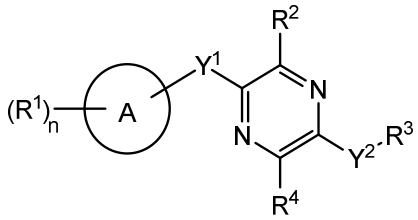
CLAIMS

1. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~ in the manufacture of a medicament for treating a disease or disorder comprising a cell containing a mutation encoding the $KRAS^{G12C}$ variant, wherein said inhibitor of SHP2 is a compound of Formula I-V2:



I-V2

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, and/or isomer thereof, wherein:

A is cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl, and heteroaryl are 5- to 12-membered monocyclic or 5- to 12-membered polycyclic;

Y^1 is –S–, a direct bond, –NH–, $–S(O)_2–$, $–S(O)_2–NH–$, $–C(=CH_2)$ –, –CH–, or –S(O)–;

Y^2 is $–NR^a–$, wherein the bond on the left side of Y^2, as drawn, is bound to the pyrazine ring and the bond on the right side of the Y^2 moiety, as drawn, is bound to R^3;

R^3 is combined with R^a to form a 3- to 12-membered polycyclic heterocycle or a 5- to 12-membered spiroheterocycle, wherein each heterocycle or spiroheterocycle is optionally substituted with one or more $–C_1$-C_6alkyl, halogen, –OH, $–OR^b$, $–NH_2$, $–NHR^b$, heteroaryl, heterocyclyl, $–(CH_2)_nNH_2$, $–(CH_2)_nOH$, $–COOR^b$, $–CONHR^b$, $–CONH(CH_2)_nCOOR^b$, $–NHCOOR^b$, $–CF_3$, $–CHF_2$, $–CH_2F$, or =O;

R^1 is independently, at each occurrence, –H, –D, $–C_1$-C_6alkyl, $–C_2$-C_6alkenyl, $–C_4$-C_8cycloalkenyl, $–C_2$-C_6alkynyl, $–C_3$-C_8cycloalkyl, –OH, $–OR^6$, halogen, $–NO_2$, –CN, $–NR^5R^6$, $–SR^5$, $–S(O)_2NR^5R^6$, $–S(O)_2R^5$, $–NR^5S(O)_2NR^5R^6$, $–NR^5S(O)_2R^6$, $–S(O)NR^5R^6$, $–S(O)R^5$, $–NR^5S(O)NR^5R^6$, $–NR^5S(O)R^6$, $–C(O)R^5$,$–CO_2R^5$, $–C(O)NR^5R^6$, $–NR^5C(O)R^6$, monocyclic or polycyclic heterocyclyl, spiroheterocyclyl, heteroaryl, or oxo, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, spiroheterocyclyl, or heteroaryl is optionally substituted with one or more –OH, halogen, $–NO_2$, oxo, =O,

–CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl;

R^2 is independently –NH_2, –OR^b, –CN, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, halogen, –$C(O)OR^b$, –C_3-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more –OH, halogen, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, heterocycle, aryl, or heteroaryl; and wherein the heterocyclyl or heteroaryl is not attached via a nitrogen atom;

R^b is independently, at each occurrence, –H, –D, –OH, –C_1-C_6alkyl, –C_3-C_8cycloalkyl, –C_2-C_6alkenyl, –$(CH_2)_n$-aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O; wherein each alkyl, cycloalkyl, alkenyl, heterocycle, heteroaryl, or –$(CH_2)_n$-aryl is optionally substituted with one or more –OH, halogen, –NO_2, oxo, –CN, −R^5, –OR^5, –NR^5R^6, −SR^5, –$S(O)_2NR^5R^6$, –$S(O)_2R^5$, –$NR^5S(O)_2NR^5R^6$, –$NR^5S(O)_2R^6$, –$S(O)NR^5R^6$, –$S(O)R^5$, –$NR^5S(O)NR^5R^6$, –$NR^5S(O)R^6$, –$C(O)NR^5R^6$, –$NR^5C(O)R^6$, heterocycle, aryl, heteroaryl, –$(CH_2)_n$OH, –C_1-C_6alkyl, –CF_3, –CHF_2, or –CH_2F;

