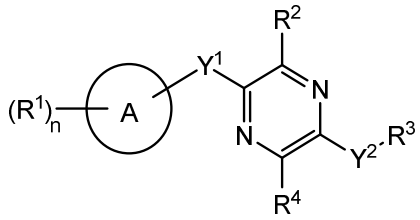
Claims

1. ~~A method of~~ Use of an allosteric SHP2 inhibitor in the manufacture of a medicament for treating a subject having a disease or disorder associated with cells containing a mutant SHP2, ~~comprising administering to the subject an allosteric SHP2 inhibitor,~~ wherein the mutant SHP2 comprises an allosteric inhibitor-sensitive mutation selected from F285S, L262R, S189A, D61G, E69K, T73I, Q506P, and any combination thereof, wherein the cells are negative for an allosteric inhibitor-resistant mutation of SHP2, and wherein the allosteric SHP2 inhibitor is a compound of Formula I-V2:



I-V2

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, and/or stereoisomer 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;

each R^1 is independently –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 $–NH_2$, $–OR^b$, –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;

each R^b is independently –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, $–(CH_2)_nOH$, $–C_1$-C_6alkyl, $–CF_3$, $–CHF_2$, or $–CH_2F$;

R^4 is –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, $–NHR^5$, $–OR^5$, $–NHC(O)R^5$, $–NHC(O)NHR^5$, $–NHS(O)_2R^5$, $–NHS(O)_2NHR^5$, $–S(O)_2OH$, $–C(O)OR^5$, $–NH(CH_2)_nOH$, $–C(O)NH(CH_2)_nOH$, $–C(O)NH(CH_2)_nR^b$, $–C(O)R^b$, $–NH_2$, –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;

each R^5 and R^6 is independently –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;

each R^7 and R^8 is independently –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

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

~~**2.** The method of claim 1, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of F285S, L262R, S189A, D61G, E69K, T73I, Q506P, and a combination thereof.~~

2. The use according to claim 1, wherein the allosteric SHP2 inhibitor 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 stereoisomer thereof.

3. The use according to ~~method of~~ claim 1 or 2, wherein the allosteric inhibitor-sensitive mutation is selected from ~~the group consisting of~~ F285S, L262R, ~~and~~ S189A, and any combination thereof.

4. The use according to ~~method of~~ claim 1 or 2, wherein the allosteric inhibitor-sensitive mutation is D61G.

5. The use according to ~~method of~~ claim 1 or 2, wherein the allosteric inhibitor-sensitive mutation is selected from ~~the group consisting of~~ E69K, T73I, ~~and~~ Q506P, and any combination thereof.

~~**6.** The method of any one of claims 1-5, wherein the cells are negative for an allosteric inhibitor-resistant mutation of SHP2.~~

~~**7.**~~**6.** The use according to any one of ~~method of~~ claim~~s~~ ~~6~~1-5, wherein the allosteric inhibitor-resistant mutation is selected from ~~the group consisting of~~ E76K, P491S, S502P, and any combination thereof.

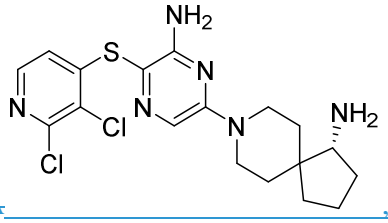
~~8.~~7. The use according to any one of ~~method of~~ claims ~~6~~1-6, wherein the allosteric inhibitor-resistant mutation is selected from ~~the group consisting of~~ E76K, ~~and~~ P491S, and a combination thereof.

~~9.~~8. The use according to any one of ~~method of~~ claims ~~6~~1-6, wherein the allosteric inhibitor-resistant mutation is S502P.

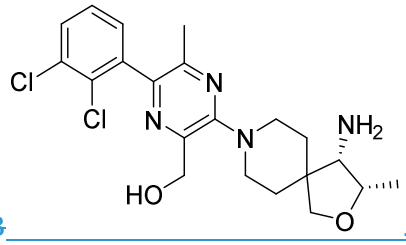
~~10.~~9. The use according to~~method of~~ any one of claims 1-~~9~~8, wherein the cells are determined to have the allosteric inhibitor-sensitive mutation prior to administering the allosteric SHP2 inhibitor.

