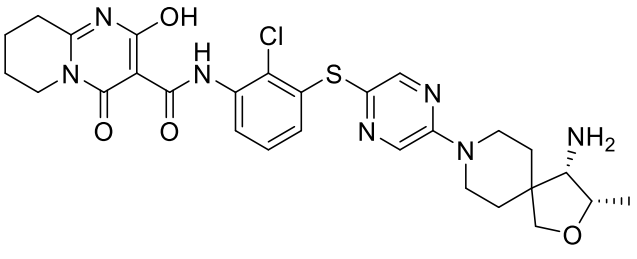
for new therapies, including, for example, combination therapies for the treatment of cancers. Provided herein are combination and methods of treating cancer.

SUMMARY

[006] Provided herein, inter alia, are combinations comprising a SHP2 inhibitor and a PD-1 inhibitor.

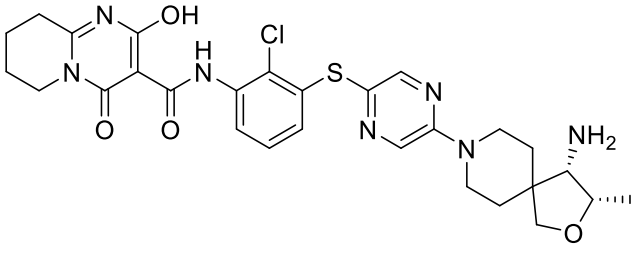
[007] Provided herein is a combination comprising a SHP2 inhibitor compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia),

and a PD-1 inhibitor.

[007a] In one aspect, provided herein is a combination comprising a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:

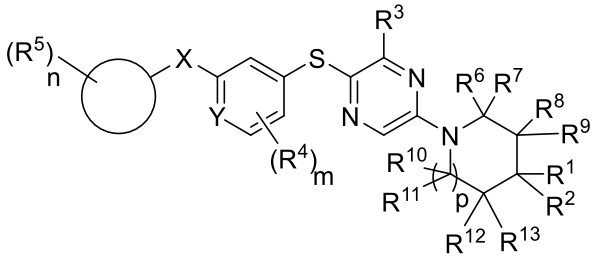


(Ia),

and a PD-1 inhibitor.

[007b] In another aspect, provided herein is a combination comprising:

(i) a therapeutically effective amount of a SHP2 inhibitor 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

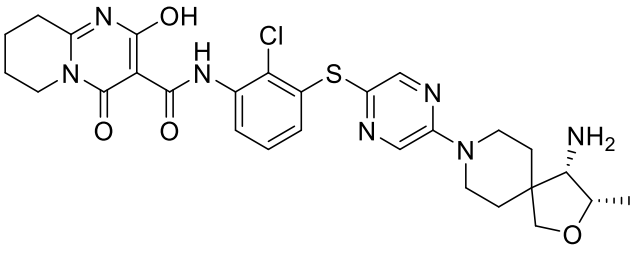
(ii) a therapeutically effective amount of a PD-1 inhibitor.

[008] In some examples, the combination comprises from about 5 mg to about 100 mg of the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof. In some examples, the combination comprises 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.

[009] In some examples, the PD-1 inhibitor is a small molecule compound, a nucleic acid, a peptide, a protein, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or a fragment or variant thereof. In some examples, the PD-1 inhibitor is an antibody. In some examples, the PD-1 antibody is selected from nivolumab, pembrolizumab, pidiluzumab, REGN2810 (also known as SAR-439684), PDR001, SHR-1210, or MEDI0680.

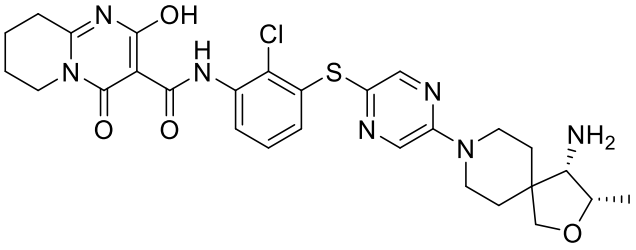
[0010] Provided herein is a pharmaceutical composition comprising a combination as described herein and a pharmaceutically acceptable excipient.

[0011] Provided herein are methods for preventing and/or treating non-receptor protein tyrosine phosphatase-mediated or dependent diseases or conditions. In some examples, provided herein is a method of treating cancer in a subject in need thereof, comprising administering to the patient a combination comprising a therapeutically effective amount of a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:


(Ia),

and a therapeutically acceptable amount of a PD-1 inhibitor.

[0011a] In another aspect, provided herein is a method of treating cancer in a patient in need thereof, said method comprising administering to the patient a combination comprising a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



and a PD-1 inhibitor.

[0012] In some examples, the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, is administered to said patient in need from about 5 mg/kg to about 25 mg/kg. In some examples, the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof is administered to said patient in need at about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, or about 25 mg/kg.

[0013] In some examples, the PD-1 inhibitor is a small molecule compound, a nucleic acid, a peptide, a protein, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or a variant thereof. In some examples, the PD-1 inhibitor is a PD-1 inhibitor antibody. In some examples, the PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, REGN2810 (also known as SAR-439684), PDR001, SHR-1210, or MEDI0680.

[0014] In some examples, the method comprises administering the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and the PD-1 inhibitor simultaneously or sequentially. In some examples, the method comprises administering the compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and the PD-1 inhibitor to the patient as a regimen. In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and a PD-1 inhibitor to said patient orally or as an intraperitoneal injection. In some examples, administration is by intravenous injection (I.V). In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and a PD-1 inhibitor to the patient daily. In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and a PD-1 inhibitor once a day (QD), twice daily (BID), once a week (QW), twice weekly (BID), three times a week (TIW), or monthly (QM).

[0015] In some examples, the patient is treatment naïve. In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable salt of solvate thereof; and a PD-1 inhibitor to said patient as a first line therapy. In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable

salt or solvate thereof; and a PD-1 inhibitor to the patient as a second, third, fourth, fifth, or sixth line of treatment. In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and a PD-1 inhibitor to the patient following treatment with at least one anti-cancer therapy, wherein the anti-cancer therapy is chemotherapy, radiotherapy, surgery, targeted therapy, immunotherapy, or a combination thereof. In some examples, the method comprises administering a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and a PD-1 inhibitor to a patient who has failed at least one PD-1 therapy. In some examples, the cancer is resistant to at least one anti-cancer agent.

[0016] In some examples, the cancer is squamous cell carcinoma, nonsquamous 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).

[0017] In some examples, the method comprises inhibiting metastasis of the cancer in the patient in need of treatment. In some examples, the method of treating cancer prolongs the time to disease progression of said cancer in the 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 a tumor or tumor burden in the patient. In some examples, the method reduces or prevent metastasis of a primary tumor in the patient in need.

[0018] Presented herein is a method of modulating one or more biomarkers (cytokines) selected from TNF- α, 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 in 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.

[0019] 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