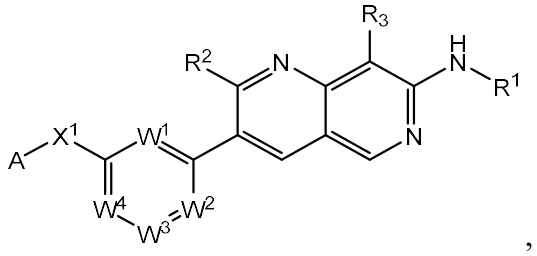
Claims

1. Use of a compound of Formula (I'):



(I')

an isomer thereof, or a pharmaceutically acceptable salt thereof, in the treatment or prevention of cancer in a subject, wherein:

W^1 is N or CR^{W1};

R^{W1} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

W^2 is N or CR^{W2};

R^{W2} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more halogen;

W^3 is N or CR^{W3};

R^{W3} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

W^4 is N or CR^{W4};

R^{W4} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or S(C_1-C_6 alkyl);

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1a};

each R^{1a} independently is halogen, cyano, OH, NH_2, NHC(=O)O(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

R^2 is H, halogen, cyano, oxo, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy;

R^3 is H, halogen, cyano, oxo, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy, or

R^1 and R^3, together with the intervening atoms, form a 4- to 12-membered heterocycloalkyl optionally substituted with one or more oxo;

X^1 is -NR^{X1}-*, -$C(=O)NR^{X1}$-*, -$NR^{X1}C(=O)$-*, -$NR^{X1}C(=O)O$-*, -$NR^{X1}N=C$-*, -$NR^{X1}C(=NR^{X1})$-*, -$NR^{X1}C(=NH)NR^{X1}$-*, or -$S(=O)_2NR^{X1}$-*, wherein * denotes attachment to A;

R^{X1} independently is H, $S(=O)_2R^{X1a}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{X1a};

each R^{X1a} independently is halogen, C_1-C_6 alkyl, or 3- to 12-membered heterocycloalkyl, wherein the C_1-C_6 alkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more halogen;

A is C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -(C_1-C_6 alkyl)-(C_3-C_{12} cycloalkyl), -(C_1-C_6 alkyl)-(3- to 12-membered heterocycloalkyl), -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -(C_1-C_6 alkyl)-(C_3-C_{12} cycloalkyl), -(C_1-C_6 alkyl)-(3- to 12-membered heterocycloalkyl), -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^A;

each R^A independently is halogen, cyano, oxo, OH, OR^{A1}, NH_2, NHR^{A1}, $N(R^{A1})_2$, $(=N)R^{A1}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{A1};

each R^{A1} independently is halogen, cyano, oxo, OH, OR^{A2}, NH_2, NHR^{A2}, $N(R^{A2})_2$, $C(=O)R^{A2}$, C_1-C_6 alkyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{A2};

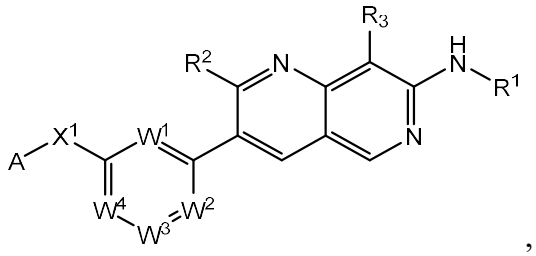
each R^{A2} independently is halogen, cyano, OH, NH_2, $N(R^{A3})_2$, $C(=O)R^{A3}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; and

each R^{A3} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl,

wherein the compound is administered at a dosage of about 6 mg, about 12 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg.

2. Use of a combination in the treatment or prevention of cancer in a subject, wherein the combination comprises:

(i) a compound of Formula (I'):



(I')

an isomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

W^1 is N or CR^{W1};

R^{W1} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

W^2 is N or CR^{W2};

R^{W2} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more halogen;

W^3 is N or CR^{W3};

R^{W3} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

W^4 is N or CR^{W4};

R^{W4} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or $S(C_1$-C_6 alkyl);

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1a};

each R^{1a} independently is halogen, cyano, OH, NH_2, NHC(=O)O(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

R^2 is H, halogen, cyano, oxo, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy;

R^3 is H, halogen, cyano, oxo, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy, or

R^1 and R^3, together with the intervening atoms, form a 4- to 12-membered heterocycloalkyl optionally substituted with one or more oxo;

X^1 is -NR^{X1}-*, -C(=O)NR^{X1}-*, -NR^{X1}C(=O)-*, -NR^{X1}C(=O)O-*, -NR^{X1}N=C-*, -NR^{X1}C(=NR^{X1})-*, -NR^{X1}C(=NH)NR^{X1}-*, or -S(=O)$_2$$NR^{X1}$-*, wherein * denotes attachment to A;