R^4 is independently –H, –D, –C_1-C_6alkyl, –C_1-C_6haloalkyl, –C_1-C_6hydroxyalkyl, –CF_2OH, –CHFOH, –NH-NHR^5, –NH-OR^5, –O-NR^5R^6, –NHR^5, –OR^5, –$NHC(O)R^5$, –$NHC(O)NHR^5$, –$NHS(O)_2R^5$, –$NHS(O)_2NHR^5$, –$S(O)_2OH$, –$C(O)OR^5$, –$NH(CH_2)_n$OH, –$C(O)NH(CH_2)_n$OH, –$C(O)NH(CH_2)_nR^b$, –$C(O)R^b$, –NH_2, –OH, –CN, –$C(O)NR^5R^6$, –$S(O)_2NR^5R^6$, C_3-C_8cycloalkyl, aryl, heterocyclyl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, or heteroaryl containing 1-5 heteroatoms selected from the group consisting of N, S, P, and O, wherein each alkyl, cycloalkyl, or heterocyclyl is optionally substituted with one or more –OH, –NH_2, –OR^b, halogen, or oxo; wherein each aryl or heteroaryl is optionally substituted with one or more –OH, –NH_2, or halogen;

R^5 and R^6 are independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, a monocyclic or polycyclic 3- to 12-membered heterocycle, –OR^7, –SR^7, halogen, –NR^7R^8, –NO_2, –CF_3, or –CN;

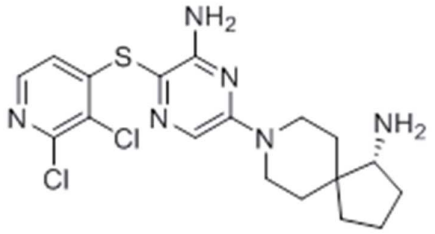
R^7 and R^8 are independently, at each occurrence, –H, –D, –C_1-C_6alkyl, –C_2-C_6alkenyl, –C_4-C_8cycloalkenyl, –C_2-C_6alkynyl, –C_3-C_8cycloalkyl, –OR^b, or a monocyclic or polycyclic 3- to 12-membered heterocycle, wherein each alkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkyl, or heterocycle is optionally substituted with one or more –OH, –SH, –NH_2, –NO_2, or –CN; and

n is independently, at each occurrence, 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10.

2. The ~~inhibitor of SHP2 for~~ use according to claim 1, wherein said inhibitor of SHP2 is selected from a compound of Formula I-V2 wherein Y^1 is -S- or a direct bond, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, and/or isomer thereof.

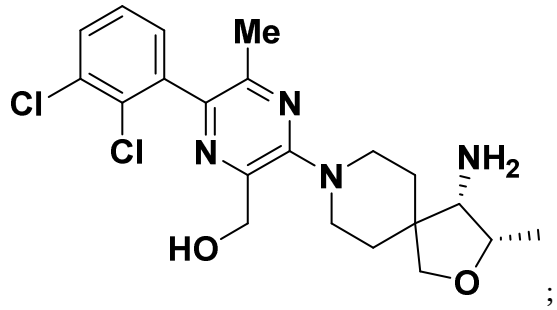
3. The ~~inhibitor of SHP2 for~~ use according to claim 1 or 2, wherein said inhibitor of SHP2 is:

Compound A having the structure:



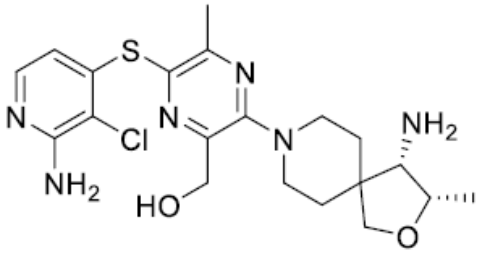
;

Compound B having the structure:



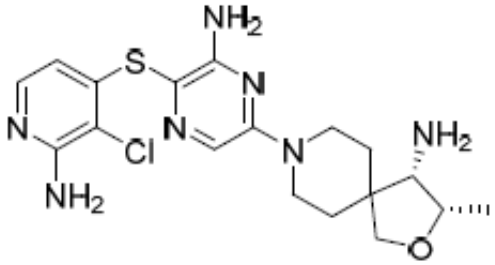
;

the compound of the following structure:



; or

TNO155 having the structure:



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4. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~ in the manufacture of a medicament for treating a disease or disorder comprising a cell with a mutation encoding an NF1 loss of function ($NF1^{LOF}$) variant, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

5. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~in the manufacture of a medicament for treating a disease or disorder associated with a RAS pathway mutation in a cell of a subject that renders the cell at least partially dependent on signaling flux through SHP2, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

6. The ~~inhibitor for~~ use according to claim 5, wherein the RAS pathway mutation is selected from a KRAS mutation, an NRAS mutation, a SOS mutation, a BRAF Class III mutation, a Class I MEK1 mutation, a Class II MEK1 mutation, and an NF1 mutation.

7. The ~~inhibitor for~~ use according to claim 6, wherein the KRAS mutation is selected from a $KRAS^{G12A}$ mutation, a $KRAS^{G12C}$ mutation, a $KRAS^{G12D}$ mutation, a $KRAS^{G12F}$ mutation, a $KRAS^{G12I}$ mutation, a $KRAS^{G12L}$ mutation, a $KRAS^{G12R}$ mutation, a $KRAS^{G12S}$ mutation, a $KRAS^{G12V}$ mutation, a $KRAS^{G12Y}$ mutation, and a $KRAS^{G13D}$ mutation.

8. The ~~inhibitor for~~ use according to claim 6 or 7, wherein the KRAS mutation is $KRAS^{G12C}$, $KRAS^{G12S}$, or $KRAS^{G12V}$.

9. The ~~inhibitor for~~ use according to claim 6, wherein the BRAF Class III mutation is selected from one or more of the following amino acid substitutions in human BRAF: D287H; P367R; V459L; G466V; G466E; G466A; S467L; G469E; N581S; N581I; D594N; D594G; D594A; D594H; F595L; G596D; G596R and A762E.

10. The ~~inhibitor for~~ use according to claim 6, wherein the NF1 mutation is a loss of function mutation ($NF1^{LOF}$).

11. The ~~inhibitor for~~ use according to claim 6, wherein the Class I MEK1 mutation is selected from one or more of the following amino acid substitutions in human MEK1: D67N; P124L; P124S; and L177V.

12. The ~~inhibitor for~~ use according to claim 6, wherein the Class II MEK1 mutation is selected from one or more of the following amino acid substitutions in human MEK1: ΔE51-Q58; ΔF53-Q58; E203K; L177M; C121S; F53L; K57E; Q56P; and K57N.

13. The ~~inhibitor for~~ use according to any one of claims 1-12, further comprising providing to the subject an inhibitor of the RAS pathway.

14. The ~~inhibitor for~~ use according to claim 13, wherein the inhibitor of the RAS pathway is a MAPK inhibitor.

15. The ~~inhibitor for~~ use according to claim 13, wherein the inhibitor of the RAS pathway is a MEK inhibitor or ERK inhibitor.

16. The ~~inhibitor for~~ use according to claim 13, wherein the inhibitor of the Ras pathway is selected from one or more of Trametinib, Binimetinib, Selumetinib, Cobimetinib, LErafAON (NeoPharm), ISIS 5132; Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; Refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766; ARS-853; LY3214996; BVD523; GSK1120212; Ulixertinib, and Abemaciclib.

17. The ~~inhibitor for~~ use according to any one of claims 1-16, wherein the disease or condition is a cancer.

18. The ~~inhibitor for~~ use according to any one of claims 1-17, wherein the disease or condition is a tumor.

19. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is selected from an NSCLC, a colon cancer, an oesophageal cancer, a rectal cancer, JMML, breast cancer, melanoma, Schwannoma, and a pancreatic cancer.

20. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~in the manufacture of a medicament for treating a disease associated with an NF1 loss of function mutation, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

21. The ~~inhibitor for~~ use according to claim 20, wherein the disease is a tumor comprising cells with an NF1 loss of function mutation.

22. The ~~inhibitor for~~ use according to claim 21, wherein the tumor is an NSCLC or melanoma tumor.

23. The ~~inhibitor for~~ use according to claim 20, wherein the disease is selected from neurofibromatosis type I, neurofibromatosis type II, schwannomatosis, and Watson syndrome.

24. The ~~inhibitor for~~ use according to any one of claims 20-23, further comprising providing to the subject an inhibitor of the RAS pathway.

25. The ~~inhibitor for~~ use according to claim 24, wherein the RAS pathway inhibitor is selected from one or more of Trametinib, Binimetinib, Selumetinib, Cobimetinib, LErafAON (NeoPharm), ISIS 5132; Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; Refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766; ARS-853; LY3214996; BVD523; GSK1120212; Ulixertinib, and Abemaciclib.

26. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~ in the manufacture of a medicament for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a KRAS mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a $KRAS^{G12C}$ mutant, a $KRAS^{G12D}$ mutant, a $KRAS^{G12S}$ mutant, or a $KRAS^{G12V}$ mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

27. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~ in the manufacture of a medicament for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as an $NF1^{LOF}$ mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as an $NF1^{LOF}$ mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

28. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~ in the manufacture of a medicament for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a Class 3 BRAF mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a Class 3 BRAF mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

29. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~ in the manufacture of a medicament for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a Class I MEK1 mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a Class I MEK1 mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

30. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~in the manufacture of a medicament for treating a tumor comprising:

(a) determining whether a biological sample obtained from a subject is classified as a Class II MEK1 mutant; and

(b) administering to the subject an inhibitor of SHP2 if the biological sample is classified as a Class II MEK1 mutant;

wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

31. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~in the manufacture of a medicament for treating or preventing drug resistance to a RAS pathway inhibitor in a subject receiving administration of a RAS pathway inhibitor, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

32. The ~~inhibitor for~~ use according to claim 31, wherein the subject comprises a tumor containing cells with an $NF1^{LOF}$ mutation.

33. The ~~inhibitor for~~ use according to claim 31 or 32, wherein the subject comprises a tumor containing a $KRAS^{G12C}$ mutation, a $KRAS^{G12D}$ mutation, a $KRAS^{G12A}$ mutation, a $KRAS^{G12S}$ mutation, a $KRAS^{G12V}$ mutation, or a $KRAS^{G13D}$ mutation.

34. The ~~inhibitor for~~ use according to any one of claims 31-33, wherein the RAS pathway inhibitor is a MEK inhibitor.

35. The ~~inhibitor for~~ use according to claim 34, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212), Selumetinib (AZD6244), Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901, Refametinib (RDEA 119/BAY 86-9766), RO5126766, AZD8330 (ARRY-424704/ARRY-704) , CH5126766, MAP855, and GSK1120212.

36. The ~~inhibitor for~~ use according to any one of claims 31-33, wherein the RAS pathway inhibitor is an ERK inhibitor.

37. The ~~inhibitor for~~ use according to claim 36, wherein the ERK inhibitor is selected from LY3214996; Ulixertinib; and BVD523.

38. ~~A combination therapy comprising~~Use of a RAS pathway inhibitor and an inhibitor of SHP2 in the manufacture of a medicament for use in the treatment of a tumor, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

39. The ~~combination therapy~~use of claim 38, wherein the RAS pathway inhibitor is a MEK inhibitor.

40. The ~~combination therapy~~ use of claim 39, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212), Selumetinib (AZD6244), Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), CI-1040; PD-0325901, Refametinib (RDEA 119/BAY 86-9766), RO5126766, AZD8330 (ARRY-424704/ARRY-704), CH5126766, MAP855, and GSK1120212.

41. The ~~combination therapy~~use of claim 38, wherein the RAS pathway inhibitor is the $KRAS^{G12C}$-specific inhibitor ARS-853.

~~42. The combination therapy of any one of claims 38-41, for use in the treatment of a tumor.~~

~~43.~~42. The combination therapy of claim ~~42~~38, wherein the tumor is selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye

cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

~~44.~~43. A pharmaceutical composition comprising a RAS pathway inhibitor, an inhibitor of SHP2, and one or more pharmaceutically acceptable carrier, excipient, diluent, and/or surfactant, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

~~45.~~44. The pharmaceutical composition of claim ~~44~~43, wherein the RAS pathway inhibitor is selected from one or more of Trametinib (GSK1120212) Selumetinib (AZD6244); Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; Refametinib (RDEA 119/BAY 86-9766); RO5126766, AZD8330 (ARRY-424704/ARRY-704); GSK1120212, Ulixertinib; and Abemaciclib.

~~46.~~45. ~~The~~ Use of the pharmaceutical composition of claim ~~44~~ 43 or ~~45~~44 in the manufacture of a medicament~~,~~ for use in the treatment of a tumor.

~~47.~~46. The use ~~pharmaceutical composition~~ of claim ~~46~~45, wherein the tumor is selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

~~48.~~47. The ~~inhibitor for~~ use according to any one of claims 18, 20, 21, 26-30, and 32-37, wherein the tumor is selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

~~49.~~48. ~~An~~ Use of an inhibitor of SHP2 ~~for use~~in the manufacture of a medicament for inhibiting the growth or proliferation of a cell containing a RAS pathway mutation, wherein the RAS pathway mutation renders the cell at least partially dependent on signaling flux through SHP2, the method comprising contacting the cell with an inhibitor of SHP2, wherein said inhibitor of SHP2 is as defined in any one of claims 1 to 3.

~~50.~~49. The ~~inhibitor of SHP2 for~~ use according to claim ~~49~~48, wherein the RAS pathway mutation is selected from a KRAS mutation, an NRAS mutation, an HRAS mutation, a SOS mutation, a Class III BRAF mutation, and an NF1 loss of function mutation.

~~51.~~50. The inhibitor of SHP2 for use according to claim 50, wherein the KRAS mutation is selected from a $KRAS^{G12A}$ mutation, a $KRAS^{G12C}$ mutation, a $KRAS^{G12D}$ mutation, a $KRAS^{G12F}$ mutation, a $KRAS^{G12I}$ mutation, a $KRAS^{G12L}$ mutation, a $KRAS^{G12R}$ mutation, a $KRAS^{G12S}$ mutation, a $KRAS^{G12V}$ mutation, a $KRAS^{G12Y}$ mutation, and a $KRAS^{G13D}$ mutation.

