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 addition, compounds disclosed herein may provide a clinical benefit for patients naïve to RAS(OFF) therapy.

In any example herein, a RAS(ON) inhibitor may be a tri-complex RAS(ON) inhibitor, as that term is defined herein.

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.

In one aspect, the present disclosure provides for a 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) a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of H95, R68, G13 and Q61, or a second RAS mutation that is selected from the group consisting of Y96C, Y96F, Y96H, Y96N, Y96S; or

(b) a first RAS mutation at position G12 selected from the group consisting of G12H, G12I, G12K, G12M, G12N, G12P, G12Q, G12T, G12W and G12Y,

wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, the subject was previously treated with the RAS(OFF) inhibitor, and the subject's cancer progresses on the RAS(OFF) inhibitor.

In another aspect, the present disclosure provides for a use of a RAS(ON) inhibitor in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, wherein the subject is to be administered a RAS(ON) inhibitor.

Numbered Examples

1. A method of treating cancer in a subject in need thereof, wherein the cancer comprises:

(a) a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of Y96, H95, R68, G13 and Q61; or

(b) a first RAS mutation at position G12,

wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, the method comprising administering to the subject a RAS(ON) inhibitor.

2. The method of example 1, wherein the cancer does not comprise a KRAS Y96D mutation.

3. The method of example 1, wherein the cancer does not comprise any of the following mutations: KRAS G12D, KRAS G12V, KRAS G12C, KRAS G12R, KRAS G12A, KRAS G12S, KRAS G12F, KRAS G12L, HRAS G12S, HRAS G12D, HRAS G12C, HRAS G12V, HRAS G12A, HRAS G12N, HRAS G12R, NRAS G12D, NRAS G12S, NRAS G12C, NRAS G12V, NRAS G12A, or NRAS G12R, or any combination thereof.

4. The method of any one of examples 1-3, wherein the cancer does not comprise a KRAS mutation selected from the group consisting of $G12C^{amp}$, G12D, G12R, G12V, G12W, G13D, Q61H, R68S, H95D, H95Q, H95R and Y96C, or any combination thereof.

5. The method of any one of examples 1-4, further comprising administering to the subject a RAS(OFF) inhibitor.

6. The method of example 5, wherein the RAS(ON) inhibitor and the RAS(OFF) inhibitor are administered simultaneously or sequentially.

7. The method of example 5 or 6 wherein the RAS(ON) inhibitor and the RAS(OFF) inhibitor are administered as a single formulation or in separate formulations.

8. The method of example 6, wherein:

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.

9. The method of example 6, wherein:

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.

10. The method of any one of examples 5-9, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

11. The method of example 1, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position Y96.

12. The method of example 1 or example 11, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96D, Y96F, Y96H, Y96N and Y96S.

13. The method of example 1 or example 11, wherein the second RAS mutation is selected from the group consisting of Y96D, Y96F, Y96H, Y96N and Y96S.

14. The method of example 1 or example 11, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96F, Y96H, Y96N and Y96S.

15. The method of example 1 or example 11, wherein the second RAS mutation is selected from the group consisting of Y96F, Y96H, Y96N and Y96S.

16. The method of example 1, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position H95 or R68.

17. The method of example 1 or example 16, wherein the first RAS mutation is G12C and the second RAS mutation is at position H95.

18. The method of any one of examples 1, 16 or 17, wherein the second RAS mutation is selected from the group consisting of H95D, H95L, H95N, H95P, H95Q, H95R and H95Y.

19. The method of any one of examples 1, 16 or 17, wherein the second RAS mutation is selected from the group consisting of H95L, H95N, H95P and H95Y.

20. The method of example 1 or example 16, wherein the first RAS mutation is G12C and the second RAS mutation is at position R68.

21. The method of any one of examples 1, 16 or 20, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68S, R68T and R68W.

22. The method of any one of examples 1, 16 or 20, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68T and R68W.

23. The method of any one of examples 1-4 and 11-22, wherein the subject has been treated with a RAS(OFF) inhibitor.

24. A method of treating cancer in a subject in need thereof, wherein the cancer comprises an amino acid substitution at RAS Y96, H95, or R68, the method comprising administering to the subject a RAS(ON) inhibitor.

25. The method of example 24, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position Y96.

26. The method of example 24 or example 25, wherein the cancer does not comprise a Y96D RAS mutation.

27. The method of example 25 or example 26, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96D, Y96F, Y96H, Y96N and Y96S.

