METHODS OF TREATING CONDITIONS WITH MUTANT P53 REACTIVATING COMPOUNDS

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application Number 63/669,209, filed July 9, 2024, U.S. Provisional Patent Application Number 63/632,458, filed April 10, 2024, U.S. Provisional Patent Application Number 63/566,417, filed March 18, 2024, and U.S. Provisional Patent Application Number 63/589,229, filed October 10, 2023, each of which is incorporated by reference herein in its entirety.

BACKGROUND

[0002] Cancer, an uncontrolled proliferation of cells, is a multifactorial disease characterized by tumor formation, growth, and in some instances, metastasis. Cells carrying an activated oncogene, damaged genome, or other cancer-promoting alterations can be prevented from replicating through an elaborate tumor suppression network. A central component of this tumor suppression network is p53, one of the most potent tumor suppressors in the cell. Both the wild-type and mutant conformations of p53 are implicated in the progression of cancer.

INCORPORATION BY REFERENCE

[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

SUMMARY

[0004] The present disclosure provides a method of treating a condition in a subject in need thereof, the method comprising administering to the subject a therapeutically-effective amount of a small molecule compound that binds a p53 mutant protein, wherein a mutational status of a KRAS gene in the subject has been previously determined.

[0005] The present disclosure provides a method of treating a condition in a subject in need thereof, the method comprising: a) based on a result of an assay performed on a biological sample of the subject, determining a mutational status of a KRAS gene in the subject; and b) based at least in part on the mutational status of the KRAS gene in the subject, administering to the subject a therapeutically-effective amount of a compound that binds a p53 mutant protein.

[0005a] In one aspect, the present disclosure provides use of a small molecule compound that binds a p53 mutant protein, in the manufacture of a medicament for the treatment of a subject with cancer wherein a mutational status of a KRAS gene in the subject has been previously determined.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIGURE 1 illustrates the dose escalation scheme for a study evaluating Compound 1 in the treatment of cancer.

[0007] FIGURE 2 is a chart illustrating day 15 (steady state) exposures of Compound 1 in human subjects.

CLAIMS

WHAT IS CLAIMED IS:

1. Use of a small molecule compound that binds a p53 mutant protein, in the manufacture of a medicament for the treatment of a subject with cancer wherein a mutational status of a KRAS gene in the subject has been previously determined.

2. The use of claim 1, wherein the mutational status of the KRAS gene in the subject has previously been determined based on an assay performed on a biological sample of the subject.

3. The use of claim 1 or claim 2, wherein the subject has been previously determined to have a mutation in a TP53 gene that encodes a p53 mutant in the subject.

4. The use of any one of claims 1-3, wherein the mutational status of the KRAS gene in the subject comprises an absence of a missense mutation at any of codons 12, 13, 59, 61, 117, and 146.

5. The use of any one of claims 1-4, wherein the mutational status of the KRAS gene in the subject comprises the lack of an oncogenic mutation.

6. The use of any one of claims 1-5, wherein the mutational status of the KRAS gene in the subject is a KRAS gene that encodes a wild type K-ras protein.

7. The use of any one of claims 1-6, wherein the p53 mutant is a p53 Y220C.

8. The use of any one of claims 2-7, wherein the assay is next-generation DNA sequencing.

9. The use of any one of claims 2-8, wherein the biological sample is a liquid biopsy.

10. The use of any one of claims 2-9, wherein the biological sample is a solid tumor sample.

11. The use of any one of claims 1-10, wherein the cancer expresses the p53 mutant.

12. The use of any one of claims 1-11, wherein the cancer is acute lymphoblastic leukemia, acute myeloid leukemia, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, appendix cancer, astrocytomas, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancers, brain tumors, such as cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, breast

cancer, bronchial adenomas, Burkitt lymphoma, carcinoma of unknown primary origin, central nervous system lymphoma, cerebellar astrocytoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, cutaneous T-cell lