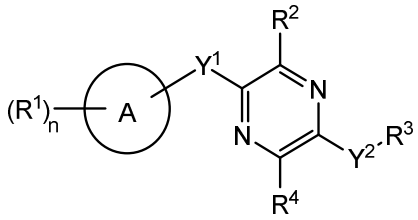
~~Claims~~

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~~a mutation of SHP2 which is resistant to an allosteric SHP2 inhibitor, 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~~4- 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, and

wherein the disease or disorder is cancer or an inherited developmental disorder.

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.

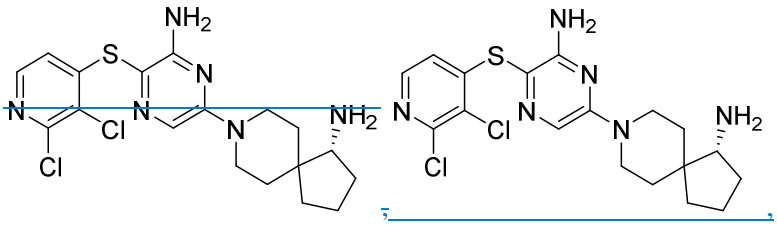
7. The use according to any one of claims 1-6, wherein the allosteric inhibitor-resistant mutation is selected from E76K, P491S, and a combination thereof.

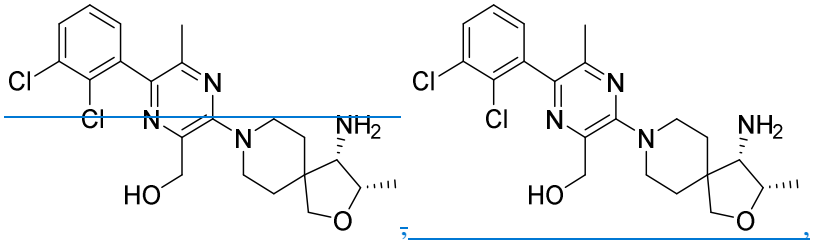
8. The use according to any one of claims 1-6, wherein the allosteric inhibitor-resistant mutation is S502P.

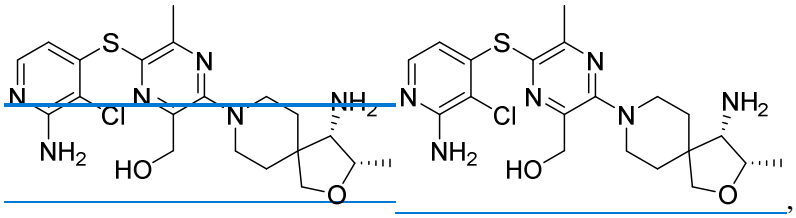
9. The use according to any one of claims 1-8, wherein the cells are determined to have the allosteric inhibitor-sensitive mutation prior to administering the allosteric SHP2 inhibitor.

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;

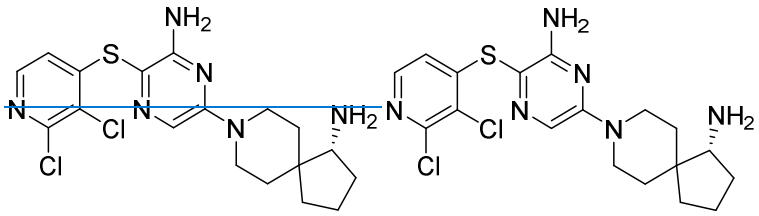
(ii)  , or a pharmaceutically acceptable salt, ~~prodrug,~~ solvate, tautomer and/or stereoisomer thereof;

(iii)  , or a pharmaceutically acceptable salt~~, prodrug~~, solvate, tautomer and/or stereoisomer thereof; and

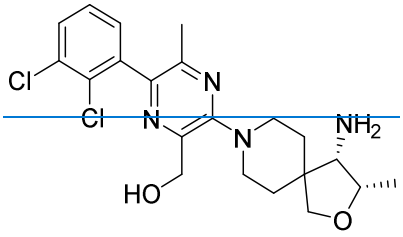
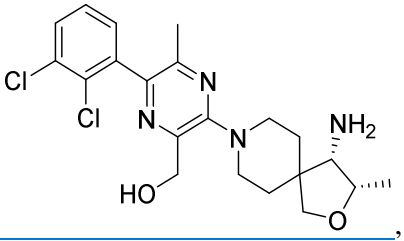
(iv) any combination thereof.

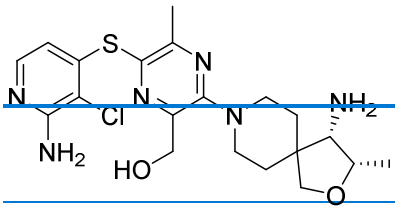
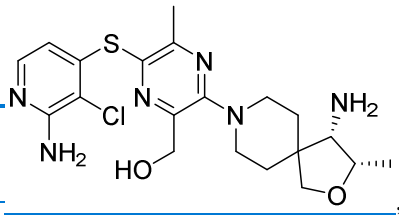
12. Use of an allosteric SHP2 inhibitor in the manufacture of a medicament for treating a subject having a disease or disorder associated with cells containing a mutant SHP2, wherein the mutant SHP2 comprises an allosteric inhibitor-sensitive mutation selected

from F285S, L262R, S189A, D61G, E69K, T73I, Q506P, and any combination thereof, 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, and

wherein the disease or disorder is cancer or an inherited developmental disorder.

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~~an 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.