~~52.~~51. The ~~inhibitor of SHP2 for~~ use according to claim ~~51~~50, wherein the KRAS mutation is $KRAS^{G12C}$, $KRAS^{G12S}$, or $KRAS^{G12V}$.

~~53.~~52. The ~~inhibitor of SHP2 for~~ use according to claim ~~50~~49, wherein the Class 3 BRAF mutation is selected from one or more of the following amino acid substitutions in human BRAF: D287H; P367R; V459L; G466V; G466E; G466A; S467L; G469E; N581S; N581I; D594N; D594G; D594A; D594H; F595L; G596D; G596R and A762E.

~~54.~~53. The ~~inhibitor of SHP2 for~~ use according to any one of claims ~~49~~48-~~53~~52, further comprising contacting the cell with an inhibitor of the RAS pathway.

~~55.~~54. The ~~inhibitor of SHP2 for~~ use according to claim ~~54~~53, wherein the inhibitor of the RAS pathway is a MAPK inhibitor.

~~56.~~55. The ~~inhibitor of SHP2 for~~ use according to claim ~~54~~53, wherein the inhibitor of the RAS pathway is a MEK inhibitor or ERK inhibitor.

~~57.~~56. The ~~inhibitor of SHP2 for~~ use according to claim ~~54~~53, wherein the inhibitor of the Ras pathway is selected from one or more of Trametinib, Binimetinib, Selumetinib, Cobimetinib, LErafAON (NeoPharm), ISIS 5132; Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655); CI-1040; PD-0325901; CH5126766; MAP855; AZD6244; Refametinib (RDEA 119/BAY 86-9766); GDC-0973/XL581; AZD8330 (ARRY-424704/ARRY-704); RO5126766; ARS-853; LY3214996; BVD523; GSK1120212; Ulixertinib; and Abemaciclib.

~~58.~~57. The ~~inhibitor for~~ use according to any one of claims 1-37 and ~~48~~47-~~57~~56, further comprising contacting the cell with a SOS inhibitor.

~~59.~~58. The ~~inhibitor for~~ use according to claim ~~58~~57, wherein the SOS inhibitor is administered to a cell comprising higher than normal SOS levels or SOS activity.

~~60.~~59. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is from a NSCLC tumor.

~~61.~~60. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a colon cancer tumor.

~~62.~~61. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is an oesophageal cancer tumor.

~~63.~~62. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a rectal cancer tumor.

~~64.~~63. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a JMML tumor.

~~65.~~64. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a breast cancer tumor.

~~66.~~65. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a melanoma tumor.

~~67.~~66. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a Schwannoma tumor.

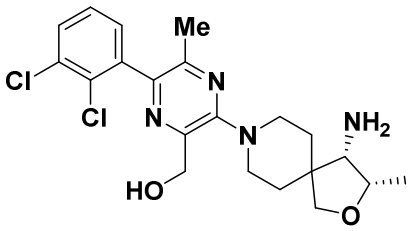
~~68.~~67. The ~~inhibitor for~~ use according to claim 18, wherein the tumor is a pancreatic cancer tumor.

~~69.~~68. The ~~combination therapy~~use of claim 39, for use in inhibiting the growth of a tumor cell, comprising contacting the tumor cell with said ~~combination therapy~~medicament.

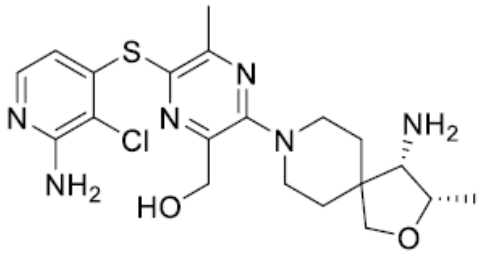
~~70.~~69. The ~~combination therapy~~use of claim ~~69~~68, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212), Selumetinib (AZD6244), Cobimetinib (GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), CI-1040; PD-0325901, CH5126766, MAP855, Refametinib (RDEA 119/BAY 86-9766), RO5126766, AZD8330 (ARRY-424704/ARRY-704), and GSK1120212.

~~71.~~70. The ~~combination therapy~~use of claim ~~69~~ 68 or ~~70~~69, wherein the MEK inhibitor is Trametinib (GSK1120212).

