

CLAIMS

What is claimed is:

1. ~~A method of treating cancer in a subject, the method comprising:~~

~~administering a therapeutically effective amount of an agent that inhibits poly [ADP-ribose] polymerase (PARP) and an agent that inhibits programmed death 1 protein (PD-1) signaling to the subject,~~

~~wherein the cancer is associated with one or more mutations in one or more of the following genes: *Kras*, *PTEN*, *TP53*, *Apc*, *BRCA1*, or *BRCA2*, and/or is associated with expression of *LPA1*.~~

2. ~~A method of treating cancer in a subject, the method comprising:~~

~~(a) determining whether a cancer cell in a sample from the subject has one or more mutations in one or more of the following genes: *Kras*, *PTEN*, *TP53*, *Apc*, *BRCA1*, or *BRCA2*, and/or determining whether a cancer cell in a sample from the subject expresses *LPA1* at a level higher than a reference sample; and~~

~~(b) administering a therapeutically effective amount of an agent that inhibits poly [ADP-ribose] polymerase (PARP) and an agent that inhibits programmed death 1 protein (PD-1) signaling to the subject if the cancer cell in the sample from the subject has one or more mutations in one or more of the following genes: *Kras*, *PTEN*, *TP53*, *Apc*, *BRCA1*, or *BRCA2*, and/or expresses *LPA1* at a level higher than a reference sample.~~

3. ~~A method of inducing or enhancing an immune response in a subject comprising:~~

~~administering a therapeutically effective amount of an agent that inhibits poly [ADP-ribose] polymerase (PARP) and an agent that inhibits programmed death 1 protein (PD-1) signaling to the subject,~~

~~wherein the subject has a cancer that is associated with one or more mutations in one or more of the following genes: *Kras*, *PTEN*, *TP53*, *Apc*, *BRCA1*, or *BRCA2*, and/or associated with expression of *LPA1*.~~

4. ~~The method of any one of the above claims, wherein the subject is human.~~

- ~~5. The method of any one of the above claims, wherein the subject is BRCA positive.~~
- ~~6. The method of any one of claims 1-4, wherein the subject is BRCA negative.~~
- ~~7. The method of claim 6, wherein the subject is gBRCA negative, tBRCA negative, or sBRCA negative.~~
- ~~8. The method of claim 6 or 7, wherein the subject is tBRCA negative.~~
- ~~9. The method of any one of the above claims, wherein the cancer is associated with one or more mutations in at least two of the following genes: *Kras*, *PTEN*, *TP53*, *Apc*, *BRCA1*, or *BRCA2*, and/or is associated with expression of *LPA1*.~~
- ~~10. The method of any one of the above claims, wherein the cancer is associated with a mutation in *Kras*.~~
- ~~11. The method of claim 10, wherein the cancer is associated with at least one additional mutation selected from a mutation in *PTEN* or in *TP53*.~~
- ~~12. The method of claim 9, wherein the cancer is associated with a mutation in *Kras* and a mutation in *PTEN*.~~
- ~~13. The method of claim 9, wherein the cancer is associated with a mutation in *Kras* and a mutation in *TP53*.~~
- ~~14. The method of any one of the above claims, wherein the cancer is associated with a *Kras* *G12D* mutation.~~
- ~~15. The method of any one of claims 1-12 or 14, wherein the cancer is associated with a *PTEN* $\neg$ mutation.~~

- ~~16. The method of any one of claims 1-11 or 13-14, wherein the cancer is associated with a *TP53* / mutation.~~
17. The method of any one of claims 1-4, wherein the subject is BRCA negative and the cancer is associated with a *Kras G12D* mutation and a *PTEN* / mutation.
18. The method of any one of claims 1-4, wherein the subject is BRCA negative and the cancer is associated with a *TP53* / mutation.
19. The method of any one of claims 1-4, wherein the subject is BRCA negative and the cancer is associated with expression of *LPA1*.
- ~~20. The method of any one of claims 1-4, wherein the subject is BRCA positive and the cancer is associated with a *Kras G12D* mutation and a *TP53* / mutation.~~
21. The method of any one of claims 1-4, wherein the subject is BRCA positive and the cancer is associated with a *BRCA1* mutation.
- ~~22. The method of any one of claims 1-4, wherein the subject is BRCA negative and the cancer is associated with a *Apc*^{min/+} mutation.~~
23. The method of any one of the above claims, wherein the cancer is selected from the group consisting of endometrial cancer, breast cancer, ovarian cancer, cervical cancer, fallopian tube cancer, testicular cancer, primary peritoneal cancer, colon cancer, colorectal cancer, small intestine cancer, squamous cell carcinoma of the anogenital region, melanoma, renal cell carcinoma, lung cancer, non-small cell lung cancer, squamous cell carcinoma of the lung, stomach cancer, bladder cancer, gall bladder cancer, liver cancer, thyroid cancer, laryngeal cancer, salivary gland cancer, esophageal cancer, head and neck cancer, squamous cell carcinoma of the head and neck, prostate cancer, pancreatic cancer, mesothelioma, Merkel cell carcinoma, sarcoma, glioblastoma, and a hematological cancer, such as multiple

myeloma, B cell lymphoma, T cell lymphoma, Hodgkin's lymphoma/primary mediastinal B-cell lymphoma, and chronic myelogenous leukemia.

24. The method of any one of the above claims, wherein the agent that inhibits PARP is administered at a reduced dose.

25. The method of any one of the above claims, wherein the agent that inhibits PARP is administered in a dose that is equivalent to 200 mg of niraparib in a human subject daily.

26. The method of any one of the above claims, wherein the dose of the agent that inhibits PARP is administered orally.

27. The method of any one of the above claims, wherein the agent that inhibits PARP is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin.

28. The method of any one of the above claims, wherein the agent that inhibits PARP is selected from the group consisting of: ABT 767, AZD 2461, BGB 290, BGP 15, CEP 8983, CEP 9722, DR 2313, E7016, E7449, fluzoparib (SHR 3162), IMP 4297, INO1001, JPI 289, JPI 547, monoclonal antibody B3-LysPE40 conjugate, MP 124, niraparib (ZEJULA) (MK-4827), NU 1025, NU 1064, NU 1076, NU1085, olaparib (AZD2281), ONO2231, PD 128763, R 503, R554, rucaparib (RUBRACA) (AG 014699, PF 01367338), SBP 101, SC 101914, Simmiparib, talazoparib (BMN 673), veliparib (ABT 888), WW 46, 2-(4-(Trifluoromethyl)phenyl) 7,8 dihydro 5H thiopyrano[4,3-d]pyrimidin 4-ol, and salts or derivatives thereof.

29. The method of any one of the above claims, wherein the agent that inhibits PARP is a small molecule.

- ~~30. The method of claim 29, wherein the agent that inhibits PARP is selected from the group consisting of: niraparib, olaparib, rucaparib, talazoparib, and veliparib, or salts or derivatives thereof.~~
- ~~31. The method of claim 30, wherein the agent that inhibits PARP is niraparib or a salt or derivative thereof.~~
- ~~32. The method of any one of the above claims, wherein the agent that inhibits PD-1 signaling is a small molecule, a nucleic acid, a polypeptide (e.g., an antibody), a carbohydrate, a lipid, a metal, or a toxin.~~
- ~~33. The method of any one of the above claims, wherein the agent that inhibits PD-1 signaling is an anti PD-1 antibody agent.~~
- ~~34. The method any one of the above claims, wherein the agent that inhibits PD-1 signaling is an anti PD-1 antibody agent selected from the group consisting of: BGB-A317, BI-754091, IBI308, INCSHR-1210, JNJ-63723283, JS-001, MEDI-0680, MGA-012, nivolumab, PDR001, pembrolizumab, PF-06801591, REGN-2810, TSR-042, and derivatives thereof.~~
- ~~35. The method of claim 33 or 34, wherein the anti PD-1 antibody agent is pembrolizumab or a derivative thereof.~~
- ~~36. The method of claim 33 or 34, wherein the anti PD-1 antibody agent is nivolumab or a derivative thereof.~~
- ~~37. The method of claim 33 or 34, wherein the anti PD-1 antibody agent is TSR-042 or a derivative thereof.~~
- ~~38. The method of claim 33, wherein the agent that inhibits PD-1 signaling is an anti PD-1 antibody agent comprising a CDR-H1 sequence of GFTFSSYD (SEQ ID NO: 14), a CDR-H2 sequence of ISGGGSYT (SEQ ID NO: 15), a CDR-H3 sequence of ASPYYAMDY~~

(SEQ ID NO: 16), a CDR L1 sequence of QDVGTA (SEQ ID NO: 17), a CDR L2 sequence of WAS (SEQ ID NO: 18), and a CDR L3 sequence of QHYSSYPWT (SEQ ID NO: 19).