R^{X1} independently is H, S(=O)$_2$$R^{X1a}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{X1a};

each R^{X1a} independently is halogen, C_1-C_6 alkyl, or 3- to 12-membered heterocycloalkyl, wherein the C_1-C_6 alkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more halogen;

A is C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -(C_1-C_6 alkyl)-(C_3-C_{12} cycloalkyl), -(C_1-C_6 alkyl)-(3- to 12-membered heterocycloalkyl), -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -(C_1-C_6 alkyl)-(C_3-C_{12} cycloalkyl), -(C_1-C_6 alkyl)-(3- to 12-membered heterocycloalkyl), -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^A;

each R^A independently is halogen, cyano, oxo, OH, OR^{A1}, NH_2, NHR^{A1}, N(R^{A1})$_2$, (=N)R^{A1}, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{A1};

each R^{A1} independently is halogen, cyano, oxo, OH, OR^{A2}, NH_2, NHR^{A2}, $N(R^{A2})_2$, $C(=O)R^{A2}$, C_1-C_6 alkyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{A2};

each R^{A2} independently is halogen, cyano, OH, NH_2, $N(R^{A3})_2$, $C(=O)R^{A3}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; and

each R^{A3} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; and

(ii) one or more additional therapeutic agent selected from a SHP2 inhibitor, SOS1 inhibitor, KRAS inhibitor, ERK inhibitor, immune checkpoint inhibitor, chemotherapy, EGFR inhibitor, MET inhibitor, TEAD inhibitor, YAP inhibitor, PI3K inhibitor, mTOR inhibitor, metabolic inhibitor, and MEK inhibitor.

3. The use of claim 2, wherein:

(i) the SHP2 inhibitor is selected from JAB-3068, JAB-3312, TNO-155, RLY-1971, and RMC-4630;

(ii) the SOS1 inhibitor is selected from BI-1701963, BI-1703880, and MRTX0902;

(iii) the KRAS inhibitor is selected from sotorasib, adagrasib, LY3537982, divarasib, JDQ443, BI-1823911, MRTX1133, RMC-9805, and RMC-6236;

(iv) the ERK inhibitor is selected from ulixertinib, MK-8353, LY3214996, ASTX029, ASN007, LTT462, and KO-947;

(v) the immune checkpoint inhibitor is selected from pembrolizumab, ipilimumab, nivolumab, and atezolizumab;

(vi) the chemotherapy is selected from oxaliplatin and irinotecan;

(vii) the EGFR inhibitor is selected from erlotinib, osimertinib, neratinib, gefitinib, cetuximab, panitumumab, dacomitinib, lapatinib, necitumumab, mobocertinib, or vandetanib;

(viii) the MET inhibitor is selected from crizotinib, capmatinib, tepotinib, savolitinib. Cabozantinib, glesatinib, foretinib, merestinib, tivantinib, SAR125844, onartuzumab, telisotuzumab, and JNJ-61186372;

(ix) the TEAD inhibitor is selected from VT3989, IK-930, and IAG933;

(x) the YAP inhibitor is verteporfin;

(xi) the PI3K inhibitor is selected from idelalisib, alpelisib, alpelisib, leniolisib, duvelisib, and copanlisib;

(xii) the mTOR inhibitor is selected from everolimus, sirolimus, temsirolimus, everolimus, sirolimus, sirolimus protein-bound, and everolimus;

(xiii) the metabolic inhibitor is selected from trifluridine, gemcitabine, fluorouracil, pentostatin, clofarabine, azacitidine, cytarabine, mercaptopurine, fludarabine, and capecitabine; and

(xiv) the MEK inhibitor is selected from trametinib, cobimetinib, and binimetinib.

4. The use of claim 2 or claim 3, wherein the compound of Formula (I') is administered at a dosage of about 6 mg, about 12 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, about 400 mg, about 600 mg, about 800 mg, about 1000 mg, or about 1200 mg.

5. The use of any one of claims 1-4, wherein the cancer is a carcinoma, a lymphoma, a blastoma, a sarcoma, a leukemia, a brain cancer, a breast cancer, a blood cancer, a bone cancer, a lung cancer, a skin cancer, a liver cancer, an ovarian cancer, a bladder cancer, a renal cancer, a kidney cancer, a gastric cancer, a thyroid cancer, a pancreatic cancer, an esophageal cancer, a prostate cancer, a cervical cancer, a uterine cancer, a stomach cancer, a soft tissue cancer, a laryngeal cancer, a small intestine cancer, a testicular cancer, an anal cancer, a vulvar cancer, a joint cancer, an oral cancer, a pharynx cancer, or a colorectal cancer.