~~72.~~71. The ~~combination therapy~~use of any one of claims ~~69~~68-~~71~~70, wherein the inhibitor of SHP2 is Compound B having the structure

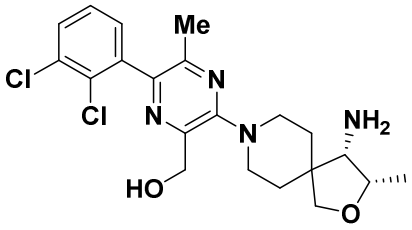


or the compound of the following structure



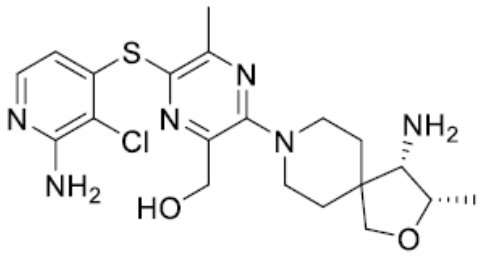
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~~73.~~72. The ~~combination therapy~~use of claim ~~69~~68, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is Compound B having the structure



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~~74.~~73. The ~~combination therapy~~use of claim ~~69~~68, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is the compound of the following structure



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~~75.~~74. The ~~combination therapy~~use of any one of claims ~~69~~68-~~74~~73, wherein the tumor cell is a cell from a tumor selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

~~76.~~75. The ~~combination therapy~~use of any one of claims ~~69~~68-~~75~~74, wherein the tumor is from a NSCLC tumor.

~~77.~~76. The ~~combination therapy~~use of any one of claims ~~69~~68-~~76~~75, wherein the contacting occurs *in vivo* in a subject.

~~78.~~77. The ~~combination therapy~~use of claim ~~77~~76, wherein the subject is a human.

~~79.~~78. The ~~combination therapy~~use of any one of claims ~~69~~68-~~78~~77, wherein the contacting of the tumor cell with the ~~combination therapy~~medicament results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of the respective MEK and inhibitor of SHP2 separately.

~~80.~~79. The ~~combination therapy~~use of any one of claims ~~69~~68-~~79~~78, wherein the MEK inhibitor and the inhibitor of SHP2 do not contact the tumor cell simultaneously.

~~81.~~80. The ~~combination therapy~~use of any one of claims ~~69~~68-~~79~~78, wherein the MEK inhibitor and the inhibitor of SHP2 contact the tumor cell simultaneously.

~~82.~~81. The ~~combination therapy~~use of any one of claims ~~69~~68-~~81~~80, wherein the contacting is via administration of the medicament comprising the MEK inhibitor and the inhibitor of SHP2 to the subject.

~~83.~~82. The ~~combination therapy~~use of claim ~~82~~81, wherein the administration of the MEK inhibitor precedes the administration of the inhibitor of SHP2.

~~84.~~83. The ~~combination therapy~~use of claim ~~82~~81, wherein the administration of the inhibitor of SHP2 precedes the administration of the MEK inhibitor.

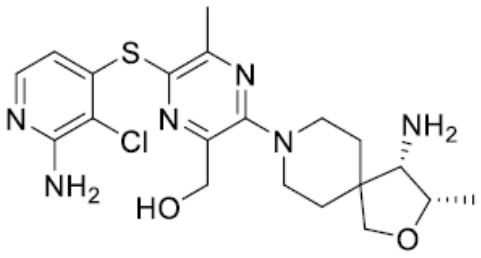
~~85.~~84. The ~~combination therapy~~use of claim ~~82~~81, wherein the administration of the inhibitor of SHP2 and the administration of the MEK inhibitor occurs simultaneously.

~~86.~~85. The ~~combination therapy~~use of claim ~~85~~84, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as a single pharmaceutical composition.

~~87.~~86. The ~~combination therapy~~use of claim ~~85~~84, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as separate pharmaceutical compositions.

~~88.~~87. The ~~combination therapy~~use of any one of claims ~~69~~68-~~87~~86, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

~~89.~~88. ~~A combination therapy for use in inhibiting the growth of a tumor cell, comprising contacting the tumor cell with a combination therapy comprising~~Use of trametinib (GSK1120212) and an inhibitor of SHP2 of the following structure



in the manufacture of a medicament for inhibiting the growth of a tumor, the use comprising contacting the tumor cell with the medicament.

~~90.~~89. The ~~combination therapy~~use of claim ~~89~~88, wherein the tumor cell is from a NSCLC tumor.

~~91.~~90. The ~~combination therapy~~use of claim ~~89~~ 88 or ~~90~~89, wherein the contacting occurs *in vivo* in a subject.

~~92.~~91. The ~~combination therapy~~use of claim ~~91~~90, wherein the subject is a human.

