CLAIMS

What is claimed is:

1. ~~A method of treating a disease or disorder, comprising administering to a subject in need thereof~~ Use of a first dose of a first Src homology region 2 (SH2)-containing protein tyrosine phosphatase 2 (SHP2) inhibitor in the manufacture of a medicament for treating cancer, by co-administration with ~~and~~ a second dose of a second SHP2 inhibitor, wherein the first dose and the second dose are to be administered on an intermittent schedule, and wherein the first SHP2 inhibitor and the second SHP2 inhibitor are identical.

~~2. The method of claim 1, wherein the subject has a mutation of SHP2.~~

~~3. The method of claim 1 or 2, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are identical.~~

~~4. The method of claim 1 or 2, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are not identical.~~

2~~5~~. The ~~method~~ use of ~~any one of~~ claim~~s~~ 1~~-4~~, wherein the first dose is to be administered on a first day (D1) of the intermittent schedule and the second dose is to be administered on a fourth day (D4) of the intermittent schedule.

3~~6~~. The ~~method~~ use of ~~any one of~~ claim~~s~~ 1~~-4~~, wherein the first dose is to be administered on a first day (D1) of the intermittent schedule and the second dose is to be administered on a second day (D2) of the intermittent schedule.

~~7. The method of claim 6, further comprising administering a third dose of a third SHP2 inhibitor on a third day (D3) of the intermittent schedule and administering a fourth dose of a fourth SHP2 inhibitor on a fourth day (D4) of the intermittent schedule.~~

~~8. The method of claim 7, wherein at least two of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor and the fourth SHP2 inhibitor are identical.~~

~~9. The method of claim 7, wherein at least three of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor and the fourth SHP2 inhibitor are identical.~~

~~10. The method of claim 7, wherein the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor and the fourth SHP2 inhibitor are identical.~~

~~11. The method of claim 7, wherein the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor and the fourth SHP2 inhibitor are not identical.~~

~~12. The method of any one of claims 1-4, wherein the first dose is administered on a first day (D1) of the intermittent schedule and wherein the method further comprises determining a plasma concentration value of the first SHP2 inhibitor of the subject on each subsequent day of the intermittent schedule.~~

~~13. The method of claim 12, wherein the second dose is administered the day after a plasma concentration value is less than an EC_{50} value of a phosphorylated extracellular signal-regulated kinase (ERK) (pERK) of the subject.~~

~~14. The method of claim 13, wherein the EC_{50} value of the pERK is a predetermined value or a measured value.~~

~~15. The method of any one of claims 12-14, wherein the wherein the second dose is administered on the fourth day (D4) of the intermittent schedule.~~

4~~16~~. The ~~method~~ use of any one of claims 1-3~~9~~, wherein an iteration of the intermittent schedule is 7 days.

~~17. The method of any one of claims 1-4, wherein the first dose is administered on the first day (D1) of the intermittent schedule, wherein the second dose is administered on a second day (D2) of the intermittent schedule, wherein the method further comprises determining a first plasma concentration value of the first SHP2 inhibitor and a second plasma concentration value the second SHP2 inhibitor of the subject on each subsequent day of the intermittent schedule, and wherein a subsequent dose of a subsequent SHP2 inhibitor is administered the day after the first plasma concentration value or the second plasma concentration value is less than an EC_{50} value of pERK of the subject.~~

~~18. The method of claim 8~~17, ~~wherein the subsequent dose of the subsequent SHP2 inhibitor is administered the day after the first plasma concentration value and the second plasma concentration value are each less than an EC_{50} value of pERK of the subject.~~

~~19. The method of claim 17 or 18, further comprising administering a third dose of a third SHP2 inhibitor on a third day (D3) of the intermittent schedule and a fourth dose of a fourth SHP2 inhibitor on a fourth day (D4) of the intermittent schedule, and determining a third plasma concentration value of the third SHP2 inhibitor and a fourth plasma concentration value the fourth SHP2 inhibitor of the subject on each subsequent day of the intermittent schedule, wherein the subsequent dose of the subsequent SHP2 inhibitor is administered the day after the first plasma concentration value, the second plasma concentration value, the third plasma concentration value, or the fourth plasma concentration value, is less than an EC_{50} value of pERK of the subject.~~

~~20. The method of claim 19, wherein the subsequent dose of the subsequent SHP2 inhibitor is administered the day after the first plasma concentration value, the second plasma concentration value, the third plasma concentration value, and the fourth plasma concentration value, are each less than an EC_{50} value of pERK of the subject.~~

~~21. The method of any one of claims 17-20, wherein the EC_{50} value of pERK is a predetermined value or a measured value.~~

~~22. The method of any one of claims 17-21 wherein a complete iteration of the intermittent schedule is 7 days.~~

5~~23~~. The ~~method~~ use of ~~any one of~~ claim~~s 17-22~~4, wherein ~~the~~ a subsequent dose is to be administered on an eighth day (D8).