28. The method of example 25 or example 26, wherein the second RAS mutation is selected from the group consisting of Y96D, Y96F, Y96H, Y96N and Y96S.

29. The method of example 25 or example 26, wherein the second RAS mutation is selected from the group consisting of Y96C, Y96F, Y96H, Y96N and Y96S.

30. The method of example 25 or example 26, wherein the second RAS mutation is selected from the group consisting of Y96F, Y96H, Y96N and Y96S.

31. The method of example 25, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position H95 or R68.

32. The method of example 25 or example 31, wherein the first RAS mutation is G12C and the second RAS mutation is at position H95.

33. The method of any one of examples 25, 31 or 32, wherein the second RAS mutation is selected from the group consisting of H95D, H95L, H95N, H95P, H95Q, H95R and H95Y.

34. The method of any one of examples 25, 31 or 32, wherein the second RAS mutation is selected from the group consisting of H95L, H95N, H95P and H95Y.

35. The method of example 25 or example 31, wherein the first RAS mutation is G12C and the second RAS mutation is at position R68.

36. The method of any one of examples 25, 31 or 35, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68S, R68T and R68W.

37. The method of any one of examples 25, 31 or 35, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68T and R68W.

38. The method of example 1, wherein the second mutation is Q61H.

39. The method of example 1, wherein the second mutation is G13D.

40. The method of any one of examples 27-39, wherein the subject has been treated with a RAS(OFF) inhibitor.

41. The method of any one of examples 27-40, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor.

42. The method of example 40 or example 41, wherein the subject’s cancer progresses on the RAS(OFF) inhibitor.

43. The method of any one of examples 1-42, wherein any RAS mutation is a KRAS mutation.

44. The method of any one of examples 1-42, wherein any RAS mutation is a NRAS mutation.

45. The method of any one of examples 1-42, wherein any RAS mutation is an HRAS mutation.

46. A method of treating cancer in a subject in need thereof, wherein the cancer comprises a RAS mutation selected from the group consisting of G12H, G12I, G12K, G12M, G12N, G12P, G12Q, G12T,

G12W and G12Y, or a combination thereof, the method comprising administering to the subject a RAS(ON) inhibitor.

47. The method of example 46, wherein the cancer further comprises a G12C RAS mutation.

48. The method of example 46 or 47, wherein the subject has been treated with a RAS(OFF) inhibitor.

49. The method of any one of examples 46-48, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor.

50. The method of example 48 or example 49, wherein the subject's cancer progresses on the RAS(OFF) inhibitor.

51. A method of inhibiting RAS in a cell, wherein the RAS comprises an amino acid substitution at Y96, H95 or R68, the method comprising contacting the cell with a RAS(ON) inhibitor.

52. A method of inhibiting RAS in a cell, wherein the RAS comprises an amino acid substitution at H95 or R68, the method comprising contacting the cell with a RAS(ON) inhibitor.

53. The method of example 51 or example 52, wherein the cell is in vitro.

54. The method of example 51 or clam 52, wherein the cell is in vivo.

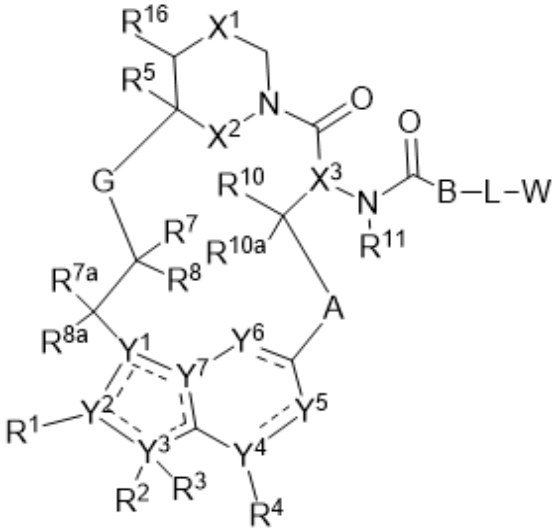
55. The method of any one of examples 1-54, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, G13D, or G12D.

56. The method of any one of examples 1-54, wherein the RAS(ON) inhibitor is a RAS(ON)^{MULTI} inhibitor.

57. The method of any one of examples 1-56, wherein the RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor.

58. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound disclosed in WO 2020132597.

