DOSAGE REGIMEN FOR SOTORASIB/CARBOPLATIN/PEMETREXED IN CANCER TREATMENT

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/459,349, filed April 18, 2023, and U.S. Provisional Patent Application No. 63/520,050, filed August 16, 2023, which is hereby incorporated by reference in its entirety.

BACKGROUND

[002] The rat sarcoma (RAS) proto-oncogene has been identified as an oncogenic driver of tumorigenesis in cancers, such as non-small cell lung cancer (NSCLC) and colorectal cancer (CRC). The RAS family consists of 3 closely related genes that express guanosine triphosphate (GTP)-ases responsible for regulating cellular proliferation and survival. The RAS proteins, Kirsten rat sarcoma viral oncogene homolog (KRAS), Harvey rat sarcoma viral oncogene homolog (HRAS), and neuroblastoma RAS viral oncogene homolog (NRAS) can be mutationally activated at codons 12, 13, or 61, leading to human cancers. Different tumor types are associated with mutations in certain isoforms of RAS, with KRAS being the most frequently mutated isoform in most cancers. While the role of KRAS mutations in human cancers has been known for decades, no anti-cancer therapies specifically targeting KRAS mutations have been successfully developed, until recently, largely because the protein had been considered intractable for inhibition by small molecules.

[003] As further detailed in this disclosure, sotorasib is a small molecule that irreversibly inhibits the $KRAS^{G12C}$ protein. In 2021, LUMAKRAS was approved by the US Food and Drug Administration (FDA) for the treatment of certain *KRAS G12C* mutated lung cancers, making it the first compound in its class approved by a regulatory agency anywhere in the world. While sotorasib monotherapy appears to drive substantial anti-tumor activity, combination therapies are desirable to improve treatment options for patients.

SUMMARY

[004] Described herein are methods of treating cancer comprising a *KRAS G12C* mutation in a subject in need thereof comprising administering to the subject (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed. In various examples, the therapeutically effective amount of sotorasib is 240 mg. In various examples, the therapeutically effective amount of sotorasib is 960 mg. In some various examples, the subject, prior to treatment, has not received a prior systemic anticancer therapy for the cancer (first line treatment). In various examples, the cancer exhibits a tumor cell (TC) score of less than 1% or a tumor proportion score (TPS) of less than 1%.

In one aspect, the present disclosure refers to use of sotorasib in the manufacture of a first medicament, use of carboplatin in the manufacture of a second medicament, and use of pemetrexed in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combinatorial therapy for treating cancer comprising a KRAS G12C mutation in a human subject, wherein the first, second and third medicaments are to be administered according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

In another aspect, the present disclosure refers to use of sotorasib, carboplatin and pemetrexed in the manufacture of a medicament for combination therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

In another aspect, the present disclosure refers to use of sotorasib in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with carboplatin and pemetrexed according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

In another aspect, the present disclosure refers to use of carboplatin in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with sotorasib and pemetrexed according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

In another aspect, the present disclosure refers to use of pemetrexed in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with sotorasib and carboplatin according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

In another aspect, the present disclosure refers to use of sotorasib and pemetrexed in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with carboplatin according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

What is claimed is:

1. Use of sotorasib in the manufacture of a first medicament, use of carboplatin in the manufacture of a second medicament, and use of pemetrexed in the manufacture of a third medicament, wherein the first, second and third medicaments are to be used in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the first, second and third medicaments are to be administered according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

2. Use of sotorasib, carboplatin and pemetrexed in the manufacture of a medicament for combination therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

3. Use of sotorasib in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with carboplatin and pemetrexed according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

4. Use of carboplatin in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with sotorasib and pemetrexed according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

5. Use of pemetrexed in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with sotorasib and carboplatin according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

6. Use of sotorasib and pemetrexed in the manufacture of a medicament for use in combinatorial therapy for treating cancer comprising a *KRAS G12C* mutation in a human subject, wherein the medicament is to be administered in combination with carboplatin according to (a) a first regimen comprising (i) a therapeutically effective amount of sotorasib, (ii) a therapeutically effective amount of carboplatin and (iii) a therapeutically effective amount of pemetrexed and then (b) a second regimen comprising (i) the therapeutically effective amount of sotorasib and (ii) the therapeutically effective amount of pemetrexed.

7. The use of any one of claims 1 to 6, wherein the first regimen is to be administered for a period of 4 cycles.

8. The use of claim 7, wherein each cycle is a period of 21 days.

9. The use of any one of claims 1 to 8, wherein the therapeutically effective amount of sotorasib is 240 mg.

10. The use of any one of claims 1 to 8, wherein the therapeutically effective amount of sotorasib is 960 mg.

11. The use of any one of claims 1 to 10, wherein the sotorasib is to be administered orally.

12. The use of any one of claims 1 to 11, wherein the sotorasib is to be administered once daily.

13. The use of any one of claims 1 to 12, wherein the sotorasib is to be administered as a solid dosage form.

14. The use of claim 13, wherein the solid dosage form is a tablet.

15. The use of claim 14, wherein the sotorasib is to be administered as one tablet comprising 240 mg of sotorasib, two tablets each comprising 120 mg of sotorasib, three tablets each comprising 320 mg of sotorasib, four tablets each comprising 240 mg of sotorasib, or eight tablets each comprising 120 mg of sotorasib.

