Claims

1. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to be administered to a patient in need thereof over a period of time as a monotherapy, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered according to an intermittent dosing schedule of at least one dosing cycle, wherein each dosing cycle is a 21-day cycle, wherein each dosing cycle comprises (a) a dosing period during which said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 14 of said 21-day cycle, and (b) a resting period during which said Compound 1 or a pharmaceutically acceptable salt thereof is not to be administered, wherein said resting period is days 15-21.

2. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to be administered to a patient in need thereof over a period of time as a monotherapy, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered according to an intermittent dosing schedule of at least one dosing cycle, wherein each dosing cycle is a 28-day cycle, wherein each dosing cycle comprises (a) a dosing period during which said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1-14, and (b) a resting period during which said Compound 1 or a pharmaceutically acceptable salt thereof is not to be administered wherein the resting period is days 15-28.

3. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically

effective amount of Compound 1 or a pharmaceutically acceptable salt thereof to be administered to a patient in need thereof over a period of time as a monotherapy, wherein Compound 1 or a pharmaceutically acceptable salt thereof is to be administered according to an intermittent dosing schedule of at least one dosing cycle, wherein each dosing cycle is a 28-day cycle, wherein each dosing cycle comprises (a) a dosing period during which said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1-7 and days 15-21, and (b) a resting period during which said Compound 1 or a pharmaceutically acceptable salt thereof is not to be administered, wherein the resting period is days 8-14 and 22-28.

4. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle, wherein each dosing cycle is a 28-day cycle, wherein each dosing cycle comprises (a) a dosing period during which said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are to be administered on days 1 through 7 and said PD-1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period during which said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein said resting period is days 16 through 28, and wherein said PD-1 inhibitor is nivolumab, sasanlimab or a biosimilar thereof.

5. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle, wherein each dosing cycle is a 28-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 14 and said PD-1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period wherein

said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein the resting period is days 16 through 28, and wherein said PD-1 inhibitor is nivolumab, sasanlimab or a biosimilar thereof.

6. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle, wherein said dosing cycle is a 28-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 21 and said PD-1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein the resting period is days 22 through 28, and wherein said PD-1 inhibitor is nivolumab, sasanlimab or a biosimilar thereof.

7. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle, wherein said dosing cycle is a 28-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 7 and days 15 through 21 and said PD-1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein the resting period is days 8 through 14 and days 22 through 28, and wherein said PD-1 inhibitor is nivolumab, sasanlimab or a biosimilar thereof.

8. The pharmaceutical composition according to any one of claims 4-7, wherein said PD-1 inhibitor is nivolumab or a biosimilar thereof and is to be administered intravenously at a dose of about 3 mg/kg or as a flat dose of about 240 mg over 30 minutes.

9. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 21-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 7 and said PD-1 inhibitor is to be administered on day 1, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein the resting period is days 8 through 21, and wherein said PD-1 inhibitor is pembrolizumab or a biosimilar thereof.

10. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 21-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 14 and said PD-1 inhibitor is to be administered on day 1, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein the resting period is days 15 through 21, and wherein said PD-1 inhibitor is pembrolizumab or a biosimilar thereof.

11. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 21-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 7 and days 15 through 21 and said PD-1 inhibitor is to be administered on day 1, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-1 inhibitor are not to be administered, wherein the resting period is days 8 through 14, and wherein said PD-1 inhibitor is pembrolizumab or a biosimilar thereof.

12. The pharmaceutical composition according to any one of claims 9-11, wherein said pembrolizumab or a biosimilar thereof is to be administered intravenously at a dose of about 2 mg/kg or as a flat dose of about 200 mg over 30 minutes.

13. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-L1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 28-day cycle, wherein each dosing cycle comprises (a) a dosing period during which said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 7 and said PD-L1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period during which said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-L1 inhibitor are not to be administered, wherein the resting period is days 16 through 28, and wherein said PD-L1 inhibitor is atezolizumab or a biosimilar thereof.

14. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-L1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 28-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 14 and said PD-L1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-L1 inhibitor are not to be administered, wherein the resting period is days 16 through 28, and wherein said PD-L1 inhibitor is atezolizumab or a biosimilar thereof.

15. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-L1 inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 28-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 21, said PD-L1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-L1 inhibitor are not to be administered, wherein the resting period is days 22 through 28, and wherein said PD-L1 inhibitor is atezolizumab or a biosimilar thereof.

