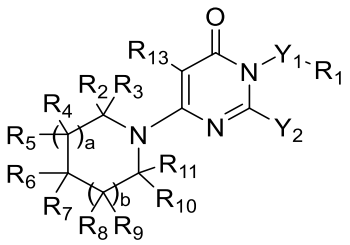
CLAIMS

1. Use of:

a) a PTPN11 inhibitor; and

b) a KRAS G12C inhibitor,

wherein the PTPN11 inhibitor is represent by formula (I):



(I),

or a pharmaceutically acceptable salt, hydrate, solvate, stereoisomer, conformational isomer, tautomer, or a combination thereof,

wherein:

subscript a is 0 or 1;

subscript b is 0 or 1;

Y_1 is a direct bond or $CR_{17}R_{18}$;

Y_2 is selected from the group consisting of $C_{1\text{-}4}$alkyl, amino, $C_{1\text{-}4}$alkylC(O)O-, $C_{1\text{-}4}$alkylamino and $C_{1\text{-}4}$aminoalkyl;

R_1 is selected from the group consisting of $C_{6\text{-}10}$aryl, $C_{3\text{-}8}$cycloalkyl, $C_{3\text{-}8}$cycloalkenyl, and a 5-10 membered heteroaryl group having 1 to 4 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and S; said aryl or heteroaryl of R_1 is unsubstituted or substituted with 1 to 5 R_{12} groups independently selected from the group consisting of halo, hydroxy, amino, $C_{1\text{-}4}$alkylamino, di($C_{1\text{-}4}$alkyl)amino, cyano, $C_{1\text{-}4}$alkyl, $C_{1\text{-}4}$alkoxy, $C_{1\text{-}4}$hydroxyalkyl, $C_{1\text{-}4}$haloalkyl, $C_{1\text{-}4}$aminoalkyl, $C_{3\text{-}8}$cycloalkyl, $C_{3\text{-}8}$cycloalkenyl, $NR_{15}C(O)R_{14}$, $NR_{15}C(O)OR_{14}$, $NR_{14}C(O)NR_{15}R_{16}$, $NR_{15}S(O)R_{14}$, $NR_{15}S(O)_2R_{14}$, $C(O)NR_{15}R_{16}$, $S(O)NR_{15}R_{16}$, $S(O)_2NR_{15}R_{16}$, $C(O)R_{14}$, $C(O)OR_{14}$, OR_{14}, SR_{14}, $S(O)R_{14}$, and $S(O)_2R_{14}$;

R_2, R_3, R_{10}, and R_{11} are each independently selected from the group consisting of hydrogen, $C_{1\text{-}4}$alkyl, and $C_{3\text{-}8}$cycloalkyl;

R_4, R_5, R_8, and R_9 are each independently selected from the group consisting of hydrogen, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, amino, hydroxy, C_{3-8}cycloalkyl, halo, and C_{1-4}alkylamino;

R_6 is selected from the group consisting of amino, C_{1-4}aminoalkyl, and C_{1-4}alkylamino;

R_7 is selected from the group consisting of hydrogen, amido, cyano, halo, and hydroxy, or is selected from the group consisting of C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{3-6}cycloalkyl, phenyl, and 5- or 6- membered heteroaryl, any of which is unsubstituted or substituted with 1 to 5 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino, and C_{1-4}aminoalkyl;

or R_6 and R_7 together with the carbon atom to which they are both attached form a 3- to 7-membered saturated or unsaturated ring, having 0 to 3 heteroatoms or groups as ring vertices independently selected from N, C(O), O, and $S(O)_m$; subscript m is 0, 1, or 2; and said saturated or unsaturated ring formed by R_6 and R_7 is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

any two groups of R_2, R_3, R_4, R_5, R_7, R_8, R_9, R_{10} and R_{11} can form a 5 to 6 membered ring, having 0 to 2 heteroatoms as ring vertices elected from N, O and S;

any two groups of R_2, R_4, R_6, R_8 and R_{10} can form a direct bond, or a 1 or 2 atom carbon bridge;