~~24. The method of any one of claims 19-22, wherein two or more of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor are identical.~~

~~25. The method of any one of claims 19-22, wherein three or more of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor are identical.~~

~~26. The method of any one of claims 19-22, wherein four or more of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor are identical.~~

~~27. The method of any one of claims 19-22, wherein the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor are identical.~~

~~28. The method of any one of claims 19-22, wherein the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor are not identical.~~

6~~29~~. The ~~method~~ use of ~~any one of~~ claim~~s 17-28~~4, wherein a first iteration comprises the first dose and the second dose and wherein ~~the~~ a subsequent dose is the first dose of a second or subsequent iteration.

~~30. The method of any one of claims 19-28, wherein a first iteration comprises the first dose, the second dose, the third dose and the fourth dose, and wherein the subsequent dose is the first dose of a second or subsequent iteration.~~

~~31. The method of claim 16, wherein the method comprises administering at least one complete iteration of the intermittent schedule.~~

~~32. The method of any one of claims 17-30, wherein the method comprises administering at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 complete iterations of the intermittent schedule.~~

7~~33~~. The ~~method~~ use of any one of claims 1-6~~32~~, wherein ~~the method further comprises administering~~ a second therapeutic agent is to be further administered.

~~34. The method of claim 33, wherein the second therapeutic agent comprises a second cell proliferation inhibitor.~~

~~35. The method of claim 33 or 34, wherein the second therapeutic agent comprises a mitogen-activated protein kinase kinase (MEK) inhibitor.~~

~~36. The method of claim 35, wherein the second therapeutic agent comprises cobimetinib.~~

8~~37~~. The ~~method~~ use of claim ~~33 or 34~~7, wherein the second therapeutic agent comprises a rat sarcoma (RAS) inhibitor.

38. The method of claim 37, wherein the RAS inhibitor inhibits one or more of Kristen rat sarcoma (KRAS), neuroblastoma RAS (NRAS) and Harvey rat sarcoma (HRAS).

39. The method of claim 37, wherein the RAS inhibitor inhibits Kristen rat sarcoma (KRAS), neuroblastoma RAS (NRAS) and Harvey rat sarcoma (HRAS).

40. The method of claim 33 or 34, wherein the second therapeutic agent comprises a KRAS inhibitor.

41. The method of any one of claims 37-40, wherein the RAS inhibitor is a non-covalent inhibitor.

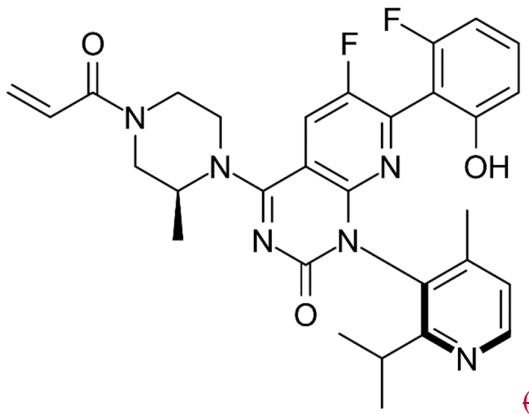
42. The method of any one of claims 37-40, wherein the RAS inhibitor is a covalent inhibitor.

43. The method of any one of claims 37-42, wherein the RAS inhibitor inhibits an activated or guanine triphosphate (GTP) bound form of RAS.

44. The method of any one of claims 37-42, wherein the RAS inhibitor inhibits an inactivated or guanine diphosphate (GDP) bound form of RAS.

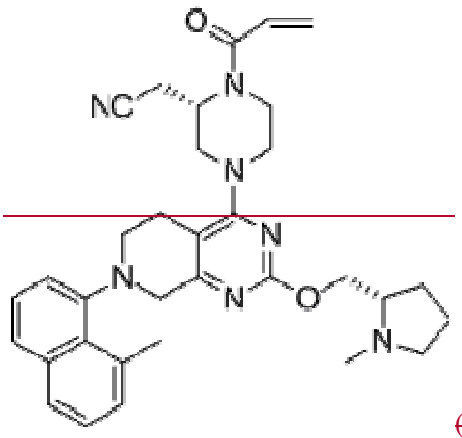
45. The method of any one of claims 40-44, wherein the second therapeutic agent comprises a $KRAS^{G12C}$ inhibitor.

