Claims

1. A method for treating a patient suffering from a proliferative disease characterized by a mutation in B-Raf, particularly a V600 mutation in B-Raf, very particularly a melanoma characterized by a V600 mutation in B-Raf, which comprises:

(a) obtaining a tumor sample from the patient and testing for a genetic alteration in a gene selected from the group comprising BRAF, CRAF, CCND1, CDK4, HER2, IGF-1R, cMET, FGFR1, FGFR2, FGFR3 EGFR, MAP2K1, MAP2K2, NRAS, KRAS HRAS, PTEN, PIK3CA, and P16,

(b) administering a drug combination therapy comprising a B-Raf inhibitor and a second inhibitor, which second inhibitor is selected based on genetic alterations discovered in the tumor sample, wherein,

(i) the second inhibitor is a Mek 1/2 inhibitor when the tumor sample has a genetic alteration in BRAF, CRAF, MAP2K1, MAPK2, NRAS, KRAS HRAS or EGFR, or

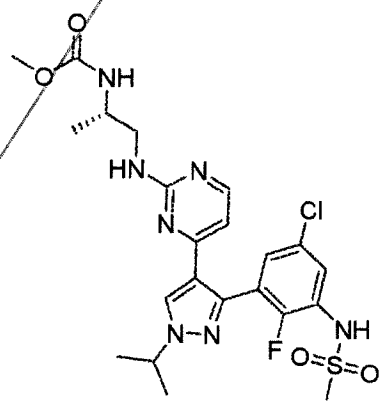
(ii) the second inhibitor is a CDK 4 inhibitor when the tumor sample has a genetic alteration in CCND1, CDK4 or P16, or

(iii) the second inhibitor is a PI3 Kinase inhibitor when the tumor sample has a genetic alteration in HER2, IGF-1R, PTEN or PIK3CA, or

(iv) the second inhibitor is a c-Met receptor tyrosine kinase inhibitor when the tumor sample has a genetic alteration in cMET,

(v) the second inhibitor is a FGFR kinase inhibitor when the tumor sample has a genetic alteration in FGFR1, FGFR2 or FGFR3.

2. A method of claim 1 wherein the B-Raf inhibitor is a compound of formula (I)a Compound of Formula (I)



(I).

3. A method according to one of claims 1 and 2, which comprises:

(a) obtaining a tumor sample from the patient and detecting a genetic alteration in BRAF, CRAF, MAP2K1, MAPK2, NRAS, KRAS HRAS or EGFR, and

(b) administering a drug combination therapy to the patient comprising the B-Raf inhibitor and a second inhibitor which is a Mek 1/2 inhibitor which is Compound B.

4. A method according to one of claims 1 and 2, which comprises:

(b) obtaining a tumor sample from the patient and detecting a genetic alteration in CCND1, CDK4 or P16, and

(d) administering a drug combination therapy to the patient comprising the B-Raf inhibitor and a second inhibitor which is a CDK 4 inhibitor.

5. A method according to one of claims 1 and 2, which comprises:

(a) obtaining a tumor sample from the patient after disease progression and detecting a genetic alteration in HER2, IGF-1R, PTEN or PIK3CA, and

(b) administering a drug combination therapy to the patient comprising the B-Raf inhibitor and a second inhibitor which is a PI3 Kinase inhibitor.

6. A method according to one of claims 1 and 2, which comprises:

(a) obtaining a tumor sample and detecting a genetic alteration in cMET, and

(b) administering a drug combination therapy to the patient comprising the B-Raf inhibitor and a second inhibitor which is a c-Met receptor tyrosine kinase inhibitor.

7. A method according to one of claims 1 and 2, which comprises:

(a) obtaining a tumor sample from the patient and detecting a genetic alteration in FGFR1, FGFR2 or FGFR3, and

(b) administering a drug combination therapy to the patient comprising the B-Raf inhibitor and a second inhibitor which is a FGFR kinase inhibitor.

8. A therapeutic combination which comprises a B-Raf inhibitor of Formula (I) and a second inhibitor which is Compound F, or a pharmaceutically acceptable salt thereof, for separate, simultaneous or sequential administration.

9. A therapeutic combination which comprises a B-Raf inhibitor of Formula (I) and a second inhibitor which is Compound G, or a pharmaceutically acceptable salt thereof, for separate, simultaneous or sequential administration.

10. A therapeutic combination comprises a B-Raf inhibitor of Formula (I) and a second inhibitor which is Compound H, or a pharmaceutically acceptable salt thereof, for separate, simultaneous or sequential administration.

11. A method for treating a patient suffering from a proliferative disease characterized by a V600 mutation in B-Raf, which comprises administering to the patient a therapeutically effective amount of a combination according to any one of claims 8, 9 or 10.

12. Use of a combination according to any one of claims 8, 9 or 10 for the preparation of a pharmaceutical composition or medicament for the treatment or prevention of a proliferative disease.

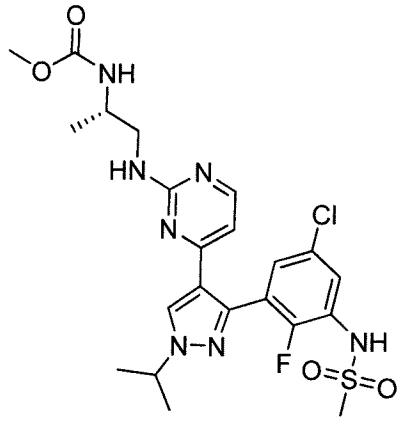
13. A diagnostic method for selecting a second inhibitor to be combined with a B-Raf inhibitor wherein a tumor sample is tested for genetic alterations in a panel of genes comprising B-Raf, C-Raf, CCND1, CDK4, HER2, IGF-1R, cMET, FGFR1, FGFR2, FGFR3 EGFR, MAP2K1, MAP2K2, NRAS, KRAS HRAS, PTEN, PIK3CA, and P16.

14. A diagnostic kit for detecting genetic alterations in a panel of genes comprising B-Raf, C-Raf, CCND1, CDK4, HER2, IGF-1R, cMET, FGFR1, FGFR2, FGFR3 EGFR, MAP2K1, MAP2K2, NRAS, KRAS HRAS, PTEN, PIK3CA, and P16.

15. A method according to any one of claims 1-11 wherein the proliferative disease is melanoma characterized by a V600 mutation in B-Raf.

CLAIMS

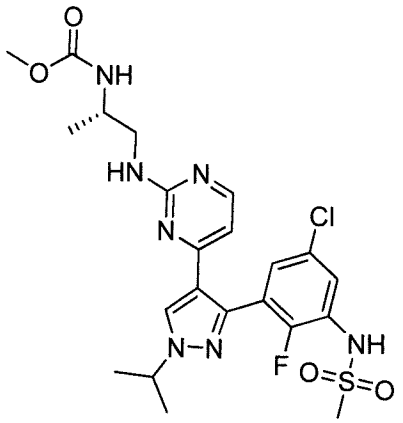
1. A therapeutic combination which comprises a B-Raf inhibitor of Formula (I)



(I), and

a second inhibitor which is a PI3 kinase inhibitor, or a pharmaceutically acceptable salt thereof, for separate, simultaneous or sequential administration.

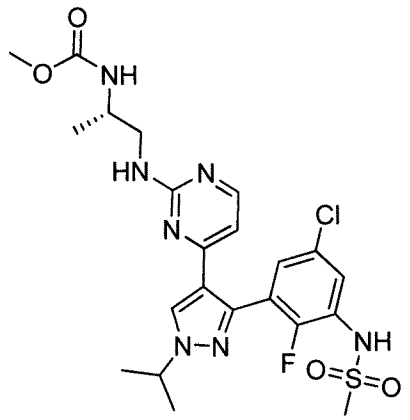
2. A therapeutic combination which comprises a B-Raf inhibitor of Formula (I)



(I); and

a second inhibitor which is a c-Met receptor tyrosine kinase inhibitor, or a pharmaceutically acceptable salt thereof, for separate, simultaneous or sequential administration.

3. A therapeutic combination which comprises a B-Raf inhibitor of Formula (I)



(I); and

a second inhibitor which is an FGFR kinase inhibitor, or a pharmaceutically acceptable salt thereof, for separate, simultaneous or sequential administration.

4. The therapeutic combination according to any one of claims 1 to 3 for use in the treatment or prevention of a proliferative disease.

5. The therapeutic combination according to claim 4, wherein the proliferative disease is characterized by a V600 mutation in B-Raf.

6. The therapeutic combination according to claim 4 or claim 5, wherein the proliferative disease is melanoma characterized by a V600 mutation in B-Raf.

7. Use of a therapeutic_combination according to any one of claims 1 to 3 for the preparation of a pharmaceutical composition or medicament for the treatment or prevention of a proliferative disease.

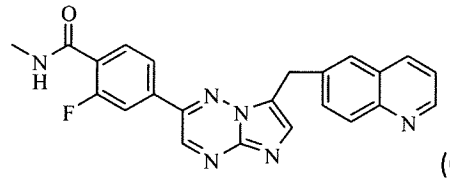
8. The use according to claim 6, wherein the proliferative disease is characterized by a V600 mutation in B-Raf.

9. The use according to claim 6 or claim 7, wherein the proliferative disease is melanoma characterized by a V600 mutation in B-Raf.

10. The therapeutic combination of claim 1, wherein the PI3 kinase inhibitor is selected from the group consisting of 2-methyl-2-[4-(3-methyl-2-oxo-8-quinolin-3-yl-2,3-dihydro-imidazo[4,5-c]quinolin-1-yl)-phenyl]propionitrile (Compound D), 8-(6-methoxy-pyridin-3-yl)-3-methyl-1-(4-piperazin-1-yl-3-trifluoromethyl-phenyl)-1,3-dihydroimidazo[4,5-c]quinolin-2-one (Compound E), 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F), 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).

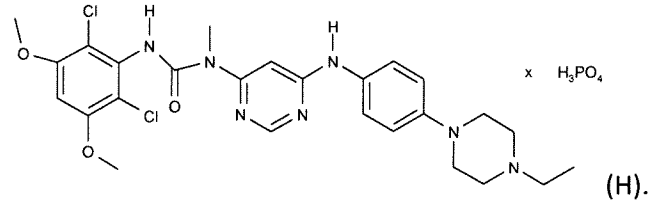
11. The therapeutic combination of claim 1, wherein the PI3 kinase inhibitor is 5-(2,6-di-morpholin-4-yl-pyrimidin-4-yl)-4-trifluoromethyl-pyridin-2-ylamine (Compound F).

12. The therapeutic combination of claim 2, wherein the c-Met tyrosine kinase inhibitor is Compound G



(G).

13. The therapeutic combination of claim 3, wherein the FGFR kinase inhibitor is Compound H



(H).