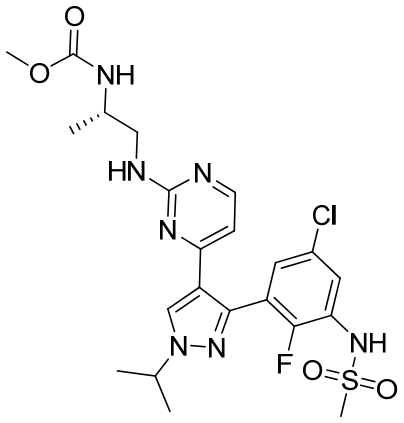
Claims

1. A pharmaceutical composition consisting essentially of a B-Raf inhibitor of Formula (I)



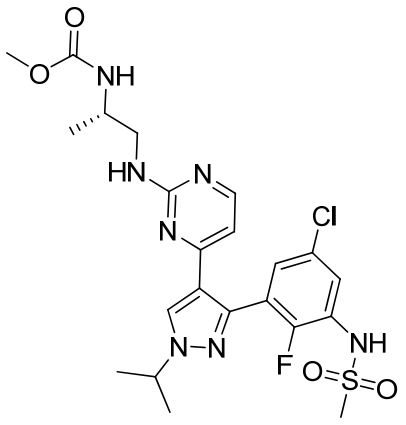
(I)

or a pharmaceutically acceptable salt thereof, and a second inhibitor which is a PI3 kinase inhibitor selected from 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof and (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof.

2. The composition according to claim 1, wherein the PI3 kinase inhibitor is 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof.

3. The composition according to claim 1, wherein the PI3 kinase inhibitor is (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof.

4. A pharmaceutical combination consisting essentially of a B-Raf inhibitor of Formula (I)



(I)

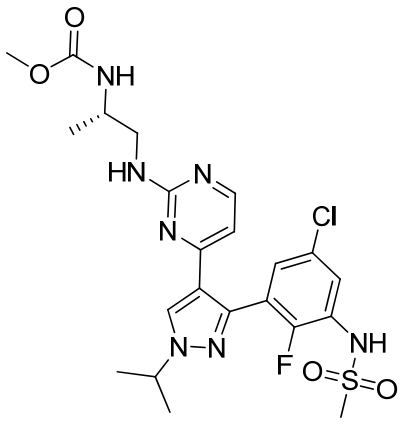
or a pharmaceutically acceptable salt thereof, and a second inhibitor which is a PI3 kinase inhibitor selected from 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof and (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof, wherein the combination is adapted for administration simultaneously or sequentially.

5. The combination according to claim 4, wherein the PI3 kinase inhibitor is 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof.

6. The combination according to claim 4, wherein the PI3 kinase inhibitor is (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof.

7. Use of the composition according to any one of claims 1-3 or the combination according to any one of claims 4-6 in the manufacture of a medicament for the treatment of a proliferative disease characterized by a mutation in B-Raf.

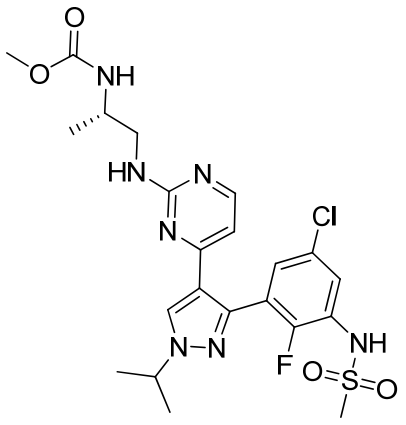
8. Use of a B-Raf inhibitor of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease characterized by a mutation in B-Raf, wherein the medicament is for co-administration with a second inhibitor, wherein the second inhibitor is selected from the group consisting essentially of a PI3 kinase inhibitor which is 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof or (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof.

9. Use of a PI3 kinase inhibitor which is selected from the group consisting essentially of 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof or (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a proliferative disease characterized by a mutation in B-Raf, wherein the medicament is for co-administration with a B-Raf inhibitor of Formula (I)



(I)

or a pharmaceutically acceptable salt thereof.

10. The use according to claim 8 or 9, wherein the PI3 kinase inhibitor is 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), or a pharmaceutically acceptable salt thereof.