~~93.~~92. The ~~combination therapy~~use of any one of claims ~~89~~88-~~92~~91, wherein the contacting of the tumor cell with said ~~combination therapy~~medicament results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of trametinib (GSK1120212) and the inhibitor of SHP2 separately.

~~94.~~93. The ~~combination therapy~~use of any one of claims ~~89~~88-~~93~~92, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

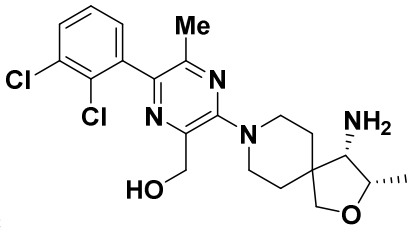
~~95.~~94. The ~~combination therapy for~~ use according to claim 39, ~~for use in treating a tumor,~~ comprising contacting a tumor cell in the tumor in a subject with said ~~combination therapy~~medicament.

~~96.~~95. The ~~combination therapy~~use of claim ~~95~~94, wherein the MEK inhibitor is selected from one or more of Trametinib (GSK1120212); Selumetinib (AZD6244); Cobimetinib

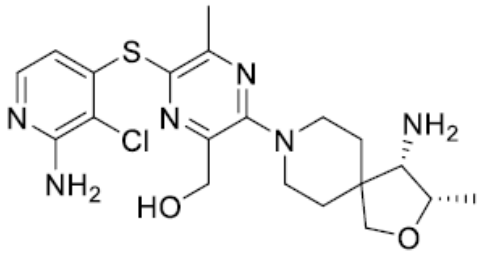
(GDC-0973/XL581), Binimetinib, Vemurafenib, Pimasertib, TAK733, RO4987655 (CH4987655), CI-1040; PD-0325901; CH5126766; MAP855; Refametinib (RDEA 119/BAY 86-9766); RO5126766, AZD8330 (ARRY-424704/ARRY-704); and GSK1120212.

~~97.~~96. The ~~combination therapy~~use of claim ~~96~~95, wherein the MEK inhibitor is Trametinib (GSK1120212).

~~98.~~97. The ~~combination therapy~~use of any one of claims ~~95~~94-~~97~~96, wherein the inhibitor of SHP2 is Compound B having the structure

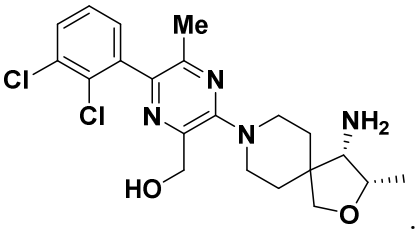


or the compound of the following structure



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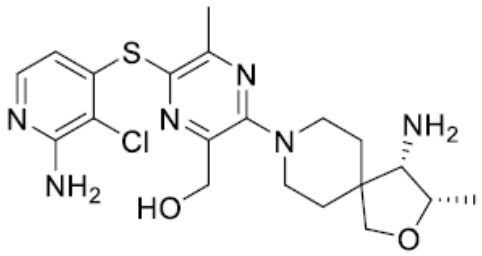
~~99.~~98. The ~~combination therapy~~use of claim ~~95~~94, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is Compound B having the structure



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~~100.~~99. The ~~combination therapy~~use of claim ~~95~~94, wherein the MEK inhibitor is Trametinib (GSK1120212) and the inhibitor of SHP2 is the compound of the following

structure



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~~101.~~100. The ~~combination therapy~~use of any one of claims ~~95~~94-~~100~~99, wherein the tumor cell is a cell from a tumor selected from tumors of hemopoietic and lymphoid system; a myeloproliferative syndrome; a myelodysplastic syndromes; leukemia; acute myeloid leukemia; juvenile myelomonocytic leukemia; esophageal cancer; breast cancer; lung cancer; colon cancer; gastric cancer; neuroblastoma; bladder cancer; prostate cancer; glioblastoma; urothelial carcinoma; uterine carcinoma; adenoid and ovarian sereous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer (small and large intestine); thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer; primary CNS lymphoma; stomach cancer; pituitary cancer; genital tract cancer; urinary tract cancer; salivary gland cancer; cervical cancer; liver cancer; eye cancer; cancer of the adrenal gland; cancer of autonomic ganglia; cancer of the upper aerodigestive tract; bone cancer; testicular cancer; pleura cancer; kidney cancer; penis cancer; parathyroid cancer; cancer of the meninges; vulvar cancer and melanoma.

~~102.~~101. The ~~combination therapy~~use of any one of claims ~~95~~94-~~101~~100, wherein the tumor cell is from a NSCLC tumor.