46. The method of any one of claims 40-45, wherein the second therapeutic agent comprises



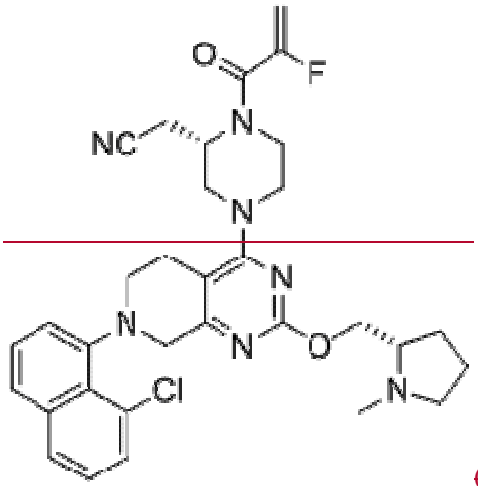
(AMG 510).

47. The method of any one of claims 40-45, wherein the second therapeutic agent comprises



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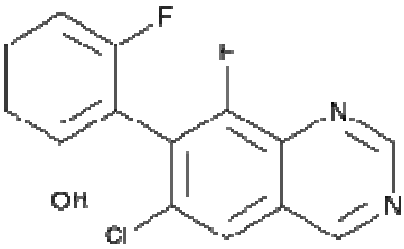
48. The method of any one of claims 40-45, wherein the second therapeutic agent comprises

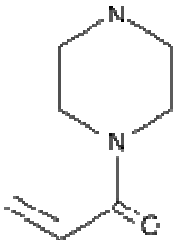


(MRTX849).

49. The method of any one of claims 40-45, wherein the second therapeutic agent comprises ARS-3248 or JNJ-74699157.

50. The method of any one of claims 40-45, wherein the second therapeutic agent comprises





~~(ARS-1620).~~

~~51. The method of any one of claims 33-50, wherein the method comprises administering a first dose of the second therapeutic agent and a second dose of the second therapeutic agent and wherein the first dose of the second therapeutic agent and the second dose of the second therapeutic agent are administered on an intermittent schedule.~~

~~52. The method of any one of claims 33-51, wherein one or more of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor, and the second therapeutic agent are administered simultaneously.~~

~~53. The method of any one of claims 33-51, wherein one or more of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor, and the second therapeutic agent are not administered simultaneously.~~

9~~54~~. The ~~method~~ use of ~~any one of~~ claim~~s~~ 7 or 8~~33-53~~, wherein the first SHP2 inhibitor or the first dose of a SHP2 inhibitor and the second therapeutic agent are to be administered simultaneously.

~~55. The method of any one of claims 33-53, wherein the first SHP2 inhibitor or the first dose of a SHP2 inhibitor and the second therapeutic agent are not administered simultaneously.~~

1056. The ~~method~~ use of any one of claims ~~33-55~~7-9, wherein ~~the second SHP2 inhibitor or~~ the second dose of a SHP2 inhibitor and the second therapeutic agent are to be administered simultaneously.

~~58. The method of any one of claims 33-57, wherein the third SHP2 inhibitor or the third dose of a SHP2 inhibitor and the second therapeutic agent are administered simultaneously.~~

~~59. The method of any one of claims 33-57, wherein the third SHP2 inhibitor or the third dose of a SHP2 inhibitor and the second therapeutic agent are not administered simultaneously.~~

~~60. The method of any one of claims 33-59, wherein the fourth SHP2 inhibitor or the fourth dose of a SHP2 inhibitor and the second therapeutic agent are administered simultaneously.~~

~~61. The method of any one of claims 33-59, wherein the fourth SHP2 inhibitor or the fourth dose of a SHP2 inhibitor and the second therapeutic agent are not administered simultaneously.~~

~~62. The method of any one of claims 33-61, wherein the subsequent SHP2 inhibitor or the subsequent dose of a SHP2 inhibitor and the second therapeutic agent are administered simultaneously.~~

~~63. The method of any one of claims 33-61, wherein the subsequent SHP2 inhibitor or the subsequent dose of a SHP2 inhibitor and the second therapeutic agent are not administered simultaneously.~~

~~64. The method of any one of claims 33-51 or 53, wherein one or more of the first SHP2 inhibitor, the second SHP2 inhibitor, the third SHP2 inhibitor, the fourth SHP2 inhibitor and the subsequent SHP2 inhibitor, and the second therapeutic agent are administered sequentially.~~

~~65. The method of claim 64, wherein the first SHP2 inhibitor or the first dose of a SHP2 inhibitor is administered before the second therapeutic agent.~~

~~66. The method of claim 64, wherein the second therapeutic agent is administered before the first SHP2 inhibitor or the first dose of a SHP2 inhibitor.~~

~~67. The method of any one of claims 64-66, wherein the second SHP2 inhibitor or the second dose of a SHP2 inhibitor is administered before the second therapeutic agent.~~

1168. The ~~method~~ use of ~~any one of~~ claim~~s~~ 7~~64-66~~, wherein the second therapeutic agent is to be administered before ~~the second SHP2 inhibitor or~~ the second dose of a SHP2 inhibitor.

