 5 to 6-membered heteroarylene;

G is optionally substituted C_1-C_4 alkylene, optionally substituted C_1-C_4 alkenylene, optionally substituted C_1-C_4 heteroalkylene, -C(O)O-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, -C(O)NH-**C**H(R^6)- where **C** is bound to -C(R^7R^8)-, optionally substituted C_1-C_4 heteroalkylene, or 3 to 8-membered heteroarylene;

L is absent or a linker;

W is a cross-linking group comprising a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, an aziridine, a trifluoromethyl ketone, a boronic acid, a boronic ester, an *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), an iso-EEDQ or other EEDQ derivative, an epoxide, an oxazolium, or a glycal;

X^1 is optionally substituted C_1-C_2 alkylene, NR, O, or S(O)$_n$;

X^2 is O or NH;

X^3 is N or CH;

n is 0, 1, or 2;

R is hydrogen, cyano, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, C(O)R', C(O)OR', C(O)N(R')$_2$, S(O)R', S(O)$_2$R', or S(O)$_2$N(R')$_2$;

each R' is, independently, H or optionally substituted C_1-C_4 alkyl;

Y^1 is C, CH, or N;

Y^2, Y^3, Y^4, and Y^7 are, independently, C or N;

Y^5 is CH, CH_2, or N;

Y^6 is C(O), CH, CH_2, or N;

R^1 is cyano, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 6-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl, or

R^1 and R^2 combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

R^2 is absent, hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R^3 is absent, or

R^2 and R^3 combine with the atom to which they are attached to form an optionally substituted 3 to 8-membered cycloalkyl or optionally substituted 3 to 14-membered heterocycloalkyl;

R^4 is absent, hydrogen, halogen, cyano, or methyl optionally substituted with 1 to 3 halogens;

R^5 is hydrogen, C_1-C_4 alkyl optionally substituted with halogen, cyano, hydroxy, or C_1-C_4 alkoxy, cyclopropyl, or cyclobutyl;

R^6 is hydrogen or methyl; R^7 is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl, or

R^6 and R^7 combine with the carbon atoms to which they are attached to form an optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^8 is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

R^7 and R^8 combine with the carbon atom to which they are attached to form $C=CR^{7'}R^{8'}$; C=N(OH), C=N(O-C_1-C_3 alkyl), C=O, C=S, C=NH, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl;

R^{7a} and R^{8a} are, independently, hydrogen, halo, optionally substituted C_1-C_3 alkyl, or combine with the carbon to which they are attached to form a carbonyl;

$R^{7'}$ is hydrogen, halogen, or optionally substituted C_1-C_3 alkyl; $R^{8'}$ is hydrogen, halogen, hydroxy, cyano, optionally substituted C_1-C_3 alkoxyl, optionally substituted C_1-C_3 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 8-membered cycloalkyl, optionally substituted 3 to 14-membered heterocycloalkyl, optionally substituted 5 to 10-membered heteroaryl, or optionally substituted 6 to 10-membered aryl, or

$R^{7'}$ and $R^{8'}$ combine with the carbon atom to which they are attached to form optionally substituted 3 to 6-membered cycloalkyl or optionally substituted 3 to 7-membered heterocycloalkyl;

R^9 is hydrogen, F, optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, or optionally substituted 3 to 7-membered heterocycloalkyl, or

R^9 and L combine with the atoms to which they are attached to form an optionally substituted 3 to 14-membered heterocycloalkyl;

$R^{9'}$ is hydrogen or optionally substituted C_1-C_6 alkyl;

R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

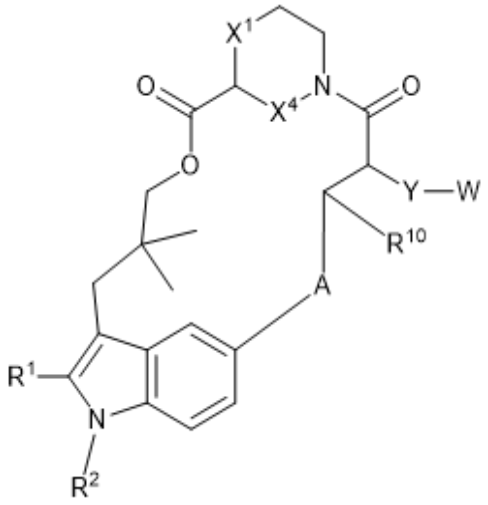
R^{10a} is hydrogen or halo; and

R^{11} is hydrogen or C_1-C_3 alkyl; and

R^{34} is hydrogen or C_1-C_3 alkyl.

30. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is selected from a compound of Table C1 or Table C2, or a pharmaceutically acceptable salt thereof.

31. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is a compound described by Formula DIa:

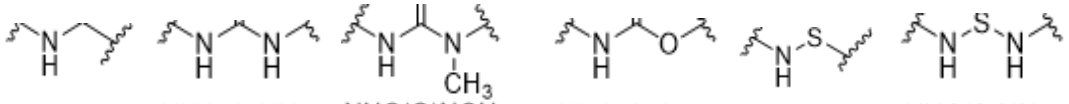


s

Formula DIa

or a pharmaceutically acceptable salt thereof,

wherein A is optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, optionally substituted 5 to 6-membered heteroarylene, optionally substituted C_2-C_4 alkylene, or optionally substituted C_2-C_4 alkenylene;

Y is  -NHC(O)-, -NHC(O)NH-, -NHC(O)NCH$_3$-, -NHC(O)O-, -NHC(S)-, -NHC(S)NH-,  -NHS(O)$_2$-, or -NHS(O)$_2$NH-;

W is hydrogen, C_1-C_4 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

X^1 and X^4 are each, independently, CH_2 or NH;

R^1 is optionally substituted C_1-C_6 alkyl, optionally substituted C_1-C_6 heteroalkyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 6-membered cycloalkenyl, optionally substituted 3 to 15-membered heterocycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl; and

R^2 is hydrogen, optionally substituted C_1-C_6 alkyl, optionally substituted C_2-C_6 alkenyl, optionally substituted C_2-C_6 alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-

membered heteroaryl; and R^{10} is hydrogen, hydroxy, optionally substituted C_1-C_3 alkyl, or optionally substituted C_1-C_6 heteroalkyl.

32. The use of any one of claims 1-25, wherein the RAS(ON) inhibitor is selected from a compound of Table D1a or D1b, or a pharmaceutically acceptable salt thereof.

33. The use of any one of claims 1-32, wherein the RAS(OFF) inhibitor selectively targets RAS G12C.

34. The use of any one of claims 1-32, wherein the RAS(OFF) inhibitor selectively targets RAS G12D.

35. The use of any one of claims 1-34, wherein the RAS(OFF) inhibitor is selected from sotorasib (AMG 510), adagrasib (MRTX849), MRTX1257, JNJ-74699157 (ARS-3248), LY3537982, LY3499446, ARS-853, ARS-1620, GDC-6036, JDQ443, BPI-421286, and JAB-21000.

36. The use of any one of claims 1-35, wherein the cancer is selected from colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, melanoma, acute myeloid leukemia, small bowel cancer, ampullary cancer, germ cell cancer, cervical cancer, cancer of unknown primary origin, endometrial cancer, esophagogastric cancer, GI neuroendocrine cancer, ovarian cancer, sex cord stromal tumor cancer, hepatobiliary cancer, bladder cancer, appendiceal cancer, endometrial cancer, and melanoma.

37. The use of claim 36, wherein the cancer is non-small cell lung cancer.

38. The use of claim 36, wherein the cancer is pancreatic cancer.