6. The use of any one of claims 1-5, wherein the cancer is a hematological cancer.

7. The use of claim 6, wherein the hematological cancer is acute myeloid leukemia.

8. The use of any one of claims 1-5, wherein the cancer is a solid cancer.

9. The use of claim 8, wherein the solid cancer is a carcinoma.

10. The use of claim 9, wherein the carcinoma is pancreatic adenocarcinoma.

11. The use of claim 8, wherein the solid cancer is non-small cell lung cancer (NSCLC), brain cancer, colorectal cancer, melanoma, thyroid cancer, histiocytosis, small bowel cancer, gastrointestinal neuroendocrine cancer, carcinoma of unknown primary, non-melanoma skin cancer, prostate cancer, gastric cancer, non-Hodgkin's lymphoma, papillary thyroid carcinoma, or glioblastoma.

12. The use of claim 11, wherein the solid cancer is NSCLC.

13. The use of claim 11, wherein the solid cancer is brain cancer.

14. The use of claim 11, wherein the solid cancer is thyroid carcinoma, colorectal carcinoma, melanoma, or a histiocytic neoplasm.

15. The use of any one of claims 1-14, wherein the cancer is characterized by at least one oncogenic mutation in the *BRAF* gene.

16. The use of any one of claims 1-15, wherein the cancer is characterized by at least one oncogenic variant of a RAS GTPase.

17. The use of any one of claims 1-16, wherein the cancer is characterized by at least one oncogenic mutation in the *KRAS* gene.

18. The use of claim 17, wherein the oncogenic mutation is not K-Ras-G12C.

19. The use of any one of claims 1-18, wherein the cancer is characterized by at least one oncogenic mutation in the *NRAS* gene.

20. The use of any one of claims 1-19, wherein the cancer is advanced or metastatic.

21. The use of any one of claims 1-20, wherein the compound of Formula (I') is administered to the subject orally or parenterally.

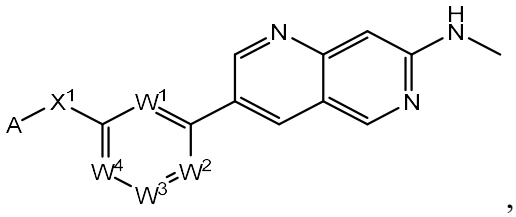
22. The use of any one of claims 1-21, wherein the compound of Formula (I') is administered to the subject once daily.

23. The use of any one of claims 1-21, wherein the compound of Formula (I') is administered to the subject twice daily.

24. The use of any one of claims 1-23, wherein the compound of Formula (I') is administered as a pharmaceutical composition to the subject.

25. The use of any one of claims 1-24, wherein the subject has been previously administered a BRAF inhibitor, a MEK inhibitor, or a combination thereof.

26. The use of any one of claims 1-25, wherein the compound of Formula (I') is of Formula (I-d):



(I-d)

an isomer thereof, or a pharmaceutically acceptable salt thereof.

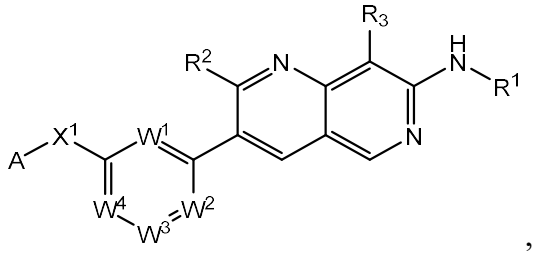
27. The use of any one of claims 1-26, wherein X^1 is -NHC(=O)-*, wherein * denotes attachment to A.

28. The use of any one of claims 1-27, wherein A is 5- to 10-membered heteroaryl substituted with one or more R^A.

29. The use of any one of claims 1-28, wherein the compound of Formula (I') is a compound described in Table I, an isomer thereof, or a pharmaceutically acceptable salt thereof.

30. A combination comprising:

(i) a compound of Formula (I'):



(I')

an isomer thereof, or a pharmaceutically acceptable salt thereof, wherein:

W^1 is N or CR^{W1};

R^{W1} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

W^2 is N or CR^{W2};

R^{W2} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl is optionally substituted with one or more halogen;

W^3 is N or CR^{W3};

R^{W3} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl;

W^4 is N or CR^{W4};

R^{W4} is H, halogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or S(C_1-C_6 alkyl);

R^1 is H, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{1a};

each R^{1a} independently is halogen, cyano, OH, NH_2, NHC(=O)O(C_1-C_6 alkyl), N(C_1-C_6 alkyl)$_2$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl;

R^2 is H, halogen, cyano, oxo, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy;

R^3 is H, halogen, cyano, oxo, OH, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, or C_1-C_6 alkoxy, or

R^1 and R^3, together with the intervening atoms, form a 4- to 12-membered heterocycloalkyl optionally substituted with one or more oxo;