R_{13} is selected from the group consisting of hydrogen, halo, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{1-6} dihydroxyalkyl, -NH-NHR_{19}, -NHR_{19}, -OR_{19}, -$NHC(O)R_{19}$, -$NHC(O)NHR_{19}$, -$NHS(O)_2NHR_{19}$, -$NHS(O)_2R_{19}$, -$C(O)OR_{19}$, -$C(O)NR_{19}R_{20}$, -$C(O)NH(CH_2)_qOH$, -$C(O)NH(CH_2)_qR_{21}$, -$C(O)R_{21}$, -NH_2, -OH, -$S(O)_2NR_{19}R_{20}$, C_{3-8}cycloalkyl, aryl, heterocyclyl having 1-5 heteroatoms as ring vertices selected from N, O, S and P, and heteroaryl having 1-5 heteroatoms as ring vertices selected from N, O, S and P; subscript q is an integer of from 0 to 6; and each of aryl, heteroaryl, heterocyclyl and cycloalkyl of R_{13} is unsubstituted or substituted with 1 to 3 groups independently selected from the group consisting of C_{1-4}alkyl, –OH, -NH_2, -OR_{21}, halo, cyano, and oxo;

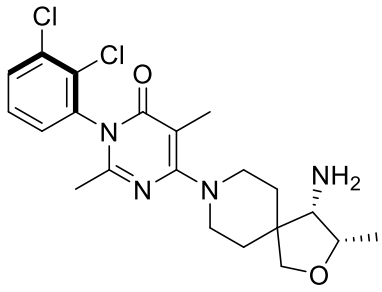
R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, C_{3-8}cycloalkyl, C_{6-10}aryl and 5-10 membered heteroaryl, any of which is unsubstituted or substituted with one or more groups independently selected from the group consisting of amido, amino, halo, hydroxy, cyano, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkyl, C_{1-4}haloalkoxy, C_{1-4}alkylamino and C_{1-4}aminoalkyl;

R_{17} and R_{18} are each independently selected from the group consisting of hydrogen, C_{1-4}alkyl, and CF_3;

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl; and

each R_{21} is independently selected from the group consisting of hydrogen, -OH, C_{1-6} alkyl, C_{1-6}haloalkyl, C_{1-6}hydroxyalkyl, C_{2-6}alkenyl, C_{2-6}alkynyl and C_{3-6}cycloalkyl,

provided that when the PTPN11 inhibitor is represented by formula (10b):

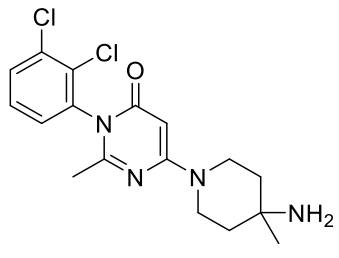
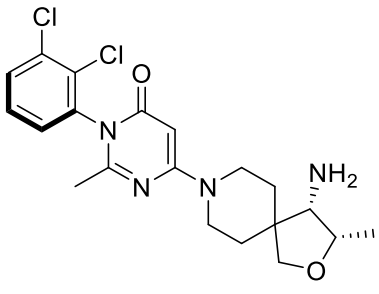
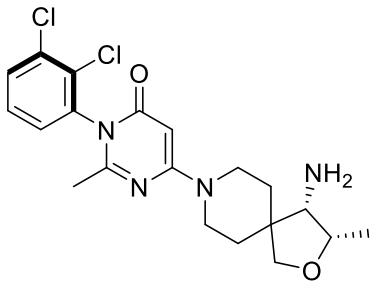


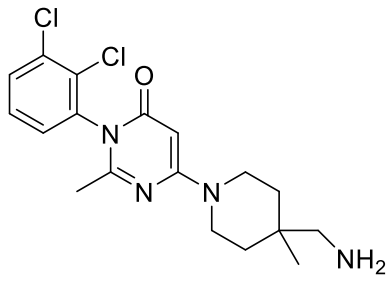
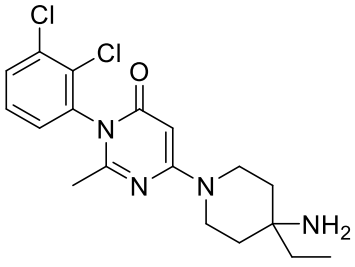
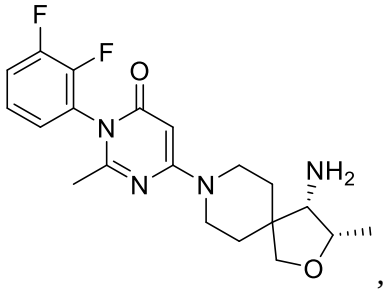
(10b),