~~11.~~10. The use according to ~~method of~~ any one of claims 1-~~10~~9, wherein the cells are determined to not have the allosteric inhibitor-resistant mutation prior to administering the allosteric SHP2 inhibitor.

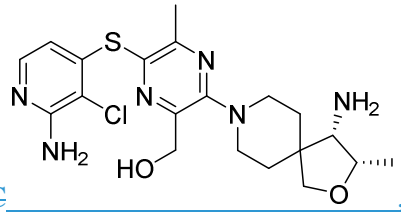
~~12.~~11. The use according to ~~method of~~ any one of claims 1-~~11~~10, wherein the allosteric SHP2 inhibitor is selected from:

(i) ~~Compound A~~ 

, or a pharmaceutically acceptable salt, prodrug, solvate, tautomer and/or stereoisomer thereof;

(ii) ~~Compound B~~ 

, or a pharmaceutically acceptable salt, prodrug, solvate, tautomer and/or stereoisomer thereof;

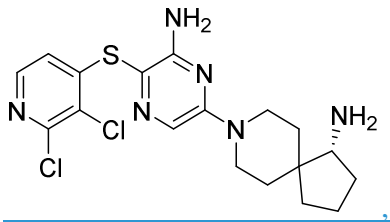
(iii) ~~Compound C~~ 

, or a pharmaceutically acceptable salt, prodrug, solvate, tautomer and/or stereoisomer thereof; and

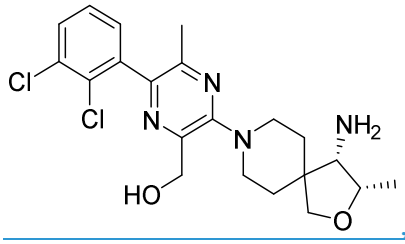
~~(iv) SHP099; (v) an allosteric SHP2 inhibitor compound of any one of Formula I, of Formula II, of Formula III, of Formula I-V1, of Formula I-V2, of Formula I-W, of Formula I-X, of Formula I-Y, of Formula I-Z, of Formula IV, of Formula V, of Formula VI, of Formula IV-X, of Formula IV-Y, of Formula IV-Z, of Formula VII, of Formula VIII, of Formula IX, and of Formula X; (vi) TNO155; (vii) a compound from Table A1, disclosed herein; (viii) a compound from Table A2, disclosed herein; and~~

(~~ix~~iv) any combination thereof.

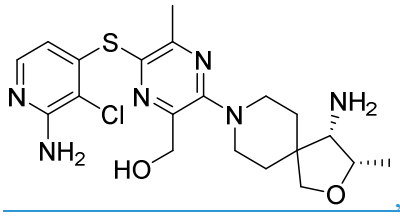
12. Use of an allosteric SHP2 inhibitor in the manufacture of a medicament for treating a subject having a disease or disorder associated with cells containing a mutant SHP2, wherein the mutant SHP2 comprises an allosteric inhibitor-sensitive mutation and wherein the allosteric SHP2 inhibitor is selected from:



, or a pharmaceutically acceptable salt, solvate, tautomer and/or stereoisomer thereof;



, or a pharmaceutically acceptable salt, solvate, tautomer and/or stereoisomer thereof;



, or a pharmaceutically acceptable salt, solvate, tautomer and/or stereoisomer thereof; and

any combination thereof.

13. The use according to claim 12, wherein the cells are determined to have the allosteric inhibitor-sensitive mutation prior to administering the SHP2 inhibitor.

14. The use according to claim 12, wherein the cells are determined not to have the allosteric inhibitor-resistant mutation prior to administering the SHP2 inhibitor.

~~13.~~**15.** The use according to ~~method of~~ any one of claims 1-~~12~~14, wherein the disease or disorder 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 ser~~e~~ous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer ~~(e.g., small and/or large intestinal cancer)~~; thyroid cancer; endometrial cancer; cancer of the biliary tract; soft tissue cancer; ovarian cancer; central nervous system cancer ~~(e.g., 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.

~~14.~~**16.** The ~~method of~~ use according to any one of claims 1-~~12~~15, wherein the disease or disorder is an inherited developmental disorder selected from the group consisting of Noonan Syndrome and LEOPARD Syndrome.

~~15.~~**17.** The ~~method of~~ use according to any one of claims 1-~~14~~16, wherein the allosteric SHP2 inhibitor is to be administered in an effective amount.