~~69. The method of any one of claims 64-68, wherein the third SHP2 inhibitor or the third dose of a SHP2 inhibitor is administered before the second therapeutic agent.~~

~~70. The method of any one of claims 64-68, wherein the second therapeutic agent is administered before the third SHP2 inhibitor or the third dose of a SHP2 inhibitor.~~

~~71. The method of any one of claims 64-70, wherein the fourth SHP2 inhibitor or the fourth dose of a SHP2 inhibitor is administered before the second therapeutic agent.~~

~~72. The method of any one of claims 64-70, wherein the second therapeutic agent is administered before the fourth SHP2 inhibitor or the fourth dose of a SHP2 inhibitor.~~

2973. ~~The method of any one of claims 64-72, wherein the subsequent SHP2 inhibitor or the subsequent dose of a SHP2 inhibitor is administered before the second therapeutic agent.~~

1274. The ~~method~~ use of ~~any one of~~ claim~~s~~ ~~64-72~~7, wherein the second therapeutic agent is to be administered before the subsequent SHP2 inhibitor or the subsequent dose of a SHP2 inhibitor.

1375. The ~~method~~ use of any one of claims 7-12~~33-74~~, wherein the first dose of the first SHP2 inhibitor and a first dose of the second therapeutic agent are to be administered on D1 of the intermittent schedule and wherein the second dose of the second SHP2 inhibitor and a second dose of the second therapeutic agent are to be administered on different days of the intermittent schedule.

~~76. The method of claim 75, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are identical.~~

~~77. The method of claim 75, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are not identical.~~

~~78. The method of any one of claims 33-74, wherein the first dose of the first SHP2 inhibitor and a first dose of the second therapeutic agent are administered on D1 of the intermittent schedule and wherein the second dose of the second SHP2 inhibitor and a first dose of a third therapeutic agent are administered on different days of the intermittent schedule.~~

~~79. The method of claim 78, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are identical.~~

~~80. The method of claim 78, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are not identical.~~

~~81. The method of any one of claims 78-80, wherein the second therapeutic agent and the third therapeutic agent are identical.~~

~~82. The method of any one of claims 78-80, wherein the second therapeutic agent and the third therapeutic agent are not identical.~~

~~83. The method of any one of claims 33-74, wherein the first dose of the SHP2 inhibitor and a first dose of the second therapeutic agent are administered on different days of the intermittent schedule and wherein the second dose of the second SHP2 inhibitor and a second dose of the second therapeutic agent are administered on the same day of the intermittent schedule.~~

~~84. The method of claim 83, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are identical.~~

~~85. The method of claim 83, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are not identical.~~

~~86. The method of any one of claims 33-74, wherein the first dose of the SHP2 inhibitor and a first dose of the second therapeutic agent are administered on different days of the intermittent schedule and wherein the second dose of the second SHP2 inhibitor and a first~~

~~dose of a third therapeutic agent are administered on the same day of the intermittent schedule.~~

~~87. The method of claim 86, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are identical.~~

~~88. The method of claim 86, wherein the first SHP2 inhibitor and the second SHP2 inhibitor are not identical.~~

~~89. The method of any one of claims 86-88, wherein the second therapeutic agent and the third therapeutic agent are identical.~~

~~90. The method of any one of claims 86-88, wherein the second therapeutic agent and the third therapeutic agent are not identical.~~

1491. The ~~method~~ use of any one of claims ~~33-90~~7-13, wherein an iteration of the intermittent schedule is 7 days.

~~92. The method of any one of claims 33-91, wherein the method comprises administering at least one complete iteration of the intermittent schedule.~~

~~93. The method of any one of claims 33-91, wherein the method comprises administering at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 complete iterations of the intermittent schedule.~~

1594. The ~~method~~ use of any one of claims 1-~~93~~14, wherein the SHP2 inhibitor is an allosteric SHP2 inhibitor.

~~95. The method of claim 94, wherein the subject has a mutation of SHP2 and wherein the mutation of SHP2 is sensitive to an allosteric SHP2 inhibitor.~~

~~96. The method of claim 95, wherein the mutation of SHP2 comprises one or more of F285S, L262R, S189A, D61G, E69K, T73I and Q506P.~~

~~97. The method of claim 95, wherein the mutation of SHP2 comprises one or more of F285S, L262R and S189A.~~

