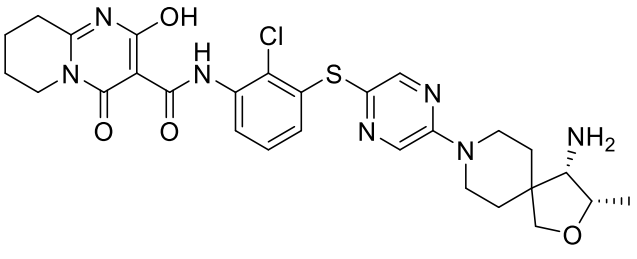
for new therapies, including, for example, combination therapies for the treatment of cancers. Provided herein are combination and methods of treating cancer.

SUMMARY

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

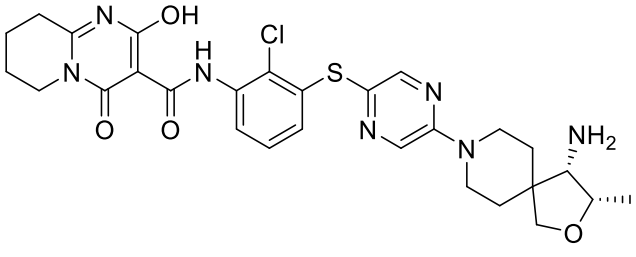
[007] Provided herein is a combination comprising a SHP2 inhibitor compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(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),

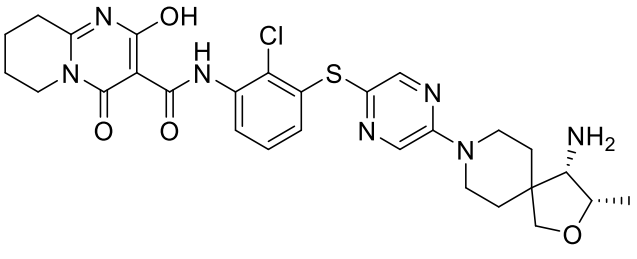
and a PD-1 inhibitor.

[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.

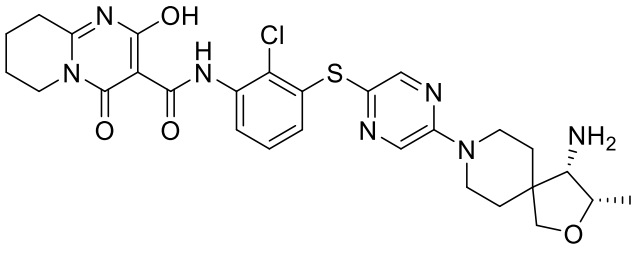
[0010] Provided herein is a pharmaceutical composition comprising a combination as described herein and a pharmaceutically acceptable excipient.

[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),

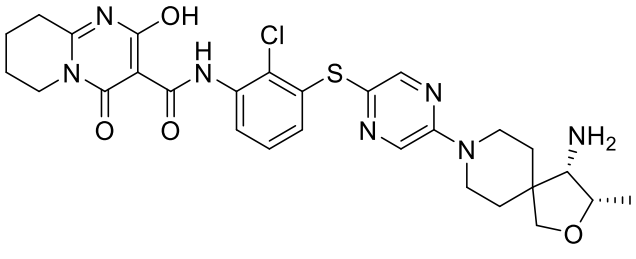
and a therapeutically acceptable amount of a PD-1 inhibitor.

[0011a] In another aspect, provided herein is a combination for use in treating cancer, wherein the combination comprises a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:


(Ia)

and a PD-1 inhibitor.

[0011b] In another aspect, provided herein is use of a combination comprising a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:


(Ia)

and a PD-1 inhibitor in the manufacture of a medicament for the treatment of cancer.

[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.

