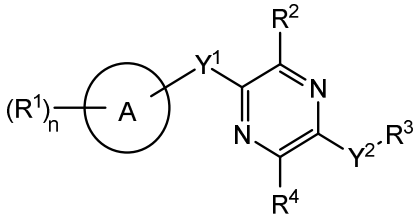
Claims

1. 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 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 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 claim 1 or 2, wherein the allosteric inhibitor-sensitive mutation is selected from F285S, L262R, S189A, and any combination thereof.

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

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

6. The use according to any one of claims 1-5, wherein the allosteric inhibitor-resistant mutation is selected from E76K, P491S, S502P, and any combination thereof.

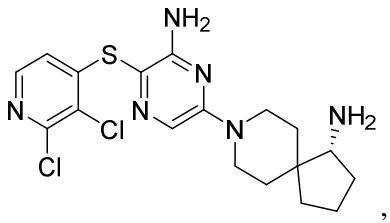
7. The use according to any one of claims 1-6, wherein the allosteric inhibitor-resistant mutation is selected from E76K, P491S, and a combination thereof.

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

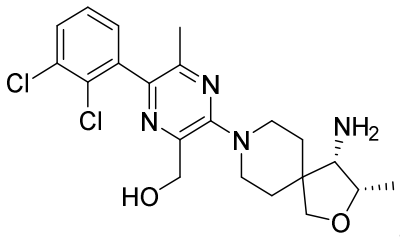
9. The use according to any one of claims 1-8, wherein the cells are determined to have the allosteric inhibitor-sensitive mutation prior to administering the allosteric SHP2 inhibitor.

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

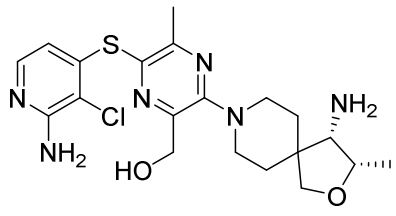
11. The use according to any one of claims 1-10, wherein the allosteric SHP2 inhibitor is selected from:

(i) 

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

(ii) 

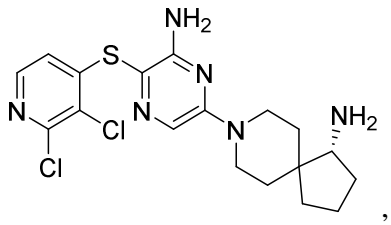
, or a pharmaceutically acceptable salt, prodrug, solvate, tautomer and/or stereoisomer thereof;

(iii) 

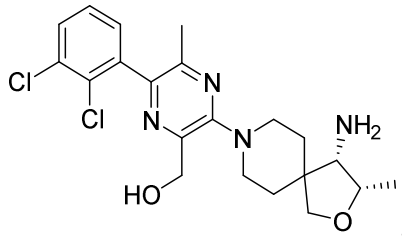
, or a pharmaceutically acceptable salt, prodrug, solvate, tautomer and/or stereoisomer thereof; and

(iv) any combination thereof.

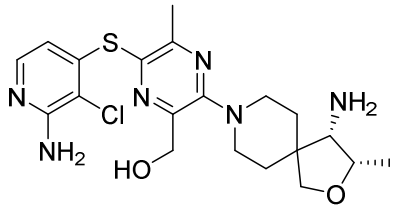
12. Use of an allosteric SHP2 inhibitor in the manufacture of a medicament for treating a subject having a disease or disorder associated with cells containing a mutant SHP2, wherein the mutant SHP2 comprises an allosteric inhibitor-sensitive mutation and wherein the allosteric SHP2 inhibitor is selected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

15. The use according to any one of claims 1-14, 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 serous cystadenocarcinoma; paraganglioma; phaeochromocytoma; pancreatic cancer; adrenocortical carcinoma; stomach adenocarcinoma; sarcoma; rhabdomyosarcoma; lymphoma; head and neck cancer; skin cancer; peritoneum cancer; intestinal cancer; thyroid cancer; endometrial cancer; cancer of the biliary tract; soft

tissue cancer; ovarian cancer; central nervous system cancer; 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.

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

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