~~98. The method of claim 95, wherein the mutation of SHP2 comprises D61G.~~

~~99. The method of claim 95, wherein the mutation of SHP2 comprises one or more of E69K, T73I and Q506P.~~

~~100. The method of any one of claims 95-99, wherein the subject does not have a mutation of SHP2 resistant to an allosteric SHP2 inhibitor.~~

~~101. The method of claim 100, wherein the mutation of SHP2 resistant to an allosteric SHP2 inhibitor comprises one or more of E76K, P491S and S502P.~~

~~102. The method of claim 100, wherein the mutation of SHP2 resistant to an allosteric SHP2 inhibitor comprises E76K or P491S.~~

~~103. The method of claim 100, wherein the mutation of SHP2 resistant to an allosteric SHP2 inhibitor comprises S502P.~~

~~104. The method of any one of claims 1-103, wherein the subject has been identified as having the mutation of SHP2 prior to administration of the first dose of a SHP2 inhibitor.~~

~~105. The method of any one of claims 1-103, wherein the subject has been identified as being at risk of developing a disease or disorder caused by the mutation of SHP2 prior to administration of the first dose of a SHP2 inhibitor.~~

~~106. The method of any one of claims 1-103, wherein the subject has been identified as having a disease or disorder caused by the mutation of SHP2 prior to administration of the first dose of a SHP2 inhibitor.~~

~~107. The method of any one of claims 104-106, wherein the SHP2 inhibitor is a first SHP2 inhibitor, a second SHP2 inhibitor, a third SHP2 inhibitor, a fourth SHP2 inhibitor or a subsequent SHP2 inhibitor.~~

16~~108~~. The ~~method~~ use of any one of claims 1-~~107~~15, wherein the SHP2 inhibitor comprises

(i) SHP099;

(ii) an allosteric SHP2 inhibitor compound of any one of Formula I, of Formula II, of Formula III, of Formula 1- VI, 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 1V-Z, of Formula VII, of Formula VIII, of Formula IX, and of Formula X;

(iii) TNO155;

(iv) JAB-3068;

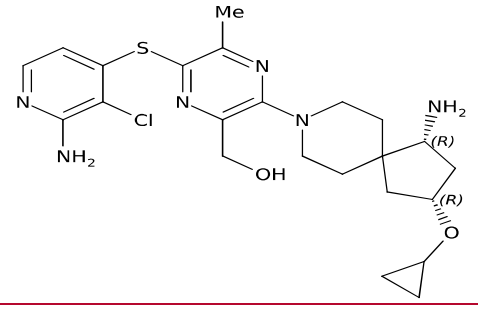
(v) a compound from Table 1, disclosed herein;

(vi) a compound from Table 2, disclosed herein;

(vii) RLY-1971; or

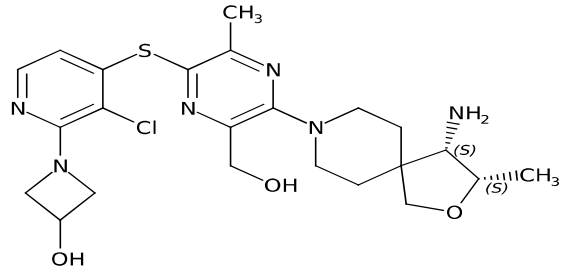
(viii) a combination thereof.

~~109. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



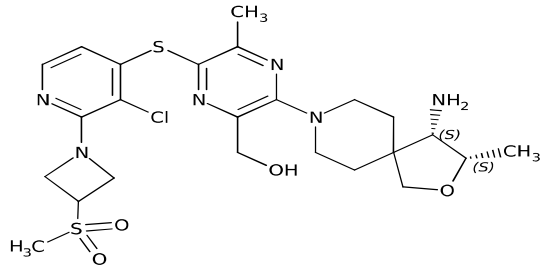
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~~110. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



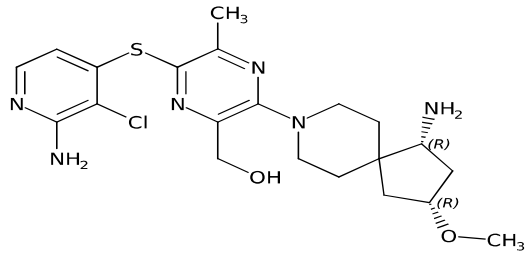
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~~111. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



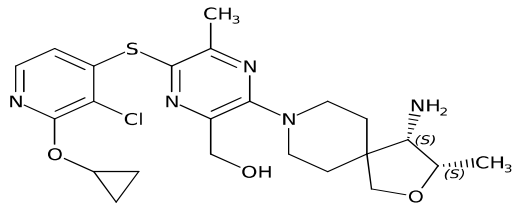
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~~112. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