~~103.~~102. The ~~combination therapy~~use of any one of claims ~~95~~94-~~102~~101, wherein the contacting occurs *in vivo* in a subject.

~~104.~~103. The ~~combination therapy~~use of claim ~~103~~102, wherein the subject is a human.

~~105.~~104. The ~~combination therapy~~use of any one of claims ~~95~~94-~~104~~103, wherein the contacting of the tumor cell with the ~~combination therapy~~medicament results in an inhibition of tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of the respective MEK and inhibitor of SHP2 separately.

~~106.~~105. The ~~combination therapy~~use of any one of claims ~~95~~94-~~105~~104, wherein the MEK inhibitor and the inhibitor of SHP2 do not contact the tumor cell simultaneously.

~~107.~~106. The ~~combination therapy~~use of any one of claims ~~95~~94-~~105~~104, wherein the MEK inhibitor and the inhibitor of SHP2 contact the tumor cell simultaneously.

~~108.~~107. The ~~combination therapy~~use of any one of claims ~~95~~94-~~107~~106, wherein the contacting is via administration of the medicament comprising the MEK inhibitor and the inhibitor of SHP2 to the subject.

~~109.~~108. The ~~combination therapy~~use of claim ~~108~~107, wherein the administration of the MEK inhibitor precedes the administration of the inhibitor of SHP2.

~~110.~~109. The ~~combination therapy~~use of claim ~~108~~107, wherein the administration of the inhibitor of SHP2 precedes the administration of the MEK inhibitor.

~~111.~~110. The ~~combination therapy~~use of claim ~~108~~107, wherein the administration of the inhibitor of SHP2 and the administration of the MEK inhibitor occurs simultaneously.

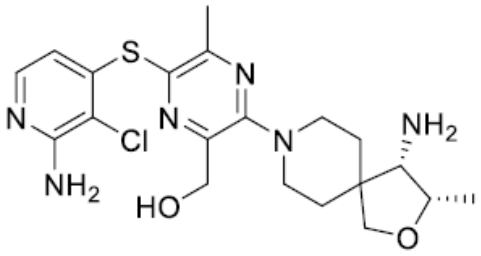
~~112.~~111. The ~~combination therapy~~use of claim ~~111~~110, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as a single pharmaceutical composition.

~~113.~~112. The ~~combination therapy~~use of claim ~~111~~110, wherein the inhibitor of SHP2 and the MEK inhibitor are administered as separate pharmaceutical compositions.

~~114.~~113. The ~~combination therapy~~use of any one of claims ~~95~~94-~~113~~112, wherein the treatment inhibits the growth of the tumor cell.

~~115.~~114. The ~~combination therapy~~use of claim ~~114~~113, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

~~116.~~115. ~~A combination therapy for use for treating a tumor, comprising contacting a tumor cell of the tumor in a subject with a combination therapy comprising~~Use of trametinib (GSK1120212) and an inhibitor of SHP2 of the following structure



in the manufacture of a medicament for treating a tumor, the use comprising contacting a tumor cell of the tumor with the medicament.

~~117.~~116. The ~~combination therapy~~use of claim ~~116~~115, wherein the tumor cell is from a NSCLC tumor.

~~118.~~117. The ~~combination therapy~~use of claim ~~116~~ 115 or ~~117~~116, wherein the contacting occurs *in vivo* in a subject.

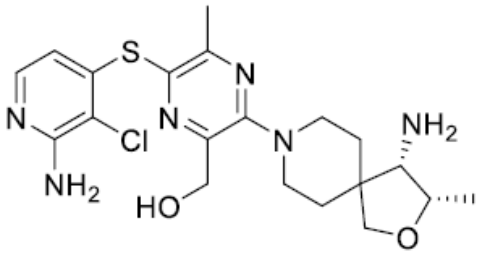
~~119.~~118. The ~~combination therapy~~use of claim ~~118~~117, wherein the subject is a human.

~~120.~~119. The ~~combination therapy~~use of any one of claims ~~116~~115-~~119~~118, wherein the contacting of the tumor cell with the combination therapy results in an inhibition of

tumor growth that is more than merely additive with respect to the amount of tumor growth inhibition achievable by contacting the tumor cell with each of trametinib (GSK1120212) and the inhibitor of SHP2 separately.

~~121.~~120. The ~~combination therapy~~use of any one of claims ~~116~~115-~~120~~119, wherein the growth of the tumor cell is inhibited enough to cause partial or complete regression of the tumor.

~~122.~~121. The pharmaceutical composition of any one of ~~claims 44-47~~claim 43 or claim 44, wherein the inhibitor of SHP2 is the compound of the following structure



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