SHP2 INHIBITOR MONOTHERAPY AND USES THEREOF

CROSS-REFERENCE

[001] This application claims the benefit of U.S. Provisional Application No. 63/184,710 filed May 05, 2021, and U.S. Provisional Application No. 63/320,991 filed March 17, 2022, the contents of which are incorporated herein by reference in their entirety.

FIELD OF THE DISCLOSURE

[002] The present disclosure relates to SHP2 inhibitors and methods of treating cancer.

BACKGROUND OF THE DISCLOSURE

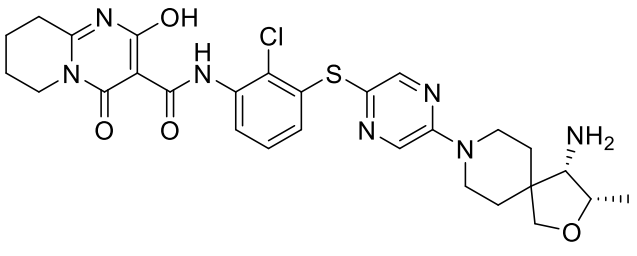
[003] Cancer is a significant cause of morbidity and mortality worldwide. While the standards of care for different cancer types have greatly improved over the years, current standards of care still fail to meet the need for effective therapies to improve treatment of cancer. Protein tyrosine phosphatase 2 (SHP2) belongs to the protein tyrosine phosphatase family, which is involved in regulating cell proliferation, survival, differentiation, migration and apoptosis. In the protein tyrosine phosphatase superfamily, SHP2 is the first true proto-oncogene to be confirmed, and it plays an important role in a variety of signaling pathways such as metabolism, differentiation, proliferation, migration and survival. SHP2 can regulate Ras-mitogen-activated protein kinase, Janus kinase-signal transducer and activator of transcription (JAK-STAT) or phosphoinositide 3-kinase-AKT and nuclear factor κB (NF-κB) and other signaling pathways. SHP2 is also the main regulator of the immune checkpoint signaling pathway of programmed cell death protein-1 (PD-1) and B and T lymphocyte attenuation factor (BTLA), which may be related to tumor immunosuppression. In addition, SHP2 mutations rarely occur in tumors.

[004] In recent years, SHP2, has been shown to play an important role in tumor inhibition, especially as the role of SHP2 in tumors has become increasingly clear. Therefore, inhibition of SHP2 has become a feasible anti-tumor strategy. There remains a need for new treatments as cancers become resistant or refractory.

SUMMARY

[005] Provided herein, are methods of treating cancer with a SHP2 inhibitor.

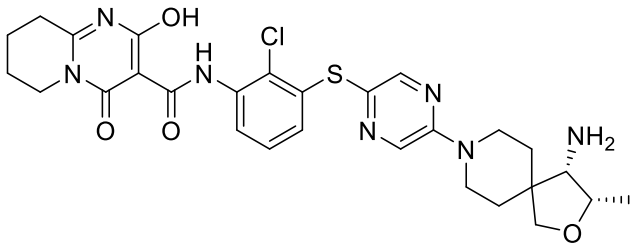
[006] Provided herein is a method of treating cancer in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia),

wherein the patient has failed an anti-cancer agent therapy.

[006a] In one aspect, provided herein is use of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia),

in the manufacture of a medicament for treating cancer, wherein at least one anti-cancer agent therapy has failed.

[007] In some examples, the method comprises administering the compound to the patient as third, fourth, fifth, or sixth line of treatment. In some examples, the cancer is resistant to at least one anti-cancer agent. In some examples, the anti-cancer agent is an immune checkpoint inhibitor. In some examples, the immune checkpoint inhibitor is PD-1, PD-L1, and/or CTLA-4. In some examples, the anti-cancer agent is an EGFR TK inhibitor. In some examples, the EGFR TK inhibitor is selected from erlotinib, afatinib, gefitinib, osimertinib, dacomitinib, icotininib, rociletinib, olmitinib, tarloxitinib, TAK-788, amivantamb (JNJ-6372), or AC0010. In some examples, the EGFR TK inhibitor is osimertinib.

[008] In some examples, about 5 mg to about 100 mg of the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof is administered to the patient in need thereof. In some examples, about 5 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, or about 50 mg of the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof is administered to the patient.