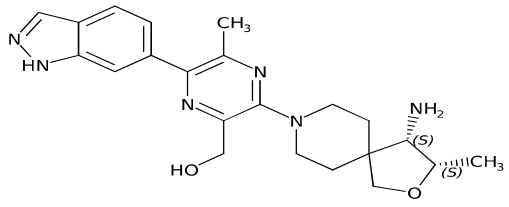
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~~113. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



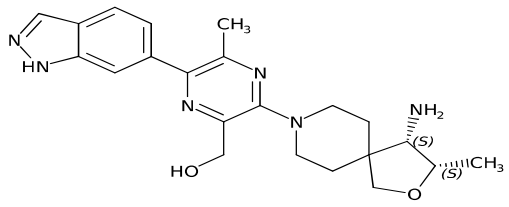
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~~114. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



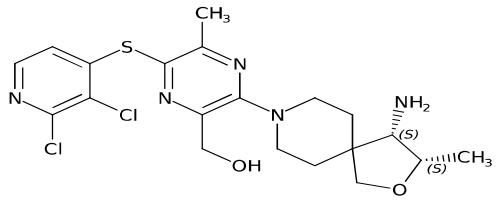
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115. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises



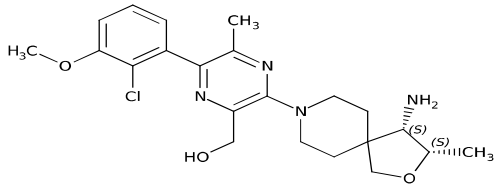
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116. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises



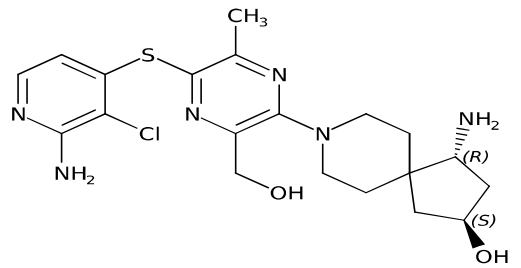
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117. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises



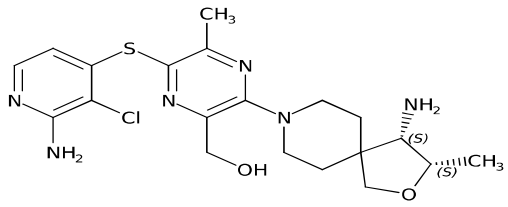
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118. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises



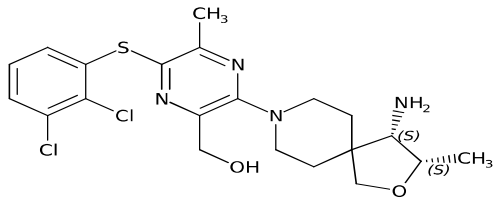
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17~~119~~. The ~~method~~ use of any one of claims 1-~~107~~16, wherein the SHP2 inhibitor comprises



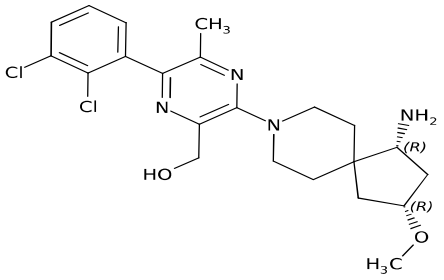
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~~120. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



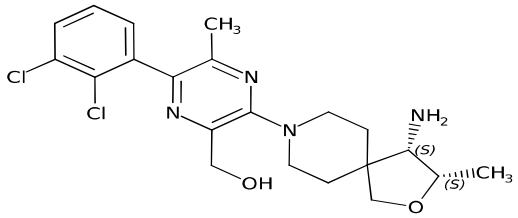
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~~121. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



~~.~~

~~122. The method of any one of claims 1-107, wherein the SHP2 inhibitor comprises~~



18~~123~~. The ~~method~~ use of any one of claims 1-~~122~~17, wherein the subject further comprises a mutation in a component of a rat sarcoma (RAS) signaling pathway.

19~~124~~. The ~~method~~ use of claim ~~123~~18, wherein the mutation in the component of the RAS signaling pathway occurs in KRAS, neurofibromin 1 (NF1), or serine/threonine-protein kinase B-raf (BRAF).