16. A pharmaceutical composition comprising (R)-N-(3-fluoro-4-((3-((1-hydroxypropan-2-yl)amino)-1H-pyrazolo[3,4-b]pyridin-4-yl)oxy)phenyl)-3-(4-fluorophenyl)-1-isopropyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Compound 1) or a pharmaceutically acceptable salt thereof for use in the treatment of cancer, wherein the treatment comprises a therapeutically effective amount of Compound 1 or a pharmaceutically acceptable salt thereof and a PD-L1

inhibitor to be administered to a patient in need thereof over a period of time according to an intermittent dosing schedule of at least one dosing cycle wherein each dosing cycle is a 28-day cycle, wherein each of said dosing cycles comprises (a) a dosing period wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered on days 1 through 7 and days 15 through 21, said PD-L1 inhibitor is to be administered on day 1 and day 15, and (b) a resting period wherein said Compound 1 or a pharmaceutically acceptable salt thereof and said PD-L1 inhibitor are not to be administered, wherein the resting period is days 8 through 14 and 22 through 28, and wherein said PD-L1 inhibitor is atezolizumab or a biosimilar thereof.

17. The pharmaceutical composition according any one of claims 13-16, wherein said atezolizumab or a biosimilar thereof is to be administered intravenously at a dose of about 840 mg over 30 minutes or 60 minutes.

18. The pharmaceutical composition according to any one of claims 1-17, wherein the cancer is a TAM-associated cancer.

19. The pharmaceutical composition according to claim 18, wherein said cancer is selected from gastrointestinal stromal tumor (GIST), acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myeloid leukemia (CML), B-cell chronic myeloid leukemia (B-CLL), lung cancer, glioblastoma, breast cancer, colorectal cancer, gastric cancer, glioma, pancreatic cancer, esophageal cancer, mantle cell lymphoma, melanoma, squamous cell skin cancer, prostate cancer, endometrial cancer, ovarian cancer, oral squamous cell carcinoma, thyroid cancer, bladder cancer, renal cancer, schwannoma, mesothelioma, Kaposi's sarcoma, osteosarcoma, rhabdomyosarcoma, erythroid leukemia, colon cancer, liver cancer, renal cell carcinoma, pituitary adenoma, urinary tract cancer, kidney cancer, colon cancer, head and neck cancer, brain cancer, and non-small cell lung cancer.

20. The pharmaceutical composition according to claim 18, wherein the TAM-associated cancer is selected from the group consisting of acute myeloid leukemia (AML), multiple myeloma, lung cancer, melanoma, prostate cancer, endometrial cancer, thyroid cancer, schwannoma, pancreatic cancer, and brain cancer.

21. The pharmaceutical composition according to any one of claims 1-17, wherein said cancer is selected from cervical cancer, gastric cancer, esophageal cancer, hepatocellular carcinoma, melanoma, Merkel Cell Carcinoma, microsatellite instability-high (MSI-H) tumors, non-small cell lung cancer, head and neck squamous cell carcinoma, small cell lung cancer, renal cell carcinoma, or urothelial carcinoma.

22. The pharmaceutical composition according to any one of claims 1-21, wherein, prior to the period of time, the patient was treated with an anticancer therapy, wherein said anticancer therapy does not comprise administration of Compound 1 or a pharmaceutically acceptable salt thereof.

23. The pharmaceutical composition according to any one of claims 1-22, wherein the treatment further comprises assessing efficacy of treatment during the period of time by determining one or more of inhibition of disease progression, inhibition of tumor growth, reduction of primary tumor, relief of tumor-related symptoms, inhibition of tumor secreted factors, delayed appearance of primary or secondary tumors, slowed development of primary or secondary tumors, decreased occurrence of primary or secondary tumors, slowed or decreased severity of secondary effects of disease, arrested tumor growth and regression of tumors, increased Time To Progression (TTP), increased Progression Free Survival (PFS), increased Overall Survival (OS) or increased Duration of Response (DOR).

24. The pharmaceutical composition according to any one of claims 1-23, wherein said Compound 1 or a pharmaceutically acceptable salt thereof is formulated as a capsule or tablet for oral administration.

25. The pharmaceutical composition according to any one of claims 1-24, wherein the patient is dosed daily with 25 mg, 50 mg, 100 mg, 200 mg or 300 mg of Compound 1 or a pharmaceutically acceptable salt thereof during each dosing period.

26. The pharmaceutical composition according to any one of claims 1-25, wherein said Compound 1 or a pharmaceutically acceptable salt thereof is to be administered as the free base of Compound 1.