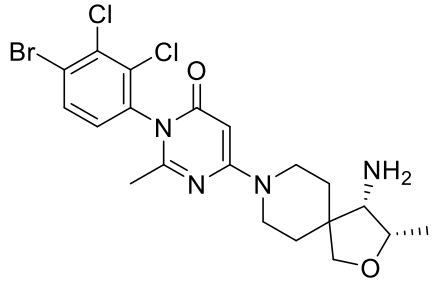
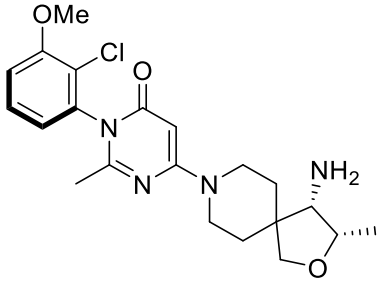
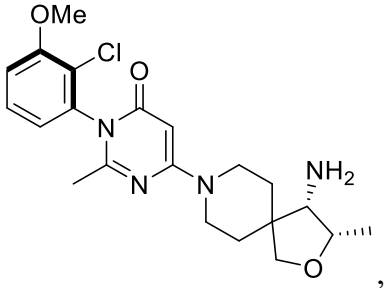
the KRAS G12C inhibitor is not sotorasib,

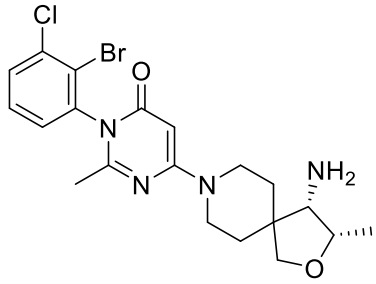
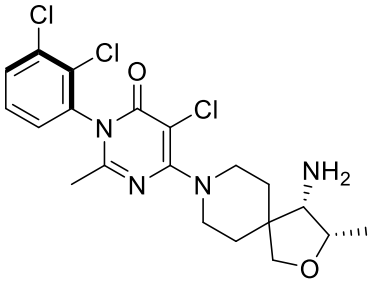
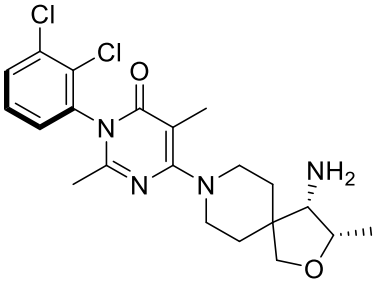
in the preparation of a medicament for the treatment of cancer, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are to be administered concomitantly or sequentially.

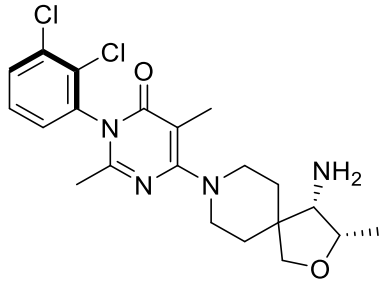
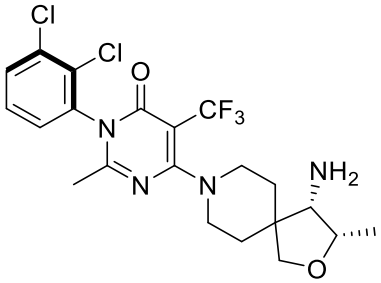
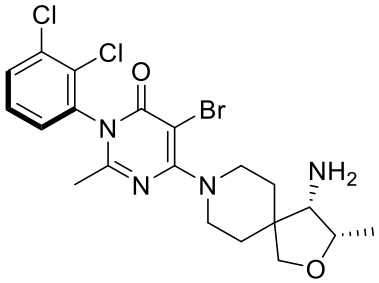
2. The use of claim **1**, wherein the PTPN11 inhibitor is selected from the group consisting of:

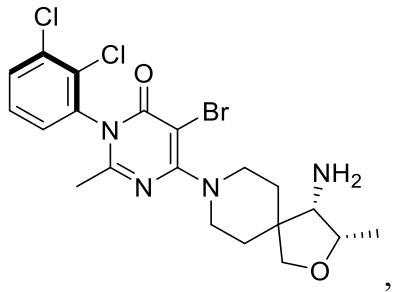
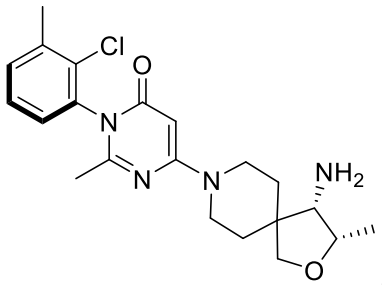
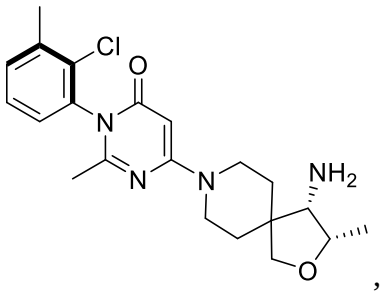
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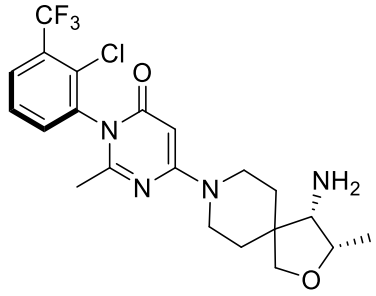
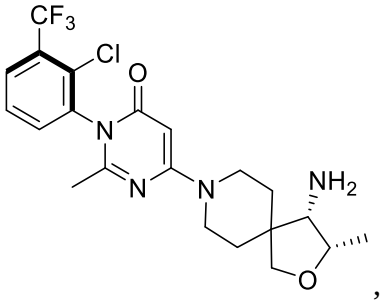
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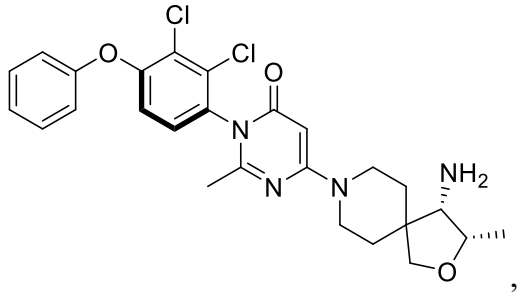
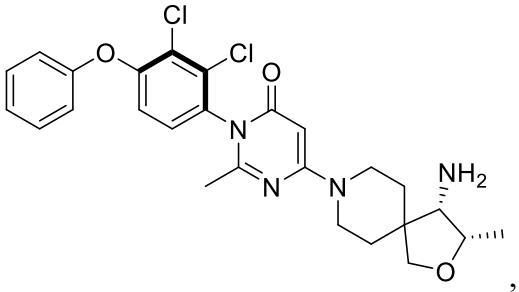
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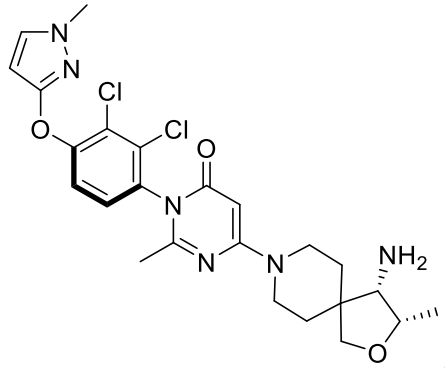
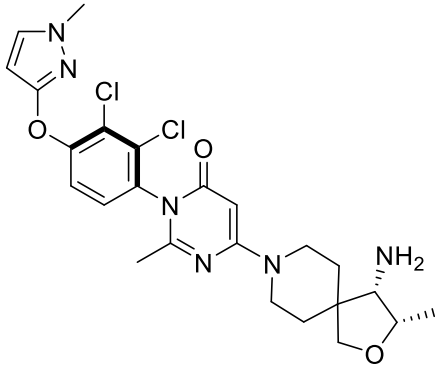
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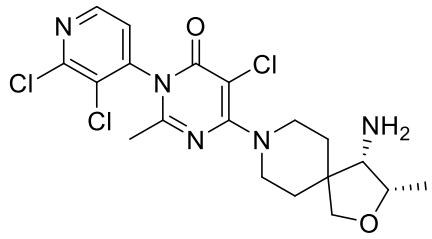
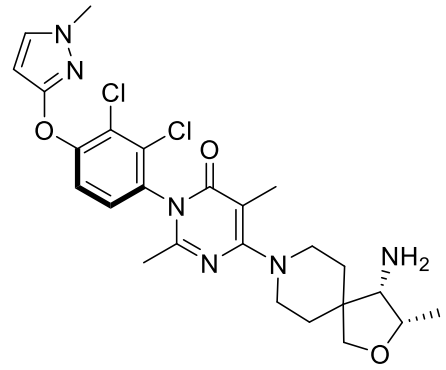