X^1 is $-NR^{X1}-*$, $-C(=O)NR^{X1}-*$, $-NR^{X1}C(=O)-*$, $-NR^{X1}C(=O)O-*$, $-NR^{X1}N=C-*$, $-NR^{X1}C(=NR^{X1})-*$, $-NR^{X1}C(=NH)NR^{X1}-*$, or $-S(=O)_2NR^{X1}-*$, wherein * denotes attachment to A;

R^{X1} independently is H, $S(=O)_2R^{X1a}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{X1a};

each R^{X1a} independently is halogen, C_1-C_6 alkyl, or 3- to 12-membered heterocycloalkyl, wherein the C_1-C_6 alkyl or 3- to 12-membered heterocycloalkyl is optionally substituted with one or more halogen;

A is C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -(C_1-C_6 alkyl)-(C_3-C_{12} cycloalkyl), -(C_1-C_6 alkyl)-(3- to 12-membered heterocycloalkyl), -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl), wherein the C_1-C_6 alkyl, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, 5- to 10-membered heteroaryl, -(C_1-C_6 alkyl)-(C_3-C_{12} cycloalkyl), -(C_1-C_6 alkyl)-(3- to 12-membered heterocycloalkyl), -(C_1-C_6 alkyl)-(C_6-C_{10} aryl), or -(C_1-C_6 alkyl)-(5- to 10-membered heteroaryl) is optionally substituted with one or more R^A;

each R^A independently is halogen, cyano, oxo, OH, OR^{A1}, NH_2, NHR^{A1}, $N(R^{A1})_2$, $(=N)R^{A1}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{A1};

each R^{A1} independently is halogen, cyano, oxo, OH, OR^{A2}, NH_2, NHR^{A2}, $N(R^{A2})_2$, $C(=O)R^{A2}$, C_1-C_6 alkyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl, wherein the C_1-C_6 alkyl, C_2-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_{12} cycloalkyl, 3- to 12-membered heterocycloalkyl, C_6-C_{10} aryl, or 5- to 10-membered heteroaryl is optionally substituted with one or more R^{A2};

each R^{A2} independently is halogen, cyano, OH, NH_2, $N(R^{A3})_2$, $C(=O)R^{A3}$, C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; and

each R^{A3} independently is C_1-C_6 alkyl, C_2-C_6 alkenyl, or C_2-C_6 alkynyl; and

(ii) one or more additional therapeutic agent selected from a SHP2 inhibitor, SOS1 inhibitor, KRAS inhibitor, ERK inhibitor, immune checkpoint inhibitor, chemotherapy, EGFR inhibitor, MET inhibitor, TEAD inhibitor, YAP inhibitor, PI3K inhibitor, mTOR inhibitor, metabolic inhibitor, and MEK inhibitor.

31. The combination of claim 30, wherein:

(i) the SHP2 inhibitor is selected from JAB-3068, JAB-3312, TNO-155, RLY-1971, and RMC-4630;

(ii) the SOS1 inhibitor is selected from BI-1701963, BI-1703880, and MRTX0902;

(iii) the KRAS inhibitor is selected from sotorasib, adagrasib, LY3537982, divarasib, JDQ443, BI-1823911, MRTX1133, RMC-9805, and RMC-6236;

(iv) the ERK inhibitor is selected from ulixertinib, MK-8353, LY3214996, ASTX029, ASN007, LTT462, and KO-947;

(v) the immune checkpoint inhibitor is selected from pembrolizumab, ipilimumab, nivolumab, and atezolizumab;

(vi) the chemotherapy is selected from oxaliplatin and irinotecan;

(vii) the EGFR inhibitor is selected from erlotinib, osimertinib, neratinib, gefitinib, cetuximab, panitumumab, dacomitinib, lapatinib, necitumumab, mobocertinib, or vandetanib;

(viii) the MET inhibitor is selected from crizotinib, capmatinib, tepotinib, savolitinib. Cabozantinib, glesatinib, foretinib, merestinib, tivantinib, SAR125844, onartuzumab, telisotuzumab, and JNJ-61186372;

(ix) the TEAD inhibitor is selected from VT3989, IK-930, and IAG933;

(x) the YAP inhibitor is verteporfin;

(xi) the PI3K inhibitor is selected from idelalisib, alpelisib, alpelisib, leniolisib, duvelisib, and copanlisib;

(xii) the mTOR inhibitor is selected from everolimus, sirolimus, temsirolimus, everolimus, sirolimus, sirolimus protein-bound, and everolimus;

(xiii) the metabolic inhibitor is selected from trifluridine, gemcitabine, fluorouracil, pentostatin, clofarabine, azacitidine, cytarabine, mercaptopurine, fludarabine, and capecitabine; and

(xiv) the MEK inhibitor is selected from trametinib, cobimetinib, and binimetinib.