59. The method of any one of examples 1-57, 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;

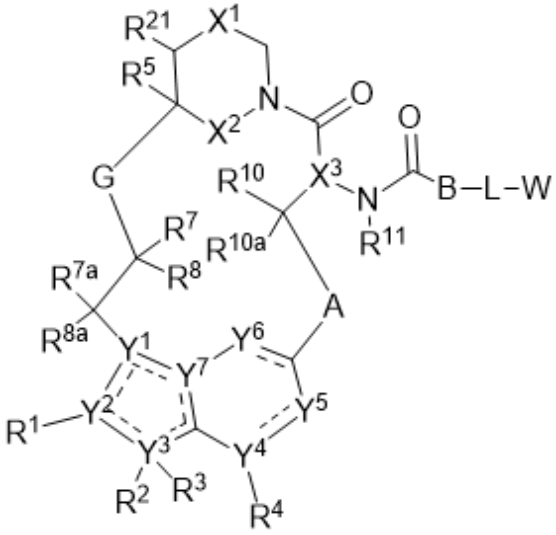
R^{10a} is hydrogen or halo;

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

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

60. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table A1 or Table A2, or a pharmaceutically acceptable salt thereof.

61. The method of any one of examples 1-57, 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;

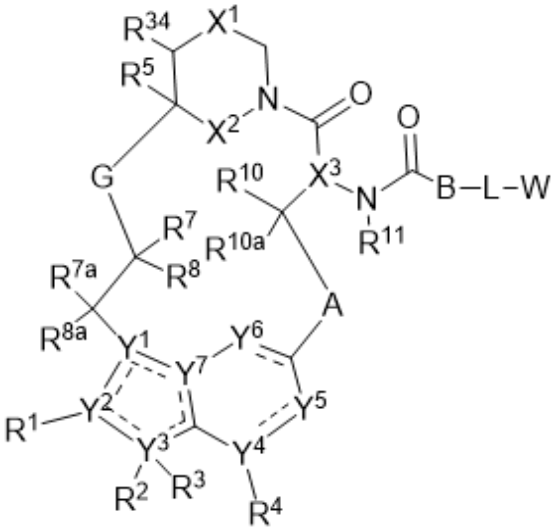
R^{10a} is hydrogen or halo;

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

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

62. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table B1 or Table B2, or a pharmaceutically acceptable salt thereof.

63. The method of any one of examples 1-57, 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;

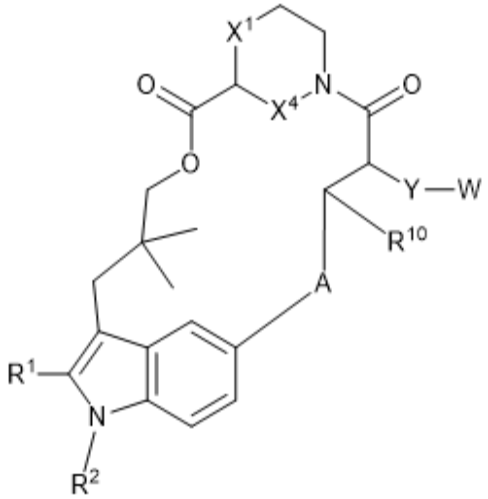
R^{10a} is hydrogen or halo; and

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

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

64. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table C1 or Table C2, or a pharmaceutically acceptable salt thereof.

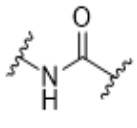
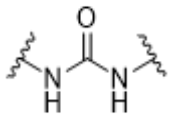
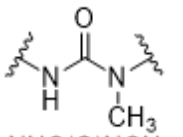
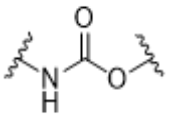
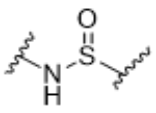
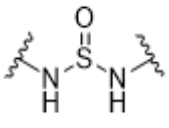
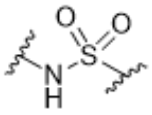
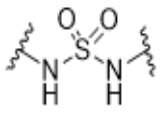
65. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is a compound of Formula DIa:



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;

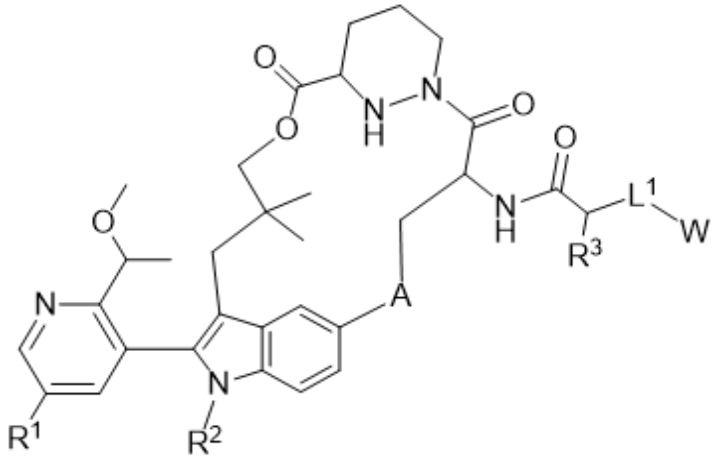
X^1 and X^4 are each, independently, CH_2 or NH;

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.

66. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table D1a or D1b, or a pharmaceutically acceptable salt thereof.

67. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is a compound of Formula EI:



Formula EI,

or a pharmaceutically acceptable salt thereof,

wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

L^1 is absent or a linker;

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

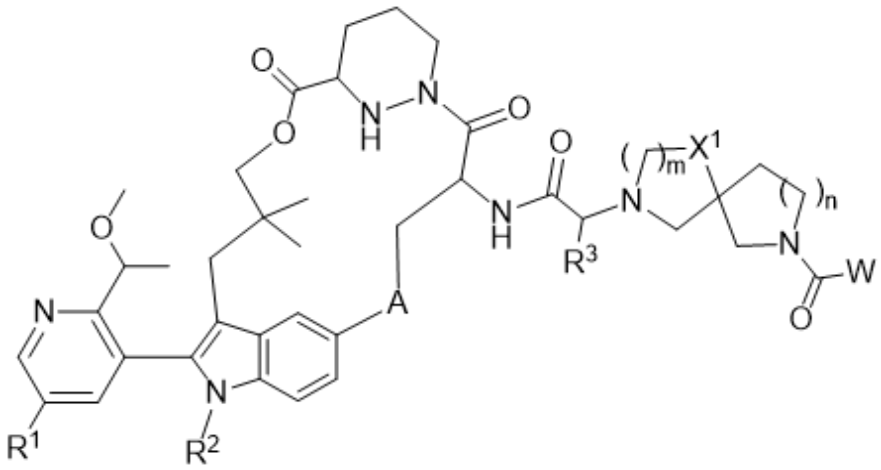
R^1 is hydrogen, optionally substituted 3 to 10-membered heterocycloalkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^2 is optionally substituted C_1-C_6 alkyl; and

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl.

68. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table E1, or a pharmaceutically acceptable salt thereof.

69. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is a compound of Formula FI:



Formula FI

wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

W is a cross-linking group comprising an aziridine, an epoxide, a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, 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 oxazolium, or a glycal;

X^1 is CH_2 or O;

m is 1 or 2;

n is 0 or 1;

R^1 is hydrogen or optionally substituted 3 to 10-membered heterocycloalkyl;

R^2 is optionally substituted C_1-C_6 alkyl; and

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl.

70. The method of any one of examples 1-57, wherein the RAS(ON) inhibitor is selected from a compound of Table F1, Table F2, Table F3, Table F4, Table F5, or Table F6.

71. The method of any one of examples 1-23, 40-45, or 48-50, wherein the RAS(OFF) inhibitor selectively targets RAS G12C.

72. The method of any one of examples 1-23, 40-45, or 48-50, 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, JAB-21000, RSC-1255, ERAS-3490, D-1553, JAB-21822, GH-35, ICP-915, IBI351, and BI1823911.

73. The method of any one of examples 1-72, wherein the cancer is selected from colorectal cancer, non-small cell lung cancer, small-cell lung cancer, pancreatic cancer, appendiceal cancer, 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 and melanoma.

74. The method of example 76, wherein the cancer is non-small cell lung cancer.

75. The method of any one of examples 1-74, wherein the method further comprises administering to the subject or the cell an additional anti-cancer therapy.

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) a first RAS mutation that is G12C and a second RAS mutation at a position selected from the group consisting of H95, R68, G13 and Q61, or a second RAS mutation that is selected from the group consisting of Y96C, Y96F, Y96H, Y96N, Y96S; or

(b) a first RAS mutation at position G12 selected from the group consisting of G12H, G12I, G12K, G12M, G12N, G12P, G12Q, G12T, G12W and G12Y,

wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, the subject was previously treated with the RAS(OFF) inhibitor, and the subject's cancer progresses on the RAS(OFF) inhibitor.

2. The use of claim 1, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position H95 or R68.

3. The use of claim 2, wherein the second RAS mutation is selected from the group consisting of H95D, H95L, H95N, H95P, H95Q, H95R and H95Y.

4. The use of claim 2, wherein the second mutation is selected from the group consisting of R68G, R68K, R68M, R68S, R68T and R68W.

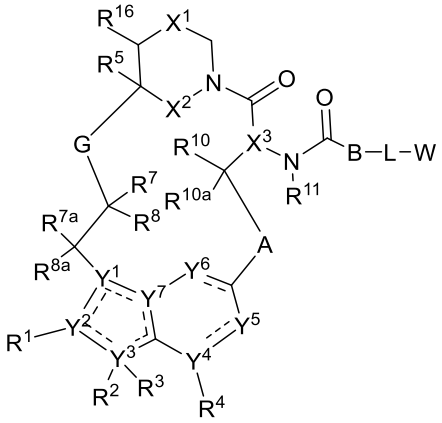
5. The use of claim 1, wherein any RAS mutation is selected from a KRAS mutation, an NRAS mutation, and an HRAS mutation.

6. The use of claim 1, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS G12C, G13D, or G12D.

7. The use of claim 1, wherein the RAS(ON) inhibitor is a RAS(ON)^{MULTI} inhibitor.

8. The use of claim 1, wherein the RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor.

9. The use of claim 1, 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;

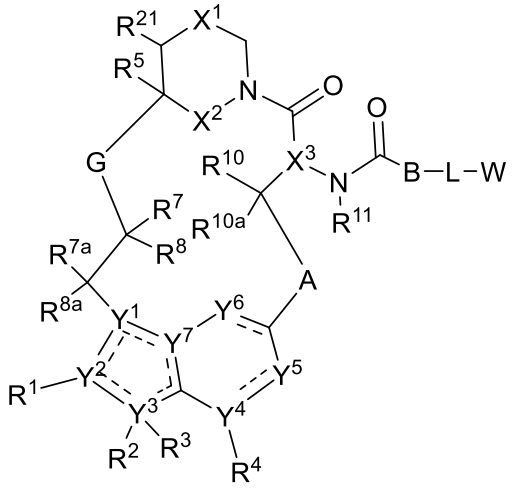
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

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.

10. The use of claim 1, 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;

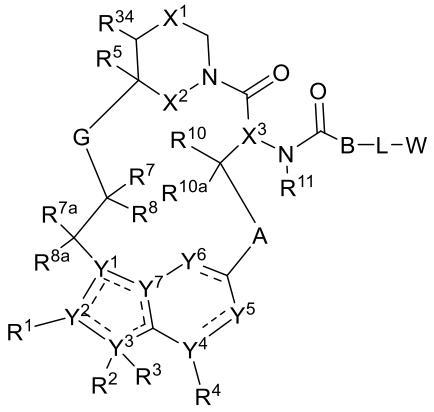
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

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.

11. The use of claim 1, wherein the RAS(ON) inhibitor is a compound of 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', $S(O)_2$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;

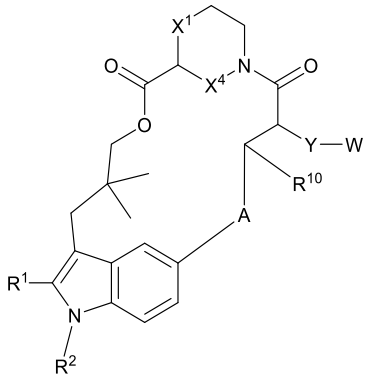
R^{10} is hydrogen, halo, hydroxy, C_1-C_3 alkoxy, or C_1-C_3 alkyl;

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.

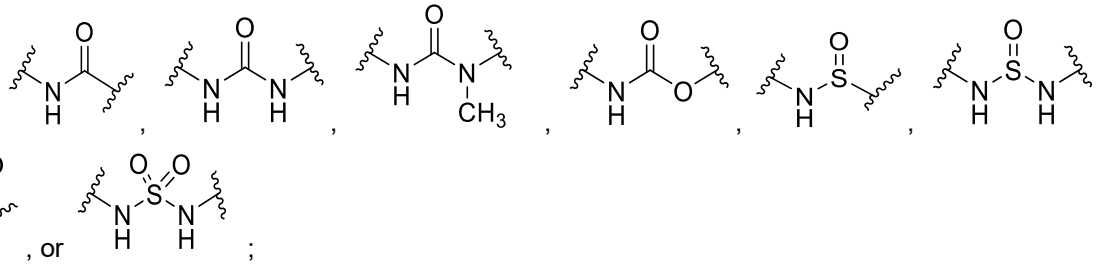
12. The use of claim 1, wherein the RAS(ON) inhibitor is a compound of Formula DIa:



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 

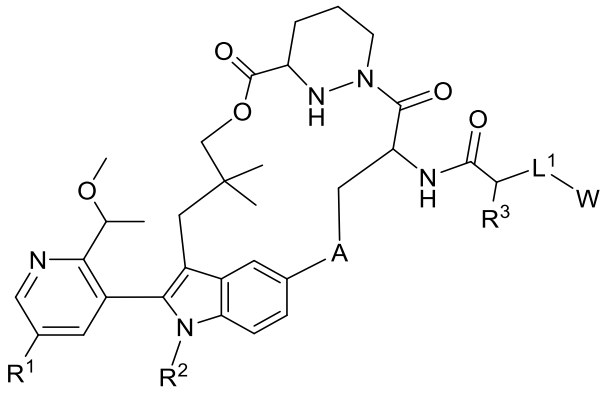
W is hydrogen, C_1-C_4 alkyl, optionally substituted C_1-C_3 heteroalkyl, optionally substituted 3 to 10-membered heterocycloalkyl, optionally substituted 3 to 10-membered cycloalkyl, optionally substituted 6 to 10-membered aryl, or optionally substituted 5 to 10-membered heteroaryl;

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.

13. The use of claim 1, wherein the RAS(ON) inhibitor is a compound of Formula EI:



Formula EI,

or a pharmaceutically acceptable salt thereof,

wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

L^1 is absent or a linker;

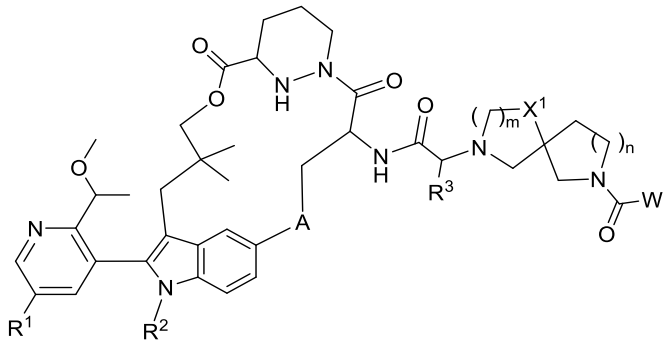
W is a cross-linking group comprising a vinyl ketone, vinyl sulfone, ynone, or an alkynyl sulfone;

R^1 is hydrogen, optionally substituted 3 to 10-membered heterocycloalkyl, or optionally substituted C_1-C_6 heteroalkyl;

R^2 is optionally substituted C_1-C_6 alkyl; and

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted C_1-C_3 heteroalkyl.

14. The use of claim 1, wherein the RAS(ON) inhibitor is a compound of Formula FI:



Formula FI

or a pharmaceutically acceptable salt thereof,

wherein A is optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene;

W is a cross-linking group comprising an aziridine, an epoxide, a carbodiimide, an oxazoline, a thiazoline, a chloroethyl urea, a chloroethyl thiourea, a chloroethyl carbamate, a chloroethyl thiocarbamate, 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 oxazolium, or a glycal;

X^1 is CH_2 or O;

m is 1 or 2;

n is 0 or 1;

R^1 is hydrogen or optionally substituted 3 to 10-membered heterocycloalkyl;

R^2 is optionally substituted C_1-C_6 alkyl; and

R^3 is optionally substituted C_1-C_6 alkyl or optionally substituted 3 to 6-membered cycloalkyl.

15. Use of a RAS(ON) inhibitor in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the cancer is resistant to treatment with a RAS(OFF) inhibitor, wherein the subject is to be administered a RAS(ON) inhibitor.

16. The use according to claim 15, wherein the cancer comprises a first RAS mutation that is G12C and a second RAS mutation at position H95 or R68.

17. The use according to claim 16, wherein the second RAS mutation is selected from the group consisting of H95D, H95L, H95N, H95P, H95Q, H95R, H95Y, R68G, R68K, R68M, R68T, and R68W.

18. The use according to claim 15, wherein any RAS mutation is selected from a KRAS mutation, an NRAS mutation, and an HRAS mutation.

19. The use according to claim 15, wherein the RAS(ON) inhibitor is an inhibitor selective for RAS g12C, G13D, or G12D.

20. The use according to claim 15, wherein the RAS(ON) inhibitor is a tri-complex RAS(ON) inhibitor.