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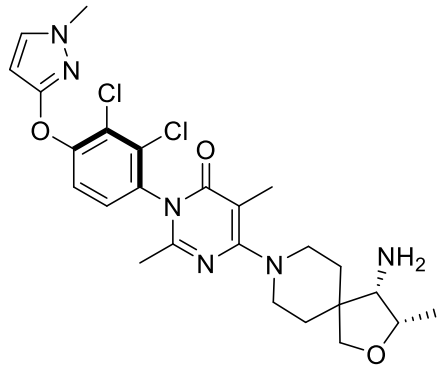
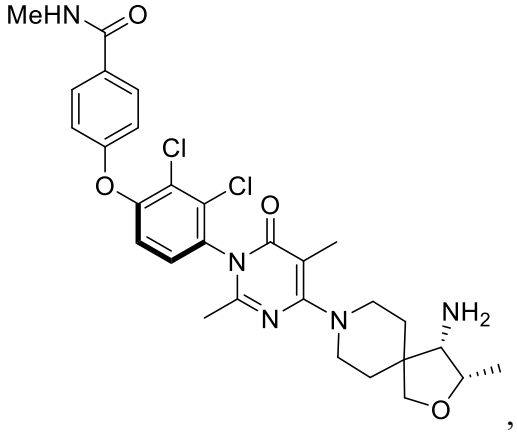
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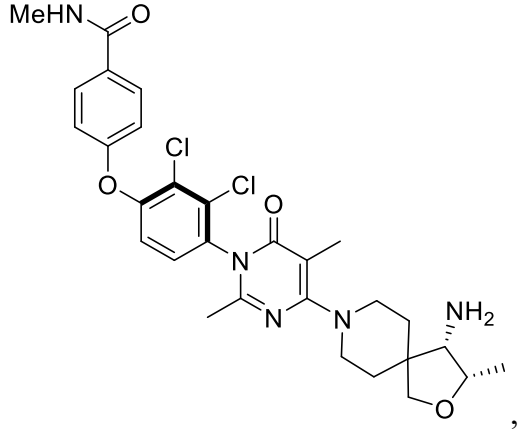
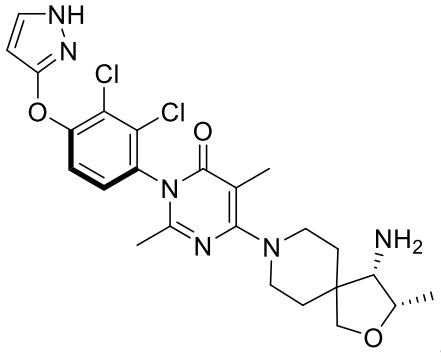
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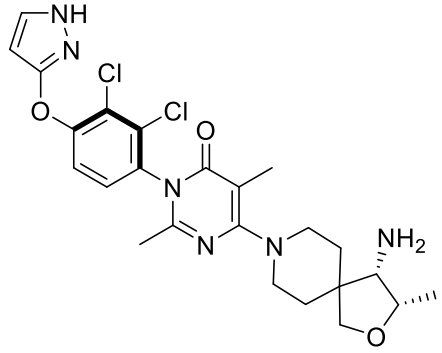
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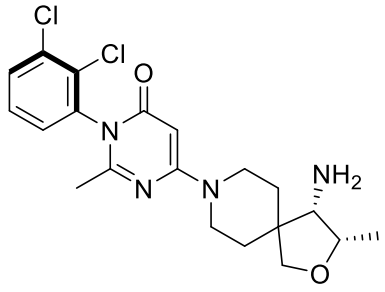
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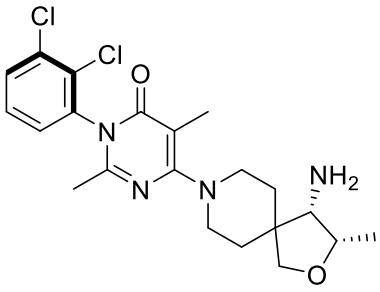
3. The use of claim **1** or **2**, wherein the PTPN11 inhibitor is represented by formula (2b):



