SOTORASIB DOSING REGIMEN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of United States Provisional Application No. 63/162,273, filed March 17, 2021, United States Provisional Application No. 63/185,054, filed May 6, 2021, and United States Provisional Application No. 63/190,096, filed May 18, 2021, all of which are incorporated by reference herein in their entireties.

BACKGROUND

[0002] 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.

SUMMARY

[0003] Provided herein are methods of treating cancer in a patient comprising administering a total daily dose of 240 mg sotorasib to the patient, wherein the cancer is a *KRAS G12C* mutated cancer.

[0003a] Use of sotorasib in the manufacture of a medicament for treating a KRAS G12C mutated cancer in a patient wherein the patient is to be administered an initial total daily dose of 960 mg of sotorasib, and, when experiencing an adverse event; wherein the adverse event is (i) a Grade 3 or Grade 4 adverse event, or (ii) a Grade 2 elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or both, with symptoms; the use comprises: (a) withholding the initial total daily dose of sotorasib from the patient until the adverse event improves to Grade 1 or less or to baseline grade and then the patient is to be administered a first reduced total daily dose of 480 mg sotorasib, and (b) provided that the patient experiences an adverse event to the first reduced total daily dose, withholding the first reduced total daily dose of sotorasib from the patient until the adverse event improves to Grade 1 or less or to baseline grade and then the patient is to be administered a second reduced total daily dose of 240 mg sotorasib.

[0004] Also provided herein are methods of treating cancer in a patient comprising administering an initial total daily dose of 960 mg sotorasib to the patient, and administering a reduced total daily dose of sotorasib to 480 mg when the patient experiences an adverse event to the initial total daily dose, wherein the cancer is a *KRAS G12C* mutated cancer. In some examples, the methods further comprise administering a second reduced

total daily dose of sotorasib of 240 mg when the patient experiences an adverse event to the reduced total daily dose.

[0005] In various examples, the sotorasib is administered once per day. In various examples, the sotorasib is administered orally. In various examples, the patient is administered sotorasib for at least one month. In various examples, the patient is administered sotorasib for at least three months. In various examples, the patient is administered sotorasib for at least six months.

[0006] In various examples, the cancer is a solid tumor. In various examples, the cancer is non-small cell lung cancer, and in some cases, is metastatic or locally advanced and unresectable. In various examples, the cancer is colorectal cancer. In various examples, the cancer is pancreatic cancer. In various examples, the cancer is small bowel cancer, appendiceal cancer, endometrial cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell tumor, ovarian cancer, gastrointestinal neuroendocrine

tumor, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

[0007] In various examples, the patient, prior to start of sotorasib therapy, had undergone at least one other systemic cancer therapy. In various examples, the patient had undergone at least two other systemic cancer therapies. In various examples, at least one systemic cancer therapy is selected from anti-PD1 immunotherapy, anti-PDL1 immunotherapy, and platinum-based chemotherapy. In various examples, the patient has previously undergone (i) an anti-PD1 therapy or anti-PDL1 therapy, unless contraindicated, or (ii) a platinum-based chemotherapy, and (iii) a EGFR, ALK or ROS1 targeted therapy if the cancer also exhibited a mutation in *EGFR, ALK, or ROS1*. In various examples, the patient has previously undergone (i) an anti-PD1 therapy or anti-PDL1 therapy, unless contraindicated, and (ii) a platinum-based chemotherapy, and (iii) a EGFR, ALK or ROS1 targeted therapy if the cancer also exhibited a mutation in *EGFR, ALK, or ROS1*.

[0008] In various examples, the patient does not have active brain metastases within four weeks of the start of sotorasib therapy. In various examples, the patient exhibits an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

[0009] In various examples, the patient exhibits at least a stable disease (SD) after 1, 3, or 6 months of sotorasib therapy, as measured by RECIST 1.1 protocol. In various examples, the stable disease is neither sufficient shrinkage to qualify for partial response (PR) nor sufficient increase to qualify for progressive disease (PD).

[0010] In various examples, the patient exhibits at least a partial response (PR) after 1, 3, or 6 months of sotorasib therapy, as measured by RECIST 1.1 protocol. In various examples, the partial response is at least a 30% decrease in the sum of diameters of target lesions.

[0011] In various examples, the patient exhibits a progression free survival (PFS) of at least 3 months. In various examples, the patient exhibits a PFS of at least 6 months.

[0012] In various examples, the cancer exhibits a PDL1 tumor proportion score (TPS) of 1-49%. In various examples, the cancer exhibits a PDL1 tumor proportion score (TPS) of less than 1%. In various examples, the cancer exhibits a PDL1 tumor proportion score (TPS) of 50-100%. In various examples, the cancer further comprises a *STK11* mutation. In various examples, the cancer further comprises a *KEAP1* mutation. In various examples, the cancer further comprises a *STK11* wild-type. In various examples, the cancer further comprises a *KEAP1* wild-type.