39. The method of claim 33, wherein the agent that inhibits PD-1 signaling is an anti-PD-1 antibody agent comprising a heavy chain variable domain comprising the amino acid sequence of SEQ ID NO: 12 and a light chain variable domain comprising the amino acid sequence of SEQ ID NO: 13.
40. The method of claim 33, wherein the agent that inhibits PD-1 signaling is an anti-PD-1 antibody agent comprising a heavy chain comprising the amino acid sequence of SEQ ID NO: 9 or SEQ ID NO: 10 and a light chain comprising the amino acid sequence of SEQ ID NO: 11.
41. The method of any one of claims 1-32, wherein the agent that inhibits PD-1 signaling is an anti-PD-L1/L2 agent.
42. The method of claim 41, wherein the anti-PD-L1/L2 agent is an anti-PD-L1 antibody agent.
43. The method of claim 41 or 42, wherein the agent that inhibits PD-1 signaling is an anti-PD-L1 antibody agent selected from the group consisting of: atezolizumab, avelumab, CX-072, durvalumab, FAZ053, LY3300054, PD-L1 millamolecule, and derivatives thereof.
44. The method of any one of the above claims, wherein the agent that inhibits PD-1 signaling and the agent that inhibits PARP are administered according to a regimen that includes at least one 2-12 week treatment cycle.
45. The method of any one of the above claims, wherein the agent that inhibits PD-1 signaling and the agent that inhibits PARP are administered in repeating cycles of 21 days.
46. The method of claim 44 or 45, wherein the agent that inhibits PD-1 signaling is administered on day one of cycle one.

- ~~47. The method of claim 46, wherein the agent that inhibits PD-1 signaling is administered on day one of a subsequent cycle.~~
- ~~48. The method of claim 46, wherein the agent that inhibits PD-1 signaling is administered between one to three days before or after day one of a subsequent cycle.~~
- ~~49. The method of any one of the above claims, wherein the agent that inhibits PD-1 signaling is administered intravenously.~~
- ~~50. The method of any one claims 1-48, wherein the agent that inhibits PD-1 signaling is administered at a dose that is equivalent to 200 mg of pembrolizumab in a human subject or 2 mg/kg of pembrolizumab.~~
- ~~51. The method of claim 50, wherein the agent that inhibits PD-1 signaling is administered intravenously over about 30 minutes.~~
- ~~52. The method of any one of claims 1-48, wherein the agent that inhibits PD-1 signaling is administered at a dose that is equivalent to 240 mg of nivolumab in a human subject or 3 mg/kg.~~
- ~~53. The method of claim 51, wherein the agent that inhibits PD-1 signaling is administered intravenously over about 60 minutes.~~
- ~~54. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose of 1, 3 or 10 mg/kg.~~
- ~~55. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose of 1, 3 or 10 mg/kg every two weeks.~~
- ~~56. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose that is equivalent to 500 mg in a human subject.~~

- ~~57. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose that is equivalent to 500 mg in a human subject every 3 weeks.~~
- ~~58. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose that is equivalent to 1000 mg in a human subject.~~
- ~~59. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose that is equivalent to 1000 mg in a human subject every 6 weeks.~~
- ~~60. The method of any one of claims 37-40, wherein the anti-PD-1 antibody agent is administered at a dose that is equivalent to 500 mg in a human subject every 3 weeks for four doses followed by a dose of least one dose that is equivalent to 1000 mg in a human subject every six weeks.~~
- ~~61. The method of claim 60, wherein the doses equivalent to 1000 mg are administered every six weeks after the first dose equivalent to 1000 mg until no further clinical benefit is achieved.~~
- ~~62. The method of any one of claims 44-53, wherein the treatment cycle is at least 2 weeks, at least 3 weeks, or at least 4 weeks.~~
- ~~63. The method of any one of claims 44-62, wherein the regimen includes at least 3 treatment cycles.~~
- ~~64. The method of any one of claims 44-63, wherein the dose of the agent that inhibits PARP is increased if the subject's hemoglobin ≥ 9 g/dL, platelets $\geq 100,000/\mu\text{L}$ and neutrophils $\geq 1500/\mu\text{L}$ for all labs performed during one or more cycles.~~
- ~~65. The method of claim 64, wherein the dose of the agent that inhibits PARP is increased after two cycles.~~

- ~~66. The method of claim 64, wherein the agent that inhibits PARP is administered in an increased dose that is equivalent to 300 mg of niraparib in a human subject.~~
- ~~67. The method of any one of the above claims, wherein the subject has previously been treated with one or more different cancer treatment modalities.~~
- ~~68. The method of claim 67, wherein the subject has previously been treated with one or more of radiotherapy, chemotherapy or immunotherapy.~~
- ~~69. The method of claim 67 or 68, wherein the subject has been treated with one, two, three, four, or five lines of prior therapy.~~
- ~~70. The method of claim 69, wherein the subject has been treated with one line of prior therapy.~~
- ~~71. The method of claim 69, wherein the subject has been treated with two lines of prior therapy.~~
- ~~72. The method of claim 69, wherein the subject has been treated with three lines of prior therapy.~~
- ~~73. The method of claim 69, wherein the subject has been treated with four lines of prior therapy.~~
- ~~74. The method of claim 69, wherein the subject has been treated with five lines of prior therapy.~~
- ~~75. The method of any one of claims 69-74, wherein the prior therapy is a cytotoxic therapy.~~

1. An invention not claimed in any divisional application