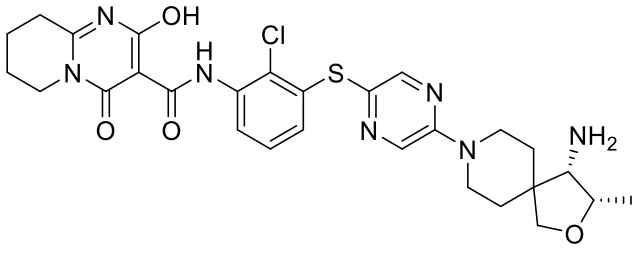
[0013] In some examples, the PD-1 inhibitor is a small molecule compound, a nucleic acid, a peptide, a protein, an antibody, a peptibody, a diabody, a minibody, a single-chain variable fragment (ScFv), or a variant thereof. In some examples, the PD-1 inhibitor is a PD-1 inhibitor antibody. In some examples, 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

WHAT IS CLAIMED IS:

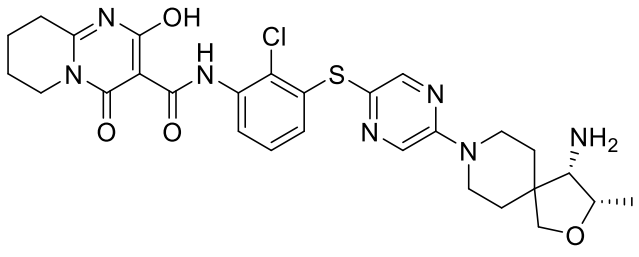
1. A combination comprising a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia),

and a PD-1 inhibitor.

2. The combination of claim 1, wherein said combination comprises from 5 mg to 100 mg of said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof.
3. The combination of claim 1, wherein said combination comprises 5 mg, 10 mg, 20 mg, 30 mg, 40 mg, or 50 mg of said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof.
4. The combination of any one of claims 1-3, wherein said 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.
5. The combination of any one of claims 1-3, wherein said PD-1 inhibitor is a PD-1 inhibitor antibody.
6. The combination of any one of claims 1-5, wherein said PD-1 inhibitor is nivolumab, pembrolizumab, pidilizumab, REGN2810 (SAR-439684), PDR 001, SHR-1210, or MEDI0680.
7. A combination for use in treating cancer, wherein the combination comprises a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



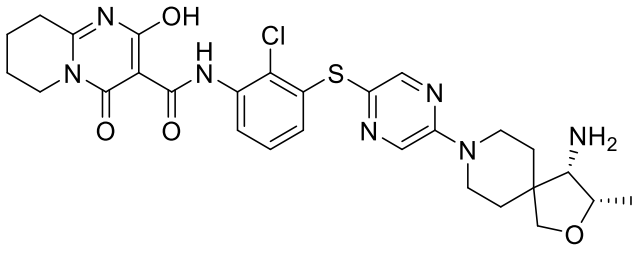
(Ia)

and a PD-1 inhibitor.

8. The combination for use defined in claim 7, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, is to be administered from 5 mg/kg to 25 mg/kg.
9. The combination for use defined in claim 7, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof is to be administered at 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, or 25 mg/kg.
10. The combination for use defined in any one of claims 7-9, wherein said 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
11. The combination for use defined in any one of claims 7-9, wherein said PD-1 inhibitor is a PD-1 inhibitor antibody.
12. The combination for use defined in any one of claims 7-9, wherein said PD-1 inhibitor is nivolumab, pembrolizumab, pidilizumab, REGN2810 (SAR-439684), PDR 001, SHR-1210, or MEDI0680.
13. The combination for use defined in any one of claims 7-12, wherein said compound or Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered simultaneously or sequentially.
14. The combination for use defined in any one of claims 7-13, wherein said 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).
15. The combination for use defined in any one of claims 7-14, wherein the cancer is in a patient that is treatment naïve.
16. The combination for use defined in any one of claims 7-14, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt of solvate thereof; and said PD-1 inhibitor are to be administered as a first line therapy.
17. The combination for use defined in any one of claims 7-14, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered as a second, third, fourth, fifth, or sixth line of treatment.
18. The combination for use defined in any one of claims 7-14, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor

are to be administered following treatment with at least one anti-cancer therapy, wherein said anti-cancer therapy is chemotherapy, radiotherapy, surgery, targeted therapy, immunotherapy, or a combination thereof.