20~~125~~. The ~~method~~ use of claim 18 or 19~~23 or 124~~, wherein the mutation in the component of the RAS signaling pathway comprises:

i) a substitution of a cysteine (C) for a glycine (G) at position 12 of KRAS ($KRAS^{G12C}$);
ii) a KRAS amplification ($KRAS^{amp}$);
iii) a loss of function (LOF) mutation of NF1 ($NF1^{LOF}$); or
~~i)~~iv) a class 3 mutant of BRAF ($BRAF^{class3}$).

~~126. The method of claim 123 or 124, wherein the mutation in the component of the RAS signaling pathway comprises a KRAS amplification ($KRAS^{amp}$).~~

~~127. The method of any one of claims 123-126, wherein the mutation in the component of the RAS signaling pathway comprises a loss of function (LOF) mutation of NF1 ($NF1^{LOF}$).~~

~~128. The method of any one of claims 123-127, wherein the mutation in the component of the RAS signaling pathway comprises a class 3 mutant of BRAF ($BRAF^{class3}$).~~

~~129. The method of any one of claims 123-128, wherein the mutation in the component of the RAS signaling pathway does not comprise a substitution of a glutamic acid (E) for a valine (V) at position 600 of BRAF.~~

21~~130~~. ~~The method of any one of claims 123-128~~18-20~~, wherein the disease or disorder is cancer.chosen from:~~

~~a tumor;~~

~~a malignant tumor~~

~~cancer.~~

~~131. The method of claim 130, wherein the tumor is a malignant tumor.~~

~~132. The method of claim 131, wherein the tumor is a cancer.~~

~~133. The method of claim 132, wherein the tumor is metastatic.~~

~~134. The method of claim 132, wherein the cancer is metastatic.~~

~~135. The method of any one of claims 131-134, wherein the tumor or the cancer has a primary presentation in one or both lung(s) of the subject.~~

~~136. The method of any one of claims 131-135, wherein the tumor or the cancer has a secondary presentation in one or both lung(s) of the subject.~~

22~~137~~. The ~~method~~ use of ~~any one of claims 131-136~~21any one of claims 18-20, wherein the ~~tumor or the~~ cancer:

(i) is non-small cell lung cancer;

(ii) presents a brain metastasis in the subject;

(iii) has a primary presentation in a pancreas of the subject;

(iv) has a secondary presentation in a pancreas of the subject;

(v) has a primary presentation in one or more of a large intestine, a small intestine, a stomach, a bladder, a kidney, a colon or a rectum of the subject;

(vi) has a secondary presentation in one or more of a large intestine, a small intestine, a stomach, a bladder, a kidney, a colon or a rectum of the subject;

(vii) has a primary presentation as a sarcoma in the subject; or

~~(i)~~(viii) has a secondary presentation as a sarcoma in the subject.

~~138. The method of any one of claims 131-136, wherein the tumor or the cancer presents a brain metastasis in the subject.~~

~~139. The method of any one of claims 131-135, wherein the tumor or the cancer has a primary presentation in a pancreas of the subject.~~

~~140. The method of any one of claims 131-134 or 139, wherein the tumor or the cancer has a secondary presentation in a pancreas of the subject.~~

~~141. The method of any one of claims 131-134, wherein the tumor or the cancer has a primary presentation in one or more of a large intestine, a small intestine, a stomach, a bladder, a kidney, a colon or a rectum of the subject.~~

~~142. The method of any one of claims 131-135 or 141, wherein the tumor or the cancer has a secondary presentation in one or more of a large intestine, a small intestine, a stomach, a bladder, a kidney, a colon or a rectum of the subject.~~

~~143. The method of any one of claims 131-135, wherein the tumor or the cancer has a primary presentation as a sarcoma in the subject.~~

~~144. The method of any one of claims 131-135 or 143, wherein the tumor or the cancer has a secondary presentation as a sarcoma in the subject.~~

~~145. The method of any one of claims 1-144, wherein the subject is human.~~

~~146. The method of any one of claims 1-145, wherein the subject is female.~~

~~147. The method of any one of claims 1-145, wherein the subject is male.~~

~~148. The method of any one of claims 1-147, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor comprises a therapeutically effective amount of a SHP2 inhibitor.~~

~~47~~149. ~~The method of any one of claims 1-147, wherein the first dose of the SHP2 inhibitor and the second dose of the SHP2 inhibitor each comprises a therapeutically effective amount of the SHP2 inhibitor.~~

~~150. The method of any one of claims 7-147, wherein the first dose of the SHP2 inhibitor, the second dose of the SHP2 inhibitor, the third dose of the third SHP2 inhibitor, or the fourth dose of the fourth SHP2 inhibitor comprises a therapeutically effective amount of a SHP2 inhibitor.~~

