## 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 cancer comprises a mutation in RAS and the cancer is resistant to treatment with a 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 any one of claims 2-6, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

8. The use of claim 1, wherein the RAS mutation is an amino acid substitution at Y96.

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

10. The use of any one of claims 1, 8, or 9, wherein the subject has been treated with a RAS(OFF) inhibitor.

11. 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, and wherein the RAS(ON) inhibitor is to be administered to the subject.

12. The use of claim 11, wherein the amino acid substitution is Y96D.

13. The use of claim 11 or 12, wherein the subject has been treated with a RAS(OFF) inhibitor.

14. The use of any one of claims 11-13, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor.

15. The use of claim 13, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

16. Use of a RAS(ON) inhibitor in the manufacture of a medicament for inhibiting RAS in a cell, wherein the RAS comprises an amino acid substitution at Y96, and wherein the cell is to be contacted with the RAS(ON) inhibitor.

17. The use of claim 16, wherein the amino acid substitution is Y96D.

18. The use of any one of claims 1-17, wherein the RAS comprises or further comprises an amino acid substitution at G12, G13, Q61, or a combination thereof.

19. The use of claim 18, wherein the amino acid substitution is selected from G12C, G12D, G12V, G13C, G13D, or Q61L.

20. The use of claim 19, wherein the amino acid substitution is G12C.

21. The use of any one of claims 1-17, wherein the RAS is KRAS.

22. The use of claim 21, 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.

23. The use of claim 22, 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.

24. The use of any one of claims 1-17, wherein the RAS is NRAS.

25. The use of claim 24, 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.

26. The use of claim 25, 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.

27. The use of any one of claims 1-17, wherein the RAS is HRAS.

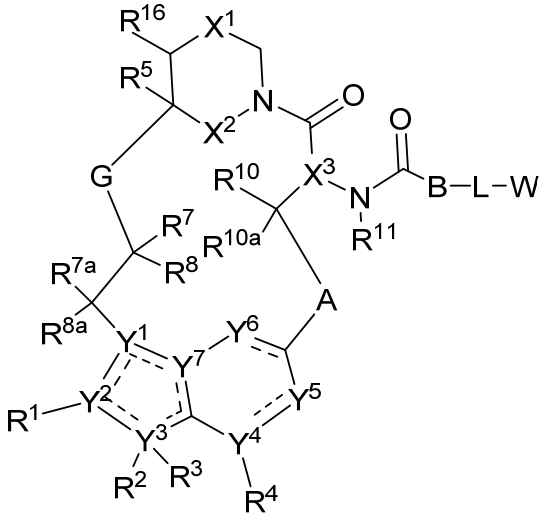
28. The use of claim 27, wherein the HRAS comprises or further comprises an amino acid substitution at G12, G13, Q61, K117, A59, A18, D119, A66, A146, or a combination thereof.

29. The use of claim 28, 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.

30. The use of any one of claims 1-29, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, G13D, or G12D.

31. The use of any one of claims 1-29, wherein the RAS(ON) inhibitor is a RAS(ON)$^{MULTI}$ inhibitor.

32. The use of any one of claims 1-31, 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)$_2$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 $C=CR^{7'}R^{8'}$; 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;

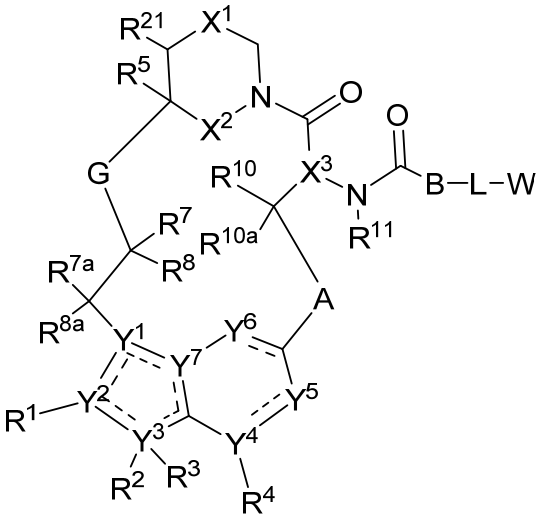
$R^{10a}$ is hydrogen or halo;

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

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

33. The use of any one of claims 1-31, wherein the RAS(ON) inhibitor is selected from a compound of Table A1 or Table A2, or a pharmaceutically acceptable salt thereof.