19. The combination for use defined in any one of claims 7-14, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered to a patient who has failed another PD-1 therapy.
20. The combination for use defined in any one of claims 7-19, wherein said cancer is resistant to at least one anti-cancer agent.
21. The combination for use defined in any one of claims 7-20, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered as a regimen.
22. The combination for use defined in any one of claim 7-21, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered orally or by intraperitoneal injection.
23. The combination for use defined in any one of clams 7-22, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered daily.
24. The combination for use defined in claim 22, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered QD, BID, or TID.
25. The combination for use defined in any one of claims 7-24, wherein treating cancer inhibits metastasis of said cancer.
26. The combination for use defined in any one of claims 7-24, wherein treating cancer prolongs the time to disease progression of said cancer.
27. The combination for use defined in any one of claims 7-24, wherein treating cancer prolongs the survival.
28. The combination for use defined in any one of claims 7-24, wherein treating cancer increases progression-free survival.
29. The combination for use defined in any one of claims 7-24, wherein treating cancer reduces tumor or tumor burden.
30. Use of a combination comprising a therapeutically effective amount of a compound having the structure of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



(Ia)

and a PD-1 inhibitor in the manufacture of a medicament for the treatment of cancer.

31. The use as defined in claim 30, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, is to be administered from 5 mg/kg to 25 mg/kg.
32. The use defined in any one of claims 30 and 31, wherein said compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof is to be administered at 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg, or 25 mg/kg.
33. The use defined in any one of claims 30 to 32, wherein said 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
34. The use defined in any one of claims 30 to 33, wherein said PD-1 inhibitor is a PD-1 inhibitor antibody.
35. The use defined in any one of claims 30 to 34, wherein said PD-1 inhibitor is nivolumab, pembrolizumab, pidilizumab, REGN2810 (SAR-439684), PDR 001, SHR-1210, or MEDI0680.
36. The use defined in any one of claims 30 to 35, wherein said compound or Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered simultaneously or sequentially.
37. The use defined in any one of claims 30 to 36, wherein said 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).
38. The use defined in any one of claims 30 to 37, wherein the cancer is in a patient that is treatment naïve.

39. The use defined in any one of claims 30 to 38, wherein said compound of Formula (I), or a pharmaceutically acceptable salt of solvate thereof; and said PD-1 inhibitor are to be administered as a first line therapy.
40. The use defined in any one of claims 30 to 38, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered as a second, third, fourth, fifth, or sixth line of treatment.
41. The use defined in any one of claims 30 to 40, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered following treatment with at least one anti-cancer therapy, wherein said anti-cancer therapy is chemotherapy, radiotherapy, surgery, targeted therapy, immunotherapy, or a combination thereof.
42. The use defined in any one of claims 30 to 41, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered to a patient who has failed another PD-1 therapy.
43. The use defined in any one of claims 30 to 42, wherein said cancer is resistant to at least one anti-cancer agent.
44. The use defined in any one of claims 30 to 43, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered as a regimen.
45. The use defined in any one of claims 30 to 44, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered orally or by intraperitoneal injection.
46. The use defined in any one of claims 30 to 45, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered daily.
47. The use defined in any one of claims 30 to 46, wherein said compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof; and said PD-1 inhibitor are to be administered QD, BID, or TID.
48. The use defined in any one of claims 30 to 47, wherein treating cancer inhibits metastasis of said cancer.
49. The use defined in any one of claims 30 to 48, wherein treating cancer prolongs the time to disease progression of said cancer.
50. The use defined in any one of claims 30 to 49, wherein treating cancer prolongs the survival.

51. The use defined in any one of claims 30 to 50, wherein treating cancer increases progression-free survival.
52. The use defined in any one of claims 30 to 51, wherein treating cancer reduces tumor or tumor burden.