(2b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(R_a)-(2,3-dichlorophenyl)-2-methylpyrimidin-4(3*H*)-one.

4. The use of claim **1** or **2**, wherein the PTPN11 inhibitor is represented by formula (10b):



(10b),

having the name of 6-((3*S*,4*S*)-4-amino-3-methyl-2-oxa-8-azaspiro[4.5]decan-8-yl)-3-(R_a)-(2,3-dichlorophenyl)-2,5-dimethylpyrimidin-4(3*H*)-one.

5. The use of any one of claims **1** to **4**, wherein the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446, provided that, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

6. The use of claim **5**, wherein the KRAS G12C inhibitor is adagrasib (MRTX-849).

7. The use of any one of claims **1** to **6**, wherein the cancer is characterized by a KRAS G12C mutation.

8. The use of any one of claims **1** to **7**, wherein the cancer comprises a solid tumor.

9. The use of any one of claims **1** to **8**, wherein the cancer is lung cancer, colorectal cancer, pancreatic cancer, urothelial carcinoma, stomach cancer, mesothelioma, or a combination thereof.

10. The useof claim **9**, wherein the cancer is non-small cell lung cancer (NSCLC).

11. The use of claim **9**, wherein the cancer is colorectal cancer.

12. The use of any one of claims **1** to **11**, wherein the cancer is a KRAS G12C-positive cancer resistant to a KRAS G12C inhibitor.

13. The use of any one of claims **1** to **12**, wherein the cancer is a KRAS G12C-positive cancer characterized by intrinsic and/or acquired resistance to a KRAS G12C inhibitor.

14. The use of any one of claims **1** to **13**, wherein the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446.

15. The use of claim **14**, wherein the cancer is a KRAS G12C-positive cancer resistant to sotorasib (AMG 510).

16. The use of claim **14**, wherein the cancer is a KRAS G12C-positive cancer resistant to adagrasib (MRTX-849).

17. The use of any one of claims **1** to **16**, wherein the cancer has progressed or recurred on or after at least one prior line of a systemic therapy comprising a platinum-based doublet chemotherapy and/or an anti-PD-1/PD-L1 therapy, each of which is given in monotherapy or both of which are given in combination therapy.

18. The use of any one of claims **1** to **17**, wherein the subject does not have an activating mutation in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X.

19. The use of any one of claims **1** to **18**, wherein the subject is not previously treated with a PTPN inhibitor.

20. The use of any one of claims **1** to **18**, wherein the subject is previously treated with a PTPN11 inhibitor other than a compound of formula (I).

21. The use of any one of claims **1** to **18**, wherein the subject is previously treated with a PTPN11 inhibitor of formula (I).

22. The use of any one of claims **1** to **20**, wherein the subject is not previously treated with a KRAS G12C inhibitor.

