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

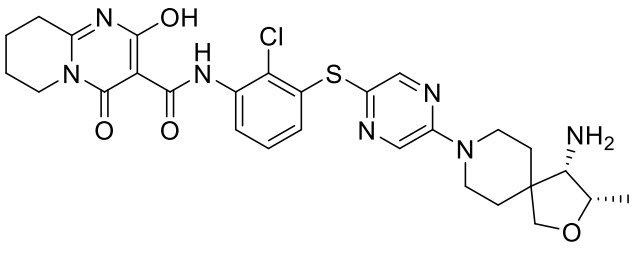
[003] Cancer is a significant cause of morbidity and mortality worldwide. While the standards of care for different cancer types have greatly improved over the years, current standards of care still fail to meet the need for effective therapies to improve treatment of cancer. Protein tyrosine phosphatase 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.

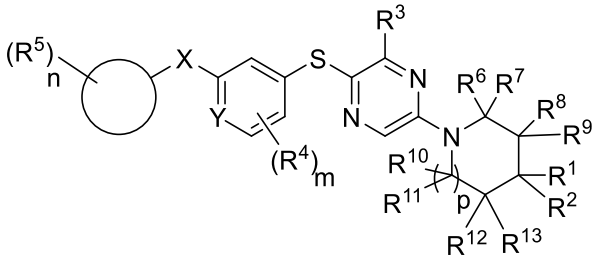
[006] In one aspect, provided herein is a method of treating cancer in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia),

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

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



Formula (I),

wherein,

R^1 and R^2 are each the same or different, and they are each independently selected from H, D, halogen, -CN, -C(O)OH, -CHO, -OH, $-NO_2$, and the following substituted or unsubstituted groups: $-NH_2$. C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkyloxy, 3-12 membered heterocyclic group, C_6-C_{10} aryl group, 5-10 membered heteroaryl group; or R^1 and R^2 form a 3-8 membered saturated or unsaturated cycloalkyl or heterocyclic group, optionally, the 3-8 membered saturated or unsaturated cycloalkyl or heterocyclic group has one to three -OH, $-NH_2$, -CN, NO_2, halogen, C_1-C_{10} alkyl, C_1-C_{10} alkaneoxy, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl or 5-10 membered heteroaryl;

R^3 is selected from H, D, or $-NH_2$;

X is selected from a bond, -NH-, or -C(O)NH-;

Y is selected from N or CR^{13}, wherein R^{13} is selected from H, D, -OH, -CN, halogen, C_1-C_{10} alkyl group, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkane amino, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, 3-8 membered heterocyclic group, halogenated C_1-C_{10} alkylamino, or C_6-C_{10} aryl or 5-10 membered heteroaryl group, the heterocyclic group or heteroaryl group optionally contains one to four heteroatoms, and the heteroatoms are selected from S, O, N or NH;

each R^4 is the same or different, and is independently selected from H, D, halogen, -CN, -C(O)OH, -CHO, -OH, $-NO_2$, $-C(O)NHR^{14}$ or $-NHC(O)R^{15}$, substituted or unsubstituted with the following groups: $-NH_2$, C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclic group, C_6-C_{10} aryl, or 5-10 membered heteroaryl; wherein R^{14} and R^{15} are each independently selected from C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6 -C_{10} aryl or 5-10 membered heteroaryl; the substitution is selected from C_1-C_{10} alkyl, halogen atom, $-NH_2$, -CN, -C(O)OH, -CHO, -OH, $-NO_2$, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, C_6-C_{10} aryl, 5-10 membered heteroaryl or 3-12 membered heterocyclic group is substituted by one or more substituents, the above-mentioned substituents are optionally substituted with one to three substituents selected from C_1-C_{10} alkyl, halogen, $-NH_2$, -CN, -C(O)OH, -CHO, -OH,- NO_2, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, or C_3-C_{12} cycloalkyl;

 is selected from C_6-C_{10} aryl, 5-10 membered heteroaryl, C_4 -C_{12} cycloalkyl, 3-12 membered heterocyclic group, C_6-C_{14} bridged ring group or spiro ring group, or C_6-C_{14} bridged heterocyclic group or spiro heterocyclic group; wherein the 5-10 membered heteroaryl, 3-12 membered heterocyclic group, C_6-C_{14} bridged heterocyclic group or spiro heterocyclic group contains one to three heteroatoms or groups selected from N, NH, O, S, C(O), or S(O);