~~16. A method of identifying a subject with SHP2 mutations susceptible to a SHP2 inhibitor, comprising genotyping a biological sample from the subject for SHP2 mutations, wherein the subject is identified as susceptible to the SHP2 inhibitor if the SHP2 mutations comprise an allosteric inhibitor-sensitive mutation.~~

17. The method of claim 16, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of F285S, L262R, S189A, D61G, E69K, T73I, Q506P, and a combination thereof.

18. The method of claim 16, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of F285S, L262R, and S189A.

19. The method of claim 16, wherein the allosteric inhibitor-sensitive mutation is D61G.

20. The method of claim 16, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of E69K, T73I, and Q506P.

21. The method of any one of claims 16-20, wherein the method further comprises identifying the subject as not expressing a SHP2 allosteric inhibitor-resistant mutation.

22. The method of claim 21, wherein the SHP2 allosteric inhibitor-resistant mutation is selected from the group consisting of E76K, P491S, S502P, and a combination thereof.

23. The method of claim 21, wherein the allosteric inhibitor-resistant mutation is selected from the group consisting of E76K and P491S

24. The method of claim 21, wherein the allosteric inhibitor-resistant mutation is S502P.

25. The method of any one of claims 16-24, wherein the allosteric SHP2 inhibitor is selected from (i) Compound A; (ii) Compound B; (iii) Compound C; (iv) SHP099; (v) an allosteric SHP2 inhibitor compound of any one of Formula I, of Formula II, of Formula III, of Formula I-V1, of Formula I-V2, of Formula I-W, of Formula I-X, of Formula I-Y, of Formula I-Z, of Formula IV, of Formula V, of Formula VI, of Formula IV-X, of Formula IV-Y, of Formula IV-Z, of Formula VII, of Formula VIII, of Formula IX, and of Formula X; (vi) TNO155; (vii) a compound from Table A1, disclosed herein; (viii) a compound from Table A2, disclosed herein; and (ix) a combination thereof.

26. A method of identifying a subject as resistant to an allosteric SHP2 inhibitor, comprising genotyping a biological sample from the subject for SHP2 mutations, wherein the subject is identified as resistant to the SHP2 inhibitor if the SHP2 mutations comprise an allosteric inhibitor-resistant mutation.

27. The method of claim 26, wherein the allosteric inhibitor-resistant mutation is selected from the group consisting of E76K, P491S, S502P, and a combination thereof.

28. The method of claim 26, wherein the allosteric inhibitor-resistant mutation is selected from the group consisting of E76K and P491S

29. The method of claim 26, wherein the allosteric inhibitor-resistant mutation is S502P.

30. The method of any one of claims 26-29, wherein the allosteric SHP2 inhibitor is selected from (i) Compound A; (ii) Compound B; (iii) Compound C; (iv) SHP099; (v) an allosteric SHP2 inhibitor compound of any one of Formula I, of Formula II, of Formula III, of Formula I-V1, of Formula I-V2, of Formula I-W, of Formula I-X, of Formula I-Y, of Formula I-Z, of Formula IV, of Formula V, of Formula VI, of Formula IV-X, of Formula IV-Y, of Formula IV-Z, of Formula VII, of Formula VIII, of Formula IX, and of Formula X; (vi) TNO155; (vii) a compound from Table A1, disclosed herein; (viii) a compound from Table A2, disclosed herein; and (ix) a combination thereof.

31. A diagnostic test for allosteric SHP2 inhibitor sensitivity, comprising a nucleic acid probe specific for an allosteric inhibitor-sensitive mutation of SHP2.

32. The diagnostic test of claim 31, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of F285S, L262R, S189A, D61G, E69K, T73I, Q506P, and a combination thereof.

33. The diagnostic test of claim 31, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of F285S, L262R, and S189A.

34. The diagnostic test of claim 31, wherein the allosteric inhibitor-sensitive mutation is D61G.

35. The diagnostic test of claim 31, wherein the allosteric inhibitor-sensitive mutation is selected from the group consisting of E69K, T73I, and Q506P.

36. A diagnostic test for allosteric SHP2 inhibitor insensitivity, comprising a nucleic acid probe specific for a SHP2 allosteric inhibitor-resistant mutation; wherein the allosteric inhibitor-resistant mutation is optionally selected from E76K, P491S, S502P.