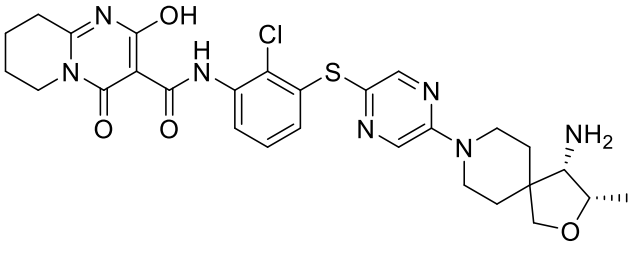
[009] In some examples, the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, is administered as a regimen. In some examples, the compound of Formula (Ia) is administered orally or by intraperitoneal methods. In some examples, the compound of Formula (Ia) is administered daily. In some examples, the compound is administered to the patient once per day (QD), twice daily (BID), or three times per day (TID). In some example, the compound of Formula (Ia) is administered for 7 days, 14 days, or 21 days.

[0010] In some examples, the cancer is squamous cell carcinoma, non-squamous cell carcinoma, non-small cell lung cancer (NSCLC), small cell lung cancer, melanoma, hepatocellular carcinoma, renal cell carcinoma, ovarian cancer, head and neck cancer, urothelial cancer, breast cancer, prostate cancer, glioblastoma, colorectal cancer, pancreatic cancer, lymphoma, leiomyosarcoma, liposarcoma, synovial sarcoma, or malignant peripheral sheath tumor (MPNST).

[0011] In some examples, the method of treating cancer inhibits metastasis of the cancer in the patient. In some examples, the method of treating cancer prolongs the time of disease progression in a cancer patient. In some examples, the method of treating cancer prolongs the survival of the patient. In some examples, the method of treating cancer increases progression-

WHAT IS CLAIMED IS:

1. Use of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia),

in the manufacture of a medicament for treating cancer, wherein at least one anti-cancer agent therapy has failed.

2. The use defined in claim 1, wherein said compound is to be administered as third, fourth, fifth, or sixth line of treatment.
3. The use defined in claims 1 or 2, wherein said anti-cancer agent is an EGFR TK inhibitor.
4. The use defined in any one of claims 1-3, wherein said compound or a pharmaceutically acceptable salt thereof, is to be administered at a dose of from 5 mg/kg to 25 mg/kg.
5. The use defined in any one of claims 1-3, wherein said compound, or a pharmaceutically acceptable salt thereof is to be administered at a dose of 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, or 25 mg/kg.
6. The use defined in any one of claims 1-5, wherein said compound is to be administered as a regimen.
7. The use defined in any one of claim 1-6, wherein said method said compound is to be administered orally or by intraperitoneal methods.
8. The use defined in any one of claims 1-7, wherein said compound is to be administered daily.
9. The use defined in claim 8, wherein said compound is to be administered QD, BID, or TID.
10. The use defined in any one of claims 1-9, wherein said cancer is squamous cell carcinoma, non-squamous cell carcinoma, non-small cell lung cancer (NSCLC), small cell lung cancer, melanoma, hepatocellular carcinoma, renal cell carcinoma, ovarian cancer, head and neck cancer, urothelial cancer, breast cancer, prostate cancer, glioblastoma, colorectal cancer, pancreatic cancer, lymphoma, leiomyosarcoma, liposarcoma, synovial sarcoma, or malignant peripheral sheath tumor (MPNST).
11. The use defined in any one of claims 1-10, wherein treating cancer inhibits metastasis of said cancer.

12. The use defined in any one of claims 1-10, wherein treating cancer prolongs the time to disease progression of said cancer.
13. The use defined in any one of claims 1-10, wherein treating cancer prolongs cancer survival.
14. The use defined in any one of claims 1-10, wherein treating cancer increases progression-free cancer survival.
15. The use defined in any one of claims 1-10, wherein treating cancer reduces tumor volume or tumor burden.
16. The use defined in any one of claims 3-15, wherein the EGFR TK inhibitor is selected from erlotinib, afatinib, gefitinib, osimertinib, dacomitinib, icotininib, rociletinib, olmitinib, tarloxitinib, TAK-788, amivantamb (JNJ-6372), or AC0010.
17. The use defined in any one of claims 3-16, wherein the EGFR TK inhibitor is osimertinib.
18. The use defined in any one of the preceding claims, wherein tumor volume is decreased by 10%, 20%, 30%, 40% or 50%.
19. The use defined in any one of the preceding claims, wherein tumor volume is decreased by at least 10%.
20. The use defined in any one of the preceding claims, wherein DUSP6 expression is reduced to 48 % compared to housekeeping genes.
21. The use defined in any one of the preceding claims, wherein DUSP6 expression levels can be used as a biomarker.
22. The use defined in any one of the preceding claims, wherein pERK expression is reduced to 95 % compared to housekeeping genes.