TREATMENT OF CANCER WITH A RAF INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims benefit of U.S. Patent Application No. 63/178,922, filed on April 23, 2021, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] RAF kinase functions in the Ras-Raf-MEK-ERK mitogen activated protein kinase (MAPK) pathway (also known as MAPK/ERK pathway) by phosphorylating and activating MEK and ultimately MAPK-dependent activation of transcriptional programs drives cell proliferation and survival. Deregulation of MAPK activity occurs frequently in tumors. Accordingly, therapies that target RAF kinase activity are desired for use in the treatment of cancer and other disorders characterized by aberrant MAPK/ERK pathway signaling.

BRIEF SUMMARY

[0002a] In a first aspect of the present disclosure, there is provided a use of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a cancer.

[0002b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of a cancer.

[0003] One example provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof.

[0004] One example provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient a pharmaceutical composition comprising (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0005] One example provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient:

(a) a composition comprising (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof; and

(b) at least one oncology therapeutic selected from a MEK inhibitor, an immune checkpoint inhibitor, a CDK inhibitor, an EGFR kinase inhibitor, an EGFR antibody, an EGFR PROTAC therapeutic, a FGFR inhibitor, a SOS1 inhibitor, a SHP2 inhibitor, a KRAS inhibitor, a taxane, a topoisomerase inhibitor, an ERK inhibitor, a platinum-based chemotherapy, folinic acid, 5-fluorouracil, or an anti-VEGF therapeutic.

BRIEF DESCRIPTION OF THE DRAWINGS

CLAIMS

WHAT IS CLAIMED IS:

1. Use of (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of a cancer.
2. Use of a pharmaceutical composition comprising (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, in the manufacture of a medicament for the treatment of a cancer.
3. The use of claim 2, wherein the pharmaceutical composition further comprises at least one oncology therapeutic selected from a MEK inhibitor, an immune checkpoint inhibitor, a CDK inhibitor, an EGFR kinase inhibitor, an EGFR antibody, an EGFR PROTAC therapeutic, a FGFR inhibitor, a SOS1 inhibitor, a SHP2 inhibitor, a KRAS inhibitor, a taxane, a topoisomerase inhibitor, an ERK inhibitor, a platinum-based chemotherapy, folinic acid, 5-fluorouracil, or an anti-VEGF therapeutic.
4. The use of claim 3, wherein the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor, or a PD-L1 inhibitor; and the CDK inhibitor is a CDK4/6 inhibitor.
5. The use of claim 4, wherein the MEK inhibitor is selected from binimetinib, trametinib, cobimetinib, selumetinib, pimasertib, or mirdametinib; the CTLA-4 inhibitor is ipilimumab; the PD-1 inhibitor is spartalizumab, nivolumab, pembrolizumab, or cemiplimab; the PD-L1 inhibitor is atezolizumab, avelumab, or durvalumab; the CDK4/6 inhibitor is palbociclib, abemaciclib, or ribociclib; the EGFR kinase inhibitor is nazartinib, gefitinib, erlotinib, afatinib, brigatinib, icotinib, neratinib, osimertinib, dacomitinib, or lapatinib; the EGFR antibody is cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab; the KRAS inhibitor is storasib, adagrasib, or BI-1701963; the topoisomerase inhibitor is irinotecan, topotecan, or belotecan; the platinum-based chemotherapy is oxaliplatin, cisplatin, or carboplatin; the anti-VEGF therapeutic is bevacizumab or aflibercept.
6. The use of claim 3, wherein the at least one oncology therapeutic is a MEK inhibitor.
7. The use of claim 6, wherein the MEK inhibitor is selected from binimetinib, trametinib, cobimetinib, selumetinib, pimasertib, or mirdametinib.
8. The use of claim 6, wherein the MEK inhibitor is binimetinib.
9. The use of claim 3, wherein the at least one oncology therapeutic is an EGFR antibody.

10. The use of claim 9, wherein the EGFR antibody is cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab.
11. The use of claim 9, wherein the EGFR antibody is cetuximab.
12. The use of any one of claims 3 to 11, wherein the pharmaceutical composition is to be administered, and wherein a topoisomerase inhibitor or a platinum-based chemotherapy, or a combination thereof, are to be further administered.
13. The use of any one of claims 1 to 12, wherein the cancer is characterized as having an oncogenic BRAF alteration.
14. The use of claim 13, wherein the oncogenic BRAF alteration is a Class I BRAF mutation, a Class II BRAF mutation, or a Class III BRAF mutation.
15. The use of claim 13, wherein the oncogenic BRAF alteration is a BRAF V600 mutation.
16. The use of claim 15, wherein the BRAF V600 mutation is a V600E or V600K mutation.
17. The use of any one of claims 1 to 16, wherein the cancer is characterized as having a wild type BRAF.
18. The use of any one of claims 1 to 174, wherein the cancer is a solid tumor.
19. The use of any one of claims 1 to 18, wherein the cancer is selected from melanoma, pancreatic cancer, pancreatic adenocarcinoma, ovarian cancer, colorectal cancer, glioma, Langerhans cell histiocytosis, leukemia, hairy cell leukemia, thyroid cancer, anaplastic thyroid cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, or medullary thyroid carcinoma.
20. The use of any one of claims 1 to 18, wherein the cancer is selected from small cell lung cancer, non-small cell lung cancer, prostate cancer, gastric cancer, and esophageal cancer.
21. The use of any one of claims 1 to 18, wherein the cancer is NRAS mutant melanoma.
22. The use of any one of claims 1 to 18, wherein the cancer is colorectal cancer.
23. The use of any one of claims 1 to 22, wherein the cancer is metastatic.
24. The use of any one of claims 1 to 23, in an adjuvant therapy following surgical resection.
25. The use of any one of claims 1 to 24, wherein the compound or pharmaceutical composition is to be administered to a patient in need thereof, and wherein the patient has relapsed after prior therapy, has acquired resistance to prior therapy or is refractory to therapy.
26. The use of any one of the preceding claims, wherein the (S)-N-(3-(2-(((R)-1-hydroxypropan-2-yl)amino)-6-morpholinopyridin-4-yl)-4-methylphenyl)-3-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide, or pharmaceutically acceptable salt or solvate thereof, is to be administered orally.

27. The use of any one of the preceding claims, wherein the medicament is to be orally administered every other day, once per day, twice per day, or three times per day.