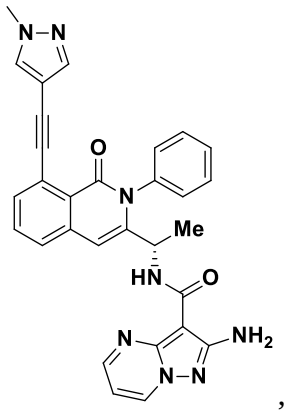
CLAIMS

1. Use of a compound of the formula:



,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with an immune checkpoint therapy in treating or preventing a cancer in a subject.

2. The use of claim 1, wherein the cancer is a solid tumor.

3. The use of claim 1, wherein the cancer is selected from one or more of: a cancer of the pulmonary system, a brain cancer, a cancer of the gastrointestinal tract, a skin cancer, a genitourinary cancer, head and neck cancer, a sarcoma, a carcinoma, and a neuroendocrine cancer;

wherein the cancer is selected from one or more of: a pancreatic cancer, a lung cancer, a breast cancer, a prostate cancer, a testicular cancer, an esophageal cancer, a liver cancer, a gastric cancer, a colon cancer, a colorectal cancer, an ovarian cancer, a cervical cancer, a uterine cancer, an endometrial cancer, a bladder cancer, a kidney cancer, and a viral-induced cancer; or

wherein the cancer is selected from one or more of: a medulloblastoma, a basal cell carcinoma, a glioma, a hepatocellular cancer, a gastrointestinal stromal tumor (GIST), a melanoma, a neuroectodermal tumor, a soft-tissue sarcoma, fibrosarcoma, myxosarcoma, liposarcoma, a chondrosarcoma, an osteogenic sarcoma, a chordoma, an angiosarcoma, an endotheliosarcoma, a lymphangiosarcoma, a lymphangioendotheliosarcoma, a synovioma, a mesothelioma, a leiomyosarcoma, a bladder carcinoma, an epithelial carcinoma, a squamous cell

carcinoma, an adenocarcinoma, a bronchogenic carcinoma, a renal cell carcinoma, a hepatoma, a bile duct carcinoma, a carcinoid tumor, diffuse type giant cell tumor, and glioblastoma.

4. The use of claim 2, wherein the solid tumor is melanoma, lung cancer, head and neck cancer, renal cell carcinoma, bladder cancer, breast cancer, colon cancer, glioblastoma, adrenal gland cancer, mesothelioma, colorectal cancer, ovarian cancer, endometrial cancer, or urothelial carcinoma.

5. The use of claim 1, wherein the cancer is a hematological cancer.

6. The use of claim 5, wherein the hematological cancer is leukemia or lymphoma; or

wherein the hematological cancer is acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL), Waldenstrom's macroglobulinemia (WM), peripheral T cell lymphomas (PTCL), adult T cell leukemia/lymphoma (ATLL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGL), acute myelocytic leukemia (AML), Hodgkin lymphoma (HL), non–Hodgkin lymphoma (NHL), follicular lymphoma, diffuse large B–cell lymphoma (DLBCL), mantle cell lymphoma (MCL), mastocytosis, multiple myeloma (MM), myelodysplastic syndrome (MDS), or myeloproliferative disorder (MPD).

7. The use of any one of claims 1–6, wherein the cancer is metastatic.

8. The use of any one of claims 1–6, wherein the cancer is relapsed after or refractory to a prior therapy, and wherein the prior therapy is an immune checkpoint therapy.

9. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a NKG2C ligand, a NKG2D ligand, a CTLA-4 inhibitor, a PD-1 inhibitor, a PD-L1 inhibitor, a LAG3 inhibitor, a TIM-3 inhibitor, a BTLA inhibitor, a VISTA inhibitor, a TIGIT inhibitor, an IDO inhibitor, a CSF1 inhibitor, an ARG1 inhibitor, an ICOS agonist, a CD137 agonist, an OX40 agonist, a GITR agonist, a CD27 agonist, a HVEM agonist, a TLR ligand, or a B7-H3 antibody.

10. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a PD-L1 inhibitor or an anti-PD-L1 antibody.

11. The use of claim 10, wherein the PD-L1 inhibitor or the anti-PD-L1 antibody is YW243.55.S70, MPDL3280A, MSB0010718C, MDX-1105, or MEDI-4736.

12. The use of claim 11, wherein the PD-L1 inhibitor or the anti-PD-L1 antibody is MPDL3280A.

13. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a PD-1 inhibitor or an anti-PD-1 antibody.