~~151. The method of any one of claims 7-147, wherein the first dose of the SHP2 inhibitor, the second dose of the SHP2 inhibitor, the third dose of the third SHP2 inhibitor, and the fourth dose of the fourth SHP2 inhibitor each comprise a therapeutically effective amount of a SHP2 inhibitor.~~

~~152. The method of claim 148 or 149, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor reduces tumor burden of the subject.~~

~~153. The method of claim 148 or 149, wherein the first dose of the first SHP2 inhibitor and the second dose of the second SHP2 inhibitor each reduce tumor burden of the subject.~~

~~154. The method of claim 148 or 149, wherein the combination of the first dose of the first SHP2 inhibitor and the second dose of the second SHP2 inhibitor reduces tumor burden of the subject.~~

~~155. The method of claim 150 or 151, wherein the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor or the fourth dose of the SHP2 inhibitor reduces tumor burden of the subject.~~

~~156. The method of claim 150 or 151, wherein the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor and the fourth dose of the SHP2 inhibitor each reduce tumor burden of the subject.~~

~~157. The method of claim 150 or 151, wherein the combination of the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor and the fourth dose of the SHP2 inhibitor reduces tumor burden of the subject.~~

~~158. The method of any one of claims 1-157, wherein treating comprises reducing tumor burden of the subject.~~

~~159. The method of claim 148 or 149, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor decreases activation of a component of a RAS signaling pathway in the subject.~~

~~160. The method of claim 148 or 149, wherein the first dose of the first SHP2 inhibitor and the second dose of the second SHP2 inhibitor each decrease activation of a component of a RAS signaling pathway in the subject.~~

~~161. The method of claim 148 or 149, wherein the combination of the first dose of the first SHP2 inhibitor and the second dose of the second SHP2 inhibitor decreases activation of a component of a RAS signaling pathway in the subject.~~

~~162. The method of claim 150 or 151, wherein the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor or the fourth dose of the SHP2 inhibitor decreases activation of a component of a RAS signaling pathway in the subject.~~

~~163. The method of claim 150 or 151, wherein the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor and the fourth dose of the SHP2 inhibitor each decrease activation of a component of a RAS signaling pathway in the subject.~~

~~164. The method of claim 150 or 151, wherein the combination of the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor and the fourth dose of the SHP2 inhibitor decreases activation of a component of a RAS signaling pathway in the subject.~~

~~165. The method of any one of claims 1-164, wherein treating comprises decreasing activation of a component of a RAS signaling pathway in the subject.~~

~~166. The method of any one of claims 159-165, wherein decreasing activation of a component of a RAS signaling pathway comprises decreasing phosphorylation of ERK.~~

~~167. The method of any one of claims 1-166, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is administered systemically.~~

~~168. The method of claim 167, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is administered orally.~~

~~169. The method of any one of claims 7-166, wherein the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor or the fourth dose of the SHP2 inhibitor is administered systemically.~~

~~170. The method of claim 169, wherein the first dose of the first SHP2 inhibitor, the second dose of the second SHP2 inhibitor, the third dose of the SHP2 inhibitor or the fourth dose of the SHP2 inhibitor is administered orally.~~

~~171. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is at least 10 milligrams (mg), 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg or at least any number of mg in between.~~

~~172. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is between 10 mg and 300 mg, inclusive of the endpoints.~~

~~173. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is at least 80 mg.~~

~~174. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is about 80 mg.~~

~~175. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is 80 mg.~~

~~176. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is at least 140 mg.~~

~~177. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is about 140 mg.~~

~~178. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is 140 mg.~~

~~179. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is at least 200 mg.~~

~~180. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is about 200 mg.~~

~~181. The method of claim 167 or 168, wherein the first dose of the first SHP2 inhibitor or the second dose of the second SHP2 inhibitor is 200 mg.~~

~~182. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of at least 10 milligrams (mg), 20 mg, 30 mg, 40 mg, 50 mg, 60 mg, 70 mg, 80 mg, 90 mg, 100 mg, 110 mg, 120 mg, 130 mg, 140 mg, 150 mg, 160 mg, 170 mg, 180 mg, 190 mg, 200 mg, 210 mg, 220 mg, 230 mg, 240 mg, 250 mg, 260 mg, 270 mg, 280 mg, 290 mg, 300 mg or at least any number of mg in between.~~

~~183. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of between 10 mg and 300 mg, inclusive of the endpoints.~~

~~184. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of at least 20 mg, 40 mg, 60 mg, 80 mg or at least any number of mg in between 20 mg and 80 mg.~~

~~185. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of between 20 mg and 80 mg, inclusive of the endpoints.~~

~~186. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of 20 mg.~~

~~187. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of 40 mg.~~

~~188. The method of any one of claims 33-181, wherein the second therapeutic agent is administered at a dose of 60 mg.~~