23. The use of any one of claims **1** to **20**, wherein the subject is previously treated with a KRAS G12C inhibitor.

24. The use of any one of claims **1** to **23**, wherein the subject is human.

25. The use of any one of claims **1** to **24**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are to be administered concomitantly.

26. The use of claim **25**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are to be administered in a pharmaceutical composition comprising the PTPN11 inhibitor and the KRAS G12C inhibitor.

27. The use of any one of claims **1** to **24**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are to be administered sequentially.

28. The use of claim **27**, wherein the PTPN11 inhibitor is to be administered prior to the administration of the KRAS G12C inhibitor.

29. The use of claim **27**, wherein the PTPN11 inhibitor is to be administered after the administration of the KRAS G12C inhibitor.

30. The use of any one of claims **1** to **29**, wherein the PTPN11 inhibitor and/or the KRAS G12C inhibitor are to be administered orally.

31. The use of any one of claims **1** to **30**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are provided in jointly therapeutically effective amounts.

32. The use of any one of claims **1** to **30**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are provided in synergistically effective amounts.

33. The use of any one of claims **1** to **30**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor is used at a dose different than when it is used alone.

34. The use of claim **33**, wherein the PTPN11 inhibitor is used at a dose lower than when it is used alone.

35. The use of claim **33**, wherein the PTPN11 inhibitor is used at a dose higher than when it is used alone.

36. The use of any one of claims **33** to **35**, wherein the KRAS G12C inhibitor is used at a dose lower than when it is used alone.

37. The use of any one of claims **33** to **35**, wherein the KRAS G12C inhibitor is used at a dose higher than when it is used alone.

38. The use of any one of claims **1** to **37**, wherein the treating comprises one or more treatment cycles; each of one or more treatment cycles has a duration of about 28 days; and the PTPN11 inhibitor and/or the KRAS G12C inhibitor are to be administered daily.

39. The use of any one of claim **1** to **38**, wherein the administration of the compound of formula (I) or (10b) and the KRAS G12C inhibitor comprises one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (I) or (10b) and/or the KRAS G12C inhibitor.

40. The use of any one of claim **1** to **38**, wherein the administration of the compound of formula (I) or (10b) and the KRAS G12C inhibitor comprises one or more dose escalations, dose retentions, or dose de-escalations of the compound of formula (I) or (10b).

41. The use of claim **40**, wherein the administration of the compound of formula (I) or (10b) comprises a dose escalation after a previous treatment cycle, when a dose-limiting toxicity (DLT) rate is less than about 19.7% as determined by a DLT assessment.

42. The use of claim **40**, wherein the administration of the compound of formula (I) or (10b) comprises a dose de-escalation after a previous treatment cycle, when a dose-limiting toxicity rate is more than about 29.8% as determined by a DLT assessment.

43. The use of claim **40**, wherein the administration of the compound of formula (I) or (10b) comprises a dose retention after a previous treatment cycle, when a dose-limiting toxicity rate is in a range of from about 21.9% to about 29.8% as determined by a DLT assessment.

44. The use of any one of claims **39** to **43**, wherein the treating comprises a dose escalation period, and wherein, after the dose escalation period, the treating further comprises a dose expansion/optimization period; and the compound of formula (I) or (10b) is administered at a dose regimen determined during the dose escalation period.

45. The use of claim **44**, wherein, during the dose expansion/optimization period, the administration of the compound of formula (I) or (10b) comprises one or more dose adjustments.

46. The use of any one of claims **4** to **45**, wherein the therapeutically effective amount of the compound of formula (I) or (10b) is a total daily dosage of from about 10 mg to

about 2000 mg, from about 50 mg to about 2000 mg, from about 80 mg to about 2000 mg, from about 80 mg to about 1000 mg, from about 80 mg to about 700 mg, from about 80 mg to about 550 mg, from about 80 mg to about 400 mg, from about 80 mg to about 250 mg, from about 80 mg to about 150 mg, 100 mg to about 2000 mg, from about 150 mg to about 1000 mg, from about 200 mg to about 1000 mg, from about 250 mg to about 1000 mg, from about 300 mg to about 1000 mg, from about 350 mg to about 1000 mg, from about 400 mg to about 1000 mg, from about 450 mg to about 1000 mg, from about 500 mg to about 1000 mg, from about 550 mg to about 1000 mg, from about 600 mg to about 1000 mg, from about 650 mg to about 1000 mg, from about 700 mg to about 1000 mg, from about 100 mg to about 700 mg, from about 150 mg to about 700 mg, from about 200 mg to about 700 mg, from about 250 mg to about 700 mg, from about 300 mg to about 700 mg, from about3 mg to about 700 mg, from about 400 mg to about 700 mg, from about 450 mg to about 700 mg, from about 500 mg to about 700 mg, from about 550 mg to about 700 mg, from about 100 mg to about 550 mg, from about 150 mg to about 550 mg, from about 200 mg to about 550 mg, from about 250 mg to about 550 mg, from about 300 mg to about 550 mg, from about 350 mg to about 550 mg, from about 400 mg to about 550 mg, from about 450 mg to about 550 mg, from about 100 mg to about 400 mg, from about 150 mg to about 400 mg, from about 200 mg to about 400 mg, from about 250 mg to about 400 mg, or from about 300 mg to about 400 mg, on a salt-free and anhydrous basis.

47. The use of claim **46**, wherein the therapeutically effective amount is a total daily dosage of from about 250 mg to about 400 mg, from about 400 mg to about 550 mg, or from about 550 mg to about 700 mg of the compound of formula (I) or (10b), on a salt-free and anhydrous basis.

48. The use of claim **46**, wherein the therapeutically effective amount of the compound of formula (10b) is a total daily dosage of about 80 mg, about 150 mg, about 250 mg, about 400 mg, about 550 mg, or about 700 mg, on a salt-free and anhydrous basis.

49. The use of any one of claims **1** to **48**, wherein the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of from about 10 mg to about 2000 mg.

50. The use of claim **49**, wherein the therapeutically effective amount of the KRAS G12C inhibitor is a total daily dosage of about 120 mg, about 150 mg, about 240 mg, about 300 mg, about 360 mg, about 480 mg, about 600 mg, about 720 mg, about 840 mg, about 960 mg, or about 1200 mg.

51. The use of any one of claims **4** to **50**, wherein the compound of formula (10b) and the KRAS G12C inhibitor are each to be administered orally.

52. The use of any one of claims **1** to **51**, wherein the PTPN11 inhibitor and/or the KRAS G12C inhibitor is to be administered once, twice, three times, or four times daily.

53. The use of claim **52**, wherein the PTPN11 inhibitor and/or the KRAS G12C inhibitor is to be administered once daily.

54. The use of any one of claims **1** to **53**, wherein the treating with the PTPN11 inhibitor and the KRAS G12C inhibitor reduces a volume of the cancer or a solid tumor at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, or about 90%.

55. The use of any one of claims **1** to **53**, wherein the treating with the PTPN11 inhibitor and the KRAS G12C inhibitor stabilizes the cancer or a solid tumor.

56. A pharmaceutical composition for treating cancer in a subject, comprising:

a) a PTPN11 inhibitor according to any one of claims **1** to **4**; and

b) a KRAS G12C inhibitor,

together with a pharmaceutically acceptable carrier or excipient.

57. The pharmaceutical composition of claim **56**, wherein the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446, provided that, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

58. A kit for treating cancer in a subject, comprising:

a) a PTPN11 inhibitor according to any one of claims **1** to **4**; and

b) a KRAS G12C inhibitor,

together with instruction for effective administration.

59. The kit of claim **58**, wherein the KRAS G12C inhibitor is sotorasib (AMG 510), adagrasib (MRTX-849), MRTX1257, ARS-853, ARS-1620, JNJ-74699157 (ARS-3248), JDQ443, GDC-6036, JAB-21822, BI 1823911, MK-1084, LY3537982, or LY3499446, provided that, when the PTPN11 inhibitor is represented by formula (10b), the KRAS G12C inhibitor is other than sotorasib.

60. The kit of claim **58** or **59**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are formulated for concomitant administration.

61. The kit of any one of claims **58** to **59**, wherein the PTPN11 inhibitor and the KRAS G12C inhibitor are formulated for sequential administration.