14. The use of claim 13, wherein the PD-1 inhibitor or the anti-PD-1 antibody is nivolumab, pembrolizumab, pidilizumab, AMP-244, or AMP-514.

15. The use of claim 14, wherein the PD-1 inhibitor or the anti-PD-1 antibody is nivolumab.

16. The use of claim 14, wherein the PD-1 inhibitor or the anti-PD-1 antibody is pembrolizumab.

17. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a CTLA-4 inhibitor or an anti-CTLA4 antibody.

18. The use of claim 17, wherein the CTLA-4 inhibitor or the anti-CTLA4 antibody is tremelimumab or ipilimumab.

19. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a combination of a PD-1 inhibitor or an anti-PD-1 antibody and a CTLA-4 inhibitor or an anti-CTLA-4 antibody.

20. The use of claim 19, wherein the PD-1 inhibitor or the anti-PD-1 antibody is selected from the group consisting of nivolumab, pembrolizumab, pidilizumab, AMP-244, and AMP-514, and

the CTLA-4 inhibitor or the anti-CTLA-4 antibody is selected from the group consisting of tremelimumab and ipilimumab.

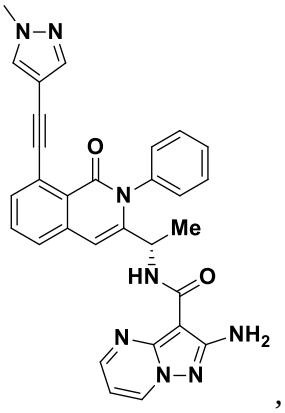
21. The use of claim 20, wherein the PD-1 inhibitor or the anti-PD-1 antibody is nivolumab.

22. The use of claim 20, wherein the PD-1 inhibitor or the anti-PD-1 antibody is pembrolizumab.

23. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a combination of a PD-1 inhibitor or an anti-PD-1 antibody, a PD-L1 inhibitor or an anti-PD-L1 antibody, and a CTLA-4 inhibitor or an anti-CTLA-4 antibody.

24. The use of any one of claims 1–8, wherein the immune checkpoint therapy is a combination of an antibody or fragment thereof, an inhibitory nucleic acid, a soluble ligand, or a fusion of PD-1 with a Fc region of an immunoglobulin; an antibody or fragment thereof, an inhibitory nucleic acid, a soluble ligand, or a fusion of PD-L1 with a Fc region of an immunoglobulin; and an antibody or fragment thereof, an inhibitory nucleic acid, a soluble ligand, or a fusion of a CTLA-4 ligand with a Fc region of an immunoglobulin.

25. Use of a compound of the formula:



,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with a PD-1 inhibitor or an anti-PD-1 antibody in treating a solid tumor in a subject.

26. The use of claim 25, wherein the solid tumor is selected from one or more of: a cancer of the pulmonary system, a brain cancer, a cancer of the gastrointestinal tract, a skin cancer, a genitourinary cancer, head and neck cancer, a sarcoma, a carcinoma, and a neuroendocrine cancer;

wherein the solid tumor is selected from one or more of: a pancreatic cancer, a lung cancer, a breast cancer, a prostate cancer, a testicular cancer, an esophageal cancer, a liver cancer, a gastric cancer, a colon cancer, a colorectal cancer, an ovarian cancer, a cervical cancer, a uterine cancer, an endometrial cancer, a bladder cancer, a kidney cancer, a viral-induced cancer, an adrenal gland cancer, and a mesothelioma; or

wherein the solid tumor is selected from one or more of: a medulloblastoma, a basal cell carcinoma, a glioma, a hepatocellular cancer, a gastrointestinal stromal tumor (GIST), a melanoma, a neuroectodermal tumor, a soft-tissue sarcoma, fibrosarcoma, myxosarcoma, liposarcoma, a chondrosarcoma, an osteogenic sarcoma, a chordoma, an angiosarcoma, an endotheliosarcoma, a lymphangiosarcoma, a lymphangioendotheliosarcoma, a synovioma, a mesothelioma, a leiomyosarcoma, a bladder carcinoma, an epithelial carcinoma, a squamous cell carcinoma, an adenocarcinoma, a bronchogenic carcinoma, a renal cell carcinoma, a hepatoma, a bile duct carcinoma, a carcinoid tumor, diffuse type giant cell tumor, glioblastoma, and urothelial carcinoma.