34. The use of any one of claims 1-31, 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', $S(O)_2R'$, 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), $C=N(O\text{-}C_1\text{-}C_3$ 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;

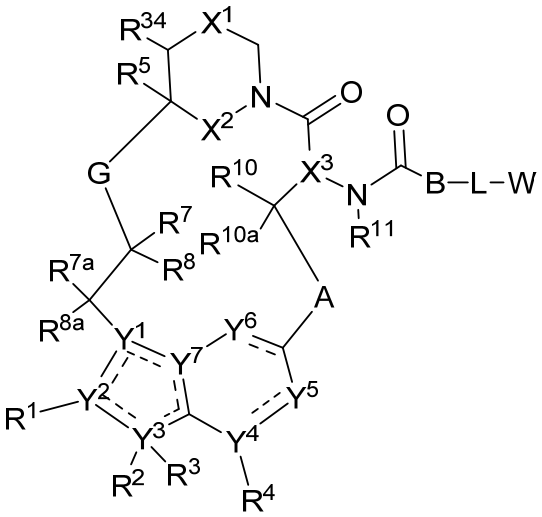
$R^{10a}$ is hydrogen or halo;

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

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

35. The use of any one of claims 1-31, wherein the RAS(ON) inhibitor is selected from a compound of Table B1 or Table B2, or a pharmaceutically acceptable salt thereof.

36. The use of any one of claims 1-31, 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;

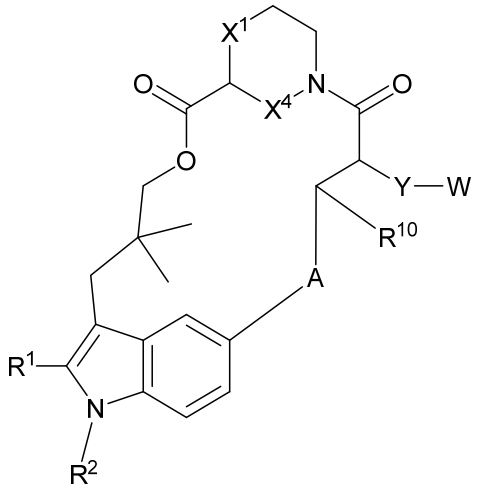
$R^{10a}$ is hydrogen or halo; and

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

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

37. The use of any one of claims 1-31, wherein the RAS(ON) inhibitor is selected from a compound of Table C1 or Table C2, or a pharmaceutically acceptable salt thereof.

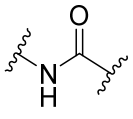
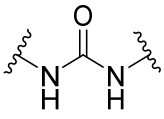
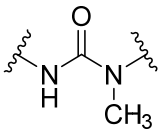
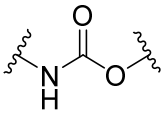
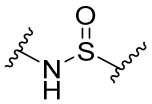
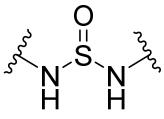
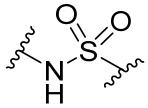
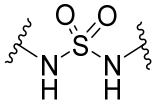
38. The use of any one of claims 1-31, wherein the RAS(ON) inhibitor is a compound described by Formula DIa:




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.

39. The use of any one of claims 1-31, wherein the RAS(ON) inhibitor is selected from a compound of Table D1a or D1b, or a pharmaceutically acceptable salt thereof.

40. The use of any one of claims 1-39, wherein the RAS(OFF) inhibitor selectively targets RAS G12C.

41. The use of any one of claims 1-39, wherein the RAS(OFF) inhibitor selectively targets RAS G12D.

42. The use of any one of claims 1-41, 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.

43. The use of any one of claims 1-42, 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.

44. The use of claim 43, wherein the cancer is non-small cell lung cancer.

45. The use of claim 43, wherein the cancer is pancreatic cancer.