16. The use of any one of claims 1 to 15, wherein the therapeutically effective amount of carboplatin is an amount corresponding to 5 mg/(mL x min) (AUC 5) multiplied with the subject's glomerular filtration rate (GFR) in mL/min increased by 25 mL/min.

17. The use of claim 16, wherein the therapeutically effective amount of carboplatin is 750 mg or less.

18. The use of any one of claims 1 to 17, wherein the carboplatin is to be administered intravenously.

19. The use of any one of claims 7 to 18, wherein the carboplatin is to be administered on day 1 of each cycle.

20. The use of any one of claims 1 to 19, wherein the carboplatin is not to be administered to the subject during the second regimen.

21. The use of any one of claims 1 to 20, wherein the therapeutically effective amount of pemetrexed is 500 mg/m^2.

22. The use of any one of claims 1 to 21, wherein pemetrexed is to be administered intravenously.

23. The use of any one of claims 1 to 22, wherein the administration of pemetrexed starts on day 1 of the first regimen.

24. The use of any one of claims 1 to 23, wherein the pemetrexed is to be administered in 21 day intervals during the first regimen and the second regimen.

25. The use of any one of claims 1 to 24, wherein the medicament is to be administered in further combination with a therapeutically effective amount of folic acid.

26. The use of claim 25, wherein the therapeutically effective amount of folic acid is 350 µg to 1000 µg once daily.

27. The use of claim 25, wherein the therapeutically effective amount of folic acid is 400 µg once daily.

28. The use of claim 25, wherein the therapeutically effective amount of folic acid is 400 µg to 1000 µg once daily.

29. The use of claim 25 or claim 28, wherein the folic acid administration commences 7 days prior to pemetrexed administration and ends 21 days after cessation of pemetrexed administration.

30. The use of any one of claims 1 to 29, wherein the medicament is to be administered in further combination with a therapeutically effective amount of vitamin B12.

31. The use of claim 30, wherein the therapeutically effective amount of vitamin B12 is 1 mg.

32. The use of claim 30 or claim 31, wherein the vitamin B12 is to be administered in the week prior to first pemetrexed administration and once every 9 weeks (± 2 weeks) thereafter until cessation of pemetrexed administration.

33. The use of claim 30 or claim 31, wherein the vitamin B12 is to be administered one week prior to first pemetrexed administration and once every 9 weeks thereafter until cessation of pemetrexed administration.

34. The use of any one of claims 30 to 33, wherein the vitamin B12 is to be administered intramuscularly.

35. The use of any one of claims 1 to 34, wherein the medicament is to be administered in further combination with a therapeutically effective amount of dexamethasone.

36. The use of claim 35, wherein the therapeutically effective amount of dexamethasone is 4 mg twice daily.

37. The use of claim 35 or claim 36, wherein the dexamethasone is to be administered the day before, the day of, and the day after each pemetrexed administration to the subject.

38. The use of any one of claims 1 to 37, wherein the subject is an adult.

39. The use of any one of claims 1 to 38, wherein the subject, prior to treatment, has not received a prior systemic anticancer therapy for the cancer (first line treatment).

40. The use of any one of claims 1 to 39, wherein the subject has a creatinine clearance (CrCl) of equal or greater than 45 mL/min as calculated by the Cockcroft-Gault formula.

41. The use of any one of claims 1 to 40, wherein the subject has an ECOG Performance Status of 0 or 1.

42. The use of any one of claims 1 to 41, wherein the cancer exhibits a TC score of less than 1%.

43. The use of claim 42, wherein the therapeutically effective amount of sotorasib is 960 mg.

44. The use of claim 42, wherein the TC score was determined using the Ventana PD-L1 (SP263) IHC assay.

45. The use of any one of claims 1 to 41, wherein the cancer exhibits a PD-L1 tumor proportion score (TPS) of less than 1%.

46. The use of claim 45, wherein the therapeutically effective amount of sotorasib is 960 mg.

47. The use of claim 45, wherein the TPS was determined using the PD-L1 IHC 22C3 pharmDx assay.

48. The use of any one of claims 1 to 47, wherein the cancer does not comprise an *EGFR* or *ALK* alteration.

49. The use of any one of claims 1 to 48, wherein the cancer is lung cancer.

50. The use of any one of claims 1 to 48, wherein the cancer is non-small cell lung cancer.

51. The use of any one of claims 1 to 48, wherein the cancer is nonsquamous non-small cell lung cancer.

52. The use of claim 51, wherein the nonsquamous non-small cell lung cancer is stage IV or advanced stage IIIB/C.

53. The use of any one of claims 1 to 52, wherein the patient is not to be concomitantly administered an antibody.

54. The use of claim 53, wherein the antibody is an anti-VEGF antibody.

55. The use of claim 54, the anti-VEGF antibody is bevacizumab.