27. The use of claim 25, wherein the solid tumor is lung cancer.

28. The use of claim 27, wherein the lung cancer is non-small cell lung cancer.

29. The use of claim 27 or 28, wherein the subject has been pre-treated or previously treated with one immunotherapy treatment that is a checkpoint treatment.

30. The use of claim 25, wherein the solid tumor is melanoma.

31. The use of claim 30, wherein the subject has been pre-treated or previously treated with one or more immunotherapy treatments that is a checkpoint treatment.

32. The use of claim 25, wherein the solid tumor is colon cancer.

33. The use of claim 25, wherein the solid tumor is head and neck cancer.

34. The use of claim 33, wherein the head and neck cancer is head and neck squamous cell carcinoma.

35. The use of claim 33, wherein the subject has been pre-treated or previously treated with one immunotherapy treatment that is a checkpoint treatment.

36. The use of claim 25, wherein the solid tumor is breast cancer.

37. The use of claim 36, wherein the breast cancer is triple negative breast cancer.

38. The use of claim 36 or 37, wherein wherein the subject is naive to immunotherapy treatment.

39. The use of claim 25, wherein the solid tumor is adrenal gland cancer.

40. The use of claim 25, wherein the solid tumor is mesothelioma.

41. The use of claim 25, wherein the solid tumor is bladder cancer.

42. The use of claim 41, wherein the subject has been pre-treated or previously treated with one immunotherapy treatment that is a checkpoint treatment.

43. The use of claim 25, wherein the solid tumor is urothelial carcinoma.

44. The use of claim 25, wherein the solid tumor is renal cell carcinoma.

45. The use of claim 44, wherein the subject has been pre-treated or previously treated with one immunotherapy treatment that is a checkpoint treatment.

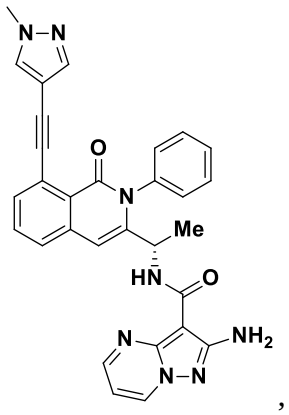
46. The use of any one of claims 25–45, wherein the PD-1 inhibitor or the anti-PD-1 antibody is nivolumab or pembrolizumab.

47. The use of claim 46, wherein the PD-1 inhibitor or the anti-PD-1 antibody is pembrolizumab.

48. The use of claim 46, wherein the PD-1 inhibitor or the anti-PD-1 antibody is nivolumab.

49. The use of any one of claims 25–48, wherein the anti-PD-1 antibody is administered at a dose of about 1 to 5 mg/kg every 2 weeks, or at a dose of about 3 mg/kg every 2 weeks.

50. Use of a compound of the formula:



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or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with an anti-PD-L1 antibody in treating breast cancer in a subject.

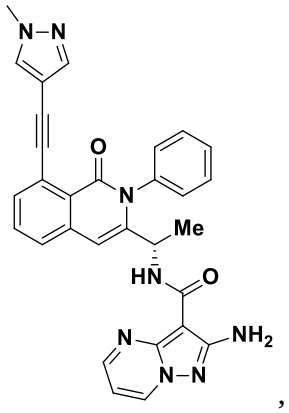
51. The use of claim 50, wherein the breast cancer is triple negative breast cancer.

52. The use of claim 50 or 51, wherein the anti-PD-L1 antibody is MPDL3280A.

53. The use of any one of claims 50–52, further in combination with paclitaxel.

54. The use of any one of claims 50–52, further in combination with nanoparticle albumin-bound paclitaxel.

55. Use of a compound of the formula:



,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with an anti-PD-L1 antibody in treating renal cancer in a subject.

56. The use of claim 55, wherein the renal cancer is renal cell carcinoma (RCC).

57. The use of claim 55, wherein the renal cell carcinoma is metastatic renal cell carcinoma.

58. The use of any one of claims 55–57, wherein the anti-PD-L1 antibody is MPDL3280A.

59. The use of any one of claims 55–58, further in combination with bevacizumab.

60. The use of any one of claims 1–59, wherein the medicament is manufactured to administer the compound at a dose of about 1–50 mg per day.

61. The use of any one of claims 1–59, wherein the medicament is manufactured to administer the compound at a dose of about 10, about 15, about 20, about 25, about 30, about 40, about 45, about 50, or about 60 mg per day.