BRIEF DESCRIPTION OF DRAWINGS

[0013] Figure 1 shows the mean plasma concentration time profile after once daily oral administration of 180, 360, 720, or 960 mg sotorasib on Day 1, where N indicates number of observations across data points.

[0014] Figure 2 shows the mean plasma concentration time profile after once daily oral administration of 180, 360, 720, or 960 mg sotorasib on Day 8, where N indicates number of observations across data points.

What is claimed is:

1. Use of sotorasib in the manufacture of a medicament for treating a *KRAS G12C* mutated cancer in a patient wherein the patient is to be administered an initial total daily dose of 960 mg of sotorasib, and, when experiencing an adverse event; wherein the adverse event is

(i) a Grade 3 or Grade 4 adverse event, or

(ii) a Grade 2 elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or both, with symptoms;

the use comprises:

(a) withholding the initial total daily dose of sotorasib from the patient until the adverse event improves to Grade 1 or less or to baseline grade and then the patient is to be administered a first reduced total daily dose of 480 mg sotorasib, and

(b) provided that the patient experiences an adverse event to the first reduced total daily dose, withholding the first reduced total daily dose of sotorasib from the patient until the adverse event improves to Grade 1 or less or to baseline grade and then the patient is to be administered a second reduced total daily dose of 240 mg sotorasib.

2. The use of claim 1, wherein the adverse event is an elevation of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or both.

3. The use of claim 1, wherein the adverse event is diarrhea.

4. The use of claim 1, wherein the adverse event is nausea or vomiting.

5. The use of any one of claims 1 to 4, wherein the sotorasib is to be administered once per day.

6. The use of any one of claims 1 to 5, wherein the sotorasib is to be administered orally.

7. The use of any one of claims 1 to 6, wherein the cancer is a solid tumor.

8. The use of any one of claims 1 to 7, wherein the cancer is non-small cell lung cancer.

9. The use of claim 8, wherein the cancer is metastatic non-small cell lung cancer.

10. The use of claim 9, wherein the cancer is locally advanced and unresectable.

11. The use of any one of claims 1 to 6, wherein the cancer is colorectal cancer.

12. The use of any one of claims 1 to 6, wherein the cancer is pancreatic cancer.

13. The use of any one of claims 1 to 6, wherein the cancer is small bowel cancer, appendiceal cancer, endometrial cancer, hepatobiliary cancer, small cell lung cancer, cervical cancer, germ cell tumor, ovarian cancer, gastrointestinal neuroendocrine tumor, bladder cancer, myelodysplastic/myeloproliferative neoplasms, head and neck cancer, esophagogastric cancer, soft tissue sarcoma, mesothelioma, thyroid cancer, leukemia, or melanoma.

14. The use of any one of claims 1 to 13, wherein the patient, prior to start of sotorasib therapy, had undergone at least one other systemic cancer therapy.

15. The use of claim 14, wherein the patient had undergone at least two other systemic cancer therapies.

16. The use of claim 14 or 15, wherein at least one systemic cancer therapy is selected from anti-PD1 immunotherapy, anti-PDL1 immunotherapy, and platinum-based chemotherapy.

17. The use of claim 16, wherein the patient has previously undergone (i) an anti-PD1 therapy or anti-PDL1 therapy, unless contraindicated, or (ii) a platinum-based chemotherapy, and (iii) an EGFR, ALK or ROS1 targeted therapy if the cancer also exhibited a mutation in *EGFR, ALK*, or *ROS1*.

18. The use of claim 16, wherein the patient has previously undergone (i) an anti-PD1 therapy or anti-PDL1 therapy, unless contraindicated, and (ii) a platinum-based chemotherapy, and (iii) an EGFR, ALK or ROS1 targeted therapy if the cancer also exhibited a mutation in *EGFR, ALK*, or *ROS1*.

19. The use of any one of claims 1 to 18, wherein the patient does not have brain metastases within four weeks of the start of sotorasib therapy.

20. The use of any one of claims 1 to 19, wherein the patient exhibits an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

21. The use of any one of claims 1 to 20, wherein the cancer exhibits a PDL1 tumor proportion score (TPS) of 1-49%.

22. The use of any one of claims 1 to 20, wherein the cancer exhibits a PDL1 tumor proportion score (TPS) of more than or equal to 0% and less than 1%.

23. The use of any one of claims 1 to 20, wherein the cancer exhibits a PDL1 tumor proportion score (TPS) of 50-100%.

24. The use of any one of claims 1 tp 23, wherein the cancer further comprises a *STK11* mutation.

25. The use of any one of claims 1 to 23, wherein the cancer further comprises a *KEAP1* mutation.

26. The use of any one of claims 1 to 23 and 25, wherein the cancer further comprises a *STK11* wild type.

27. The use of any one of claims 1 to 24 and 26, wherein the cancer further comprises a *KEAP1* wild type.