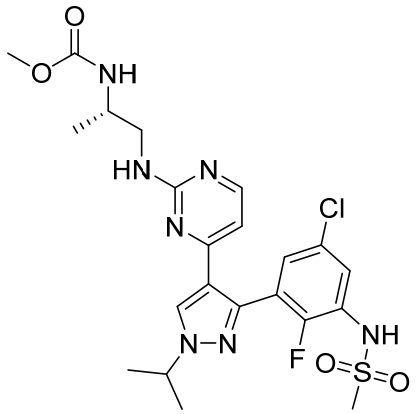
11. The use according to claim 8 or 9, wherein the PI3 kinase inhibitor is (S)-pyrrolidine-1,2-dicarboxylic acid 2-amide 1-({4-methyl-5-[2-(2,2,2-trifluoro-1,1-dimethyl-ethyl)-pyridin-4-yl]-thiazol-2-yl}-amide) (Compound X), or a pharmaceutically acceptable salt thereof.

12. The use according to any one of claims 7 to 11, wherein the B-Raf mutation is a V600 mutation.

13. The use according to claim 12, wherein the proliferative disease is melanoma characterized by a V600 mutation in B-Raf.

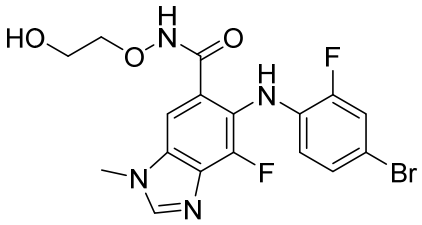
14. The use according to claim 12, wherein the proliferative disease is colorectal cancer characterized by a V600 mutation in B-Raf.

15. Use of a compound of formula (I):



(**I**)

in combination with a Mek 1/2 inhibitor which is Compound B:



Compound B

in the manufacture of a medicament for use in treating a patient suffering from melanoma and who has exhibited disease progression despite prior treatment with said compound of formula (I) or a pharmaceutically acceptable salt thereof as monotherapy, which use comprises:

(a) providing f said compound of formula (I), or a pharmaceutically acceptable salt thereof, to be administered to the patient as monotherapy until the patient exhibits disease progression;

(b) obtaining a tumor sample from the patient after disease progression and detecting a genetic alteration in one or more genes selected from the group consisting of BRAF, CRAF, MAP2K1, MAPK2, NRAS, KRAS HRAS and EGFR; and

(c) providing the medicament to be administered as a drug combination therapy comprising said compound of formula (I) and said Compound B.

16. The use of claim 15, wherein the gene is BRAF.

17. The use of claim 15 or 16, wherein the genetic alteration results from amplification of the one or more genes, mutations in the one or more genes, or loss of the one or more genes' activity.

18. The use of any one of claims 15-17, wherein the genetic alteration results from a mutation in one or more genes.

19. The use of claim 18, wherein the one or more genes is BRAF.

20. The use of claim 19, wherein the mutation is a V600 mutation in BRAF.

21. The use of claim 20, wherein the V600 mutation in BRAF is a V600E mutation or a V600K mutation.

22. The use of claim 20, wherein the V600 mutation in BRAF is a V600E mutation.

23. The use of any one of claims 15-22, wherein disease progression is evaluated using RECIST criteria.

24. The use of any one of claims 15-23, wherein said compound of formula (I) in step (a) is to be administered continuously.

25. The use of any one of claims 15-23, wherein said compound of formula (I) in step (a) is to be administered intermittently.

26. The use of any one of claims 15-25, wherein the compound of formula (I) in step (c) is to be administered continuously.

27. The use of any one of claims 15-25, wherein the compound of formula (I) in step (c) is to be administered intermittently.

28. The use of any one of claims 15-27, wherein said compound of formula (I) in step (a) is to be administered orally.

29. The use of any one of claims 15-28, wherein the compound of formula (I) and Compound B in step (c) are each to be administered orally.

30. The use of any one of claims 15-29, wherein the compound of formula (I) in step (c) is to be administered at a dose of 450 mg/day.

31. The use of any one of claims 15-30, wherein Compound B in step (c) is to be administered at a dose of 45 mg twice daily.

32. The use of claim 31, wherein the two doses of Compound B are to be administered 12 hours apart.

33. The use of any one of claims 15-32, wherein the compound of formula (I) and Compound B are to be administered during a 21 day cycle.

34. The use of any one of claims 15-33, wherein the melanoma is a locally advanced or metastatic melanoma.

35. The use of any one of claims 15-34, wherein the melanoma is an unresectable stage III melanoma or a stage IIIC to IV metastatic melanoma.

36. The use of any one of claims 15-35, wherein prior to step (a), the patient is naïve to a BRAF inhibitor.