62. The use of claim 61, wherein the medicament is manufactured to administer the compound at a dose of about 30 mg once daily.

63. The use of claim 61, wherein the medicament is manufactured to administer the compound at a dose of about 40 mg once daily.

64. The use of any one of claims 1–59, wherein the medicament is manufactured to administer the compound a dose such that the level of the compound in the subject is higher than the compound's IC_{50} of PI3K-gamma inhibition during at least 70%, 80%, 90%, 95%, 97%, 98%, or 99% of a selected time period of 6 hours, 12 hours, 24 hours, or 48 hours immediately following the administration;

wherein the medicament is manufactured to administer the compound at a dose such that the level of the compound in the subject is higher than the compound's IC_{90} of PI3K-gamma inhibition during at least 50%, 60%, 70%, 80%, 90%, 95%, 97%, 98%, or 99% of a selected time period of 6 hours, 12 hours, 24 hours, or 48 hours, immediately following the administration; or

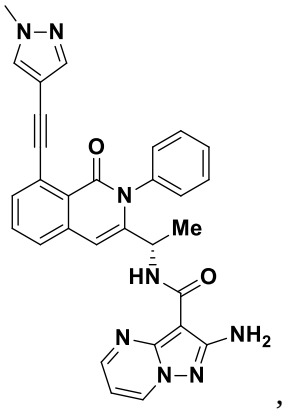
wherein the medicament is manufactured to administer the compound at a dose such that the level of the compound in the subject does not rise higher than the compound's IC_{20} or IC_{50} of PI3K-delta inhibition within a selected time period of 6 hours, 12 hours, 24 hours, or 48 hours, immediately following the administration.

65. The use of claim 64, wherein the level of the compound is measured from the subject's plasma or tissue.

66. The use of any one of claims 1–59, wherein the medicament is manufactured to administer the compound at a dose such that it provides at least 50% inhibition of PI3K-gamma in the subject but less than 10% or 20% inhibition of PI3K-delta in the subject.

67. The use of any one of claims 1–66, wherein the subject is a human and the compound has a half life of about 10-13 hours in the subject.

68. Use of a compound of the formula:



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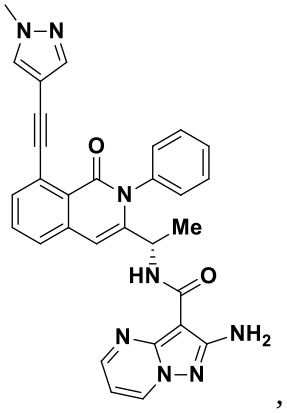
or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in combination with a PD-1 inhibitor or an anti-PD-1 antibody in treating a carcinoma or melanoma in a subject, wherein the medicament is manufactured to administer the compound at a dose of 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 40 mg, 45 mg, 50 mg, or 60 mg per day.

69. The use of claim 68, wherein the carcinoma is a non-small cell lung cancer (NSCLC).

70. The use of claim 68 or 69, wherein the PD-1 inhibitor or the anti-PD-1 antibody is pembrolizumab.

71. The use of claim 68 or 69, wherein the PD-1 inhibitor or the anti-PD-1 antibody is nivolumab.

72. Use of a compound of the formula:



,

or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a solid tumor or a hematological cancer in a subject, wherein the solid tumor or hematological cancer is relapsed after or refractory to a prior therapy, wherein the prior therapy is an immune checkpoint therapy.

73. The use of claim 72, wherein the solid tumor or hematological cancer is melanoma, and the subject has been pre-treated or previously treated with one or more immune checkpoint therapy;

wherein the solid tumor or hematological cancer is head and neck cancer, and the subject has been pre-treated or previously treated with one immune checkpoint therapy;

wherein the solid tumor or hematological cancer is lung cancer, and the subject has been pre-treated or previously treated with one immune checkpoint therapy;

wherein the solid tumor or hematological cancer is non-small cell lung cancer, and the subject has been pre-treated or previously treated with one immune checkpoint therapy;

wherein the solid tumor or hematological cancer is renal cell carcinoma, and the subject has been pre-treated or previously treated with one immune checkpoint therapy; or

wherein the solid tumor or hematological cancer is bladder cancer, and the subject has been pre-treated or previously treated with one immune checkpoint therapy.

74. The use of claim 72 or 73, wherein the immune checkpoint therapy is a PD-1 inhibitor or an anti-PD-1 antibody.