each R^5 is the same or different, and is independently selected from H, D, halogen, -CN, -C(O)OH, -CHO, -OH, $-NO_2$, aminoacyl, substituted or unsubstituted following groups: C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, $-NH_2$, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclic group, C_6-C_{10} aryl or 5-10 membered heteroaryl, the substitution is selected from C_1-C_{10} alkyl, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclic group, halogen, $-NH_2$, -CN, -C(O)OH, -CHO, -OH, $-NO_2$, hydroxy-C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, 5-10 membered heteroaromatic

group, C_6-C_{10} aryl group or 3-12 membered heterocyclic group substituted by one or more substituents; or any two adjacent R^5 form a 3-6 membered saturated or unsaturated ring, and optionally the 3-6 membered saturated or unsaturated ring is substituted with one to three -OH, -NH_2, -CN, halogen, C_1 -C_{10} alkyl, C_1 -C_{10} alkoxy, C_3-C_{12} cycloalkylamino, C_1-C_{10} alkylamino, C_3-C_{12} cycloalkyl, halogenated C_1 -C_{10} alkylamino, C_6-C_{10} aryl or 5-10 member heteroaryl;

R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, and R^{13} are each independently selected from H, D, halogen, -CN, -C(O)OH, -CHO, -OH, -NO_2, substituted or unsubstituted the group selected from -NH_2, C_1-C_{10} alkyl, C_1-C_{10} alkylamino, C_1-C_{10} alkoxy, C_3-C_{12} cycloalkyl, C_3-C_{12} cycloalkyloxy group, 3-12 membered heterocyclic group, C_6 -C_{10} aryl, and 5-10 membered heteroaryl, the substitution is selected from C_1-C_{10} alkyl, C_3-C_{12} cycloalkyl, 3-12 membered heterocyclic group, halogen, -NH_2, -CN, -C(O)OH, -CHO, -OH, -NO_2, hydroxy-C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_1-C_{10} alkylamino, 5-10 membered heteroaryl or C_6-C_{10} aryl;

m is 0, 1, 2 or 3;

n is 0, 1, 2 or 3; and

p is 0, 1, or 2; and

wherein the patient in need has failed at least one anti-cancer agent therapy.

[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.

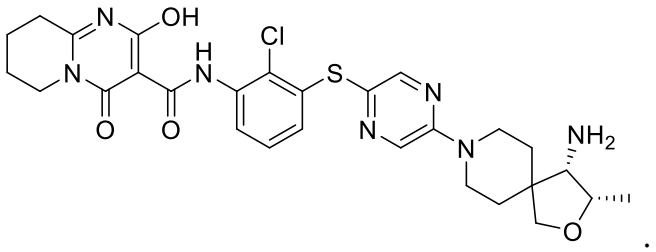
[009] In some examples, the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, is administered as a regimen. In some examples, the compound of Formula (Ia) is administered orally or by intraperitoneal methods. In some examples, the compound of Formula (Ia) is administered 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-

free survival of the patient. In some examples, the method of treating cancer reduces tumor or tumor burden in the patient.

[0012] In another aspect, provided herein is a method of decreasing tumor volume in a patient in need thereof, said method comprising administering to the patient a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



[0013] In some examples, the tumor volume is decreased by about 10%, about 20%, about 30%, about 40%, 50%, about 60%, about 70%, about 80%, or about 90%. In some examples, the tumor volume is decreased by at least about 10%.

[0014] Presented herein is a method of modulating one or more biomarkers (cytokines) selected from INF-γ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, and KC/GRO (CXCL1). In some examples, the one or more biomarkers increased or lowered over baseline levels. In some examples, the one or more biomarkers is lowered or increased by at least 5%, at least 10%, at least 15%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 100%, or at least 150%. In some examples, the one or more biomarkers is lowered or increased by at least 1.5 times, 2 times, 3 times, 4 times, 5 times, 10 times, 15 times, 20 times, or 25 times.

[0015] Other objects, features and advantages of the combinations and methods described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

INCORPORATION BY REFERENCE

[0016] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF DRAWINGS