TREATMENT OF CANCER WITH AN FGFR KINASE INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Patent Application No. 63/287,456, filed on December 8, 2021, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Fibroblast growth factor receptors (FGFRs) are a subfamily of receptor tyrosine kinases (RTKs) that bind to members of the fibroblast growth factor family of proteins. Deregulation of the fibroblast growth factor/FGF receptor network occurs frequently in tumors. Accordingly, therapies that target aberrant FGFR kinase activity are desired for use in the treatment of cancer and other disorders. One such modulator of FGFR kinase is 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide.

BRIEF SUMMARY

[0002a] In an aspect of the present disclosure, there is provided a use of 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a cancer in a patient in need thereof.

[0002b] In another aspect of the present disclosure, there is provided a use of a pharmaceutical composition comprising 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, in the manufacture of a medicament for treating a cancer in a patient in need thereof.

[0002c] In a further aspect of the present disclosure, there is provided a use of a composition comprising 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein:

the composition is to be administered to the patient; and

at least one oncology therapeutic selected from the group consisting of an mTOR inhibitor, a MAPK / PI3K inhibitor, an immune checkpoint inhibitor, an EGFR kinase inhibitor or antibody, a HER2 kinase inhibitor, an estrogen receptor antagonist, an androgen receptor antagonist, a CDK kinase inhibitor, an ALK receptor tyrosine kinase inhibitor, a ROS receptor

tyrosine kinase inhibitor, a NTRK receptor tyrosine kinase inhibitor, or a chemotherapy regimen, is to be further administered.

[0003] One example provides a method of treating a cancer in a patient in need thereof, comprising administering to the patient 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, wherein the cancer is selected from bladder cancer, urinary bladder carcinoma, urothelial carcinoma, urothelial cancer, renal cell carcinoma, prostate cancer, double negative prostate, castration-resistant prostate cancer, gastric carcinoma, gastric cancer, gastroesophageal junction adenocarcinoma, hepatocellular carcinoma, cholangiocarcinoma, intrahepatic cholangiocarcinoma, pancreatic adenocarcinoma, pancreatic cancer, breast cancer, HER2(-)/ER(+) breast cancer, HER2(-)/ER(+)/PR(+) breast cancer, non-Hodgkin lymphoma, acute myeloid leukemia, myeloproliferative neoplasm, polycythemia vera, essential thrombocythemia, primary myelofibrosis, multiple myeloma, glioblastoma, glioma, astrocytoma, anaplastic astrocytoma, medulloblastoma, oligodendroglioma, anaplastic oligodendroglioma, meningioma, lung cancer, or non-small cell lung cancer. Another example provides the method, wherein the cancer is characterized as having an oncogenic FGFR alteration. Another example provides the method, wherein the cancer is characterized as having an oncogenic FGFR2 alteration. Another example provides the method, wherein the cancer is characterized as having an oncogenic FGFR3 alteration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0004] Figures 1A-1C illustrate antitumor activity of Compound 1 in a RT-112 FGFR3-driven human cancer cell line-derived xenograft model.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a cancer in a patient in need thereof.
2. Use of a pharmaceutical composition comprising 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient, in the manufacture of a medicament for treating a cancer in a patient in need thereof.
3. Use of a composition comprising 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a cancer in a patient in need thereof, wherein:

   the composition is to be administered to the patient; and

   at least one oncology therapeutic selected from the group consisting of an mTOR inhibitor, a MAPK / PI3K inhibitor, an immune checkpoint inhibitor, an EGFR kinase inhibitor or antibody, a HER2 kinase inhibitor, an estrogen receptor antagonist, an androgen receptor antagonist, a CDK kinase inhibitor, an ALK receptor tyrosine kinase inhibitor, a ROS receptor tyrosine kinase inhibitor, a NTRK receptor tyrosine kinase inhibitor, or a chemotherapy regimen, is to be further administered.
4. The use of claim 1, 2, or 3, wherein the cancer is characterized by the presence of at least one oncogenic FGFR1, FGFR2 or FGFR3 gene alteration.
5. The use of claim 4, wherein the oncogenic FGFR alteration is selected from the group consisting of:

   FGFR2 [K660M];

   FGFR2 [K659M];

   FGFR2 [L618V];

   FGFR2 [L617V];

   FGFR2 [N550H];

   FGFR2 [N549H];

FGFR2 [N550K];

FGFR2 [N549K];

FGFR2 [V565F];

FGFR2 [V564F];

FGFR2 [N550S/T];

FGFR2 [N549S/T];

FGFR3 [G697C];

FGFR3 [V555M];

FGFR3 [K650E];

FGFR3 [N540K/S];

FGFR3 [K650M]; and

FGFR1 [V561M]; or a combination thereof.

6. The use of claim 4, wherein the oncogenic FGFR alteration is FGFR2 amplification, FGFR3-TACC3, or FGFR3-BAIAP2L1.
7. The use of claim 1, 2 or 3, wherein the cancer is characterized as having a wild type FGFR2 or FGFR3.
8. The use of any one of the preceding claims, wherein the patient is selected due to a FGFR2 or FGFR3 fusion or rearrangement as detected by an FDA-approved test.
9. The use of any one of the preceding claims, wherein the cancer is a solid tumor.
10. The use of any one of the preceding claims, wherein the cancer is selected from the group consisting of bladder cancer, urinary bladder carcinoma, urothelial carcinoma, urothelial cancer, renal cell carcinoma, prostate cancer, double negative prostate, castration-resistant prostate cancer, gastric carcinoma, gastric cancer, gastroesophageal junction adenocarcinoma, hepatocellular carcinoma, cholangiocarcinoma, intrahepatic cholangiocarcinoma, pancreatic adenocarcinoma, pancreatic cancer breast cancer, HER2(-)/ER(+) breast cancer, HER2(-)/ER(+)/PR(+) breast cancer, non-Hodgkin lymphoma, acute myeloid leukemia, myeloproliferative neoplasm, polycythemia vera, essential thrombocythemia, primary myelofibrosis, multiple myeloma, glioblastoma, glioma, astrocytoma, anaplastic astrocytoma, medulloblastoma, oligodendroglioma, anaplastic oligodendroglioma, meningioma, lung cancer, and non-small cell lung cancer.
11. The use of claim 10, wherein the cancer is selected from bladder cancer, urinary bladder carcinoma, urothelial carcinoma, urothelial cancer, cholangiocarcinoma, or intrahepatic cholangiocarcinoma.

12. The use of any one of the preceding claims, wherein the cancer is metastatic.
13. The use of any one of the preceding claims, wherein the use is adjuvant therapy following surgical resection.
14. The use of any one of claims 1-12, wherein the use is neo-adjuvant therapy before surgical resection.
15. The use of any one of claims 1-14, wherein the patient has relapsed after prior therapy.
16. The use of any one of claims 1-14, wherein the patient has acquired resistance to prior therapy.
17. The use of any one of claims 1-14, wherein the patient is refractory to therapy.
18. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is an immune checkpoint inhibitor.
19. The use of claim 18, wherein the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor, or a PD-L1 inhibitor.
20. The use of claim 19, wherein the CTLA-4 inhibitor is ipilimumab.
21. The use of claim 19, wherein the PD-1 inhibitor is spartalizumab, nivolumab, pembrolizumab, or cemiplimab.
22. The use of claim 19, wherein the PD-L1 inhibitor is atezolizumab, avelumab, or durvalumab.
23. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is a CDK inhibitor.
24. The use of claim 23, wherein the CDK inhibitor is a CDK4/6 inhibitor.
25. The use of claim 24, wherein the CDK4/6 inhibitor is palbociclib, abemaciclib, or ribociclib.
26. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is an EGFR kinase inhibitor or antibody.
27. The use of claim 26, wherein the EGFR kinase inhibitor is nazartinib, gefitinib, erlotinib, afatinib, brigatinib, icotinib, neratinib, osimertinib, dacomitinib, or lapatinib.
28. The use of claim 26, wherein the EGFR antibody is cetuximab, panitumumab, zalutumumab, nimotuzumab, or matuzumab.
29. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is an mTOR inhibitor.
30. The use of claim 29, wherein the mTOR inhibitor is rapamycin.

31. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is a MAPK / PI3K inhibitor.
32. The use of claim 31, wherein the MAPK / PI3K inhibitor is binimetinib or copanlisib.
33. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is a HER2 kinase inhibitor.
34. The use of claim 33, wherein the HER2 inhibitor is lapatinib.
35. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is an estrogen receptor antagonist.
36. The use of claim 35, wherein the estrogen receptor antagonist is fulvestrant.
37. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is an androgen receptor antagonist.
38. The use of claim 37, wherein the androgen receptor antagonist is enzalutamide.
39. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is selected from an ALK receptor tyrosine kinase inhibitor, a ROS receptor tyrosine kinase inhibitor, or a NTRK receptor tyrosine kinase inhibitor.
40. The use of any one of claims 3-17, wherein the at least one oncology therapeutic is a chemotherapy regimen.
41. The use of claim 40, wherein the chemotherapy regimen comprises a platinum-based chemotherapy.
42. The use of claim 41, wherein the platinum-based chemotherapy is oxaliplatin, cisplatin, or carboplatin.
43. The use of claim 40, wherein the chemotherapy regimen comprises a gemcitabine regimen.
44. The use of claim 40, wherein the chemotherapy regimen comprises a FOLFOX regimen.
45. The use of claim 40, wherein the FOLFOX regimen comprises folinic acid.
46. The use of claim 40, wherein the FOLFOX regimen comprises 5-fluorouracil.
47. The use of claim 40, wherein the FOLFOX regimen comprises folinic acid and folinic acid.
48. The use of any one of the preceding claims, wherein the 1-((3S,5R)-1-acryloyl-5-(methoxymethyl)pyrrolidin-3-yl)-3-((1-cyclopropyl-4,6-difluoro-1H-benzo[d]imidazol-5-yl)ethynyl)-5-(methylamino)-1H-pyrazole-4-carboxamide, or pharmaceutically acceptable salt or solvate thereof, is to be administered orally.

49. The use of claim 48, wherein the oral administration occurs every other day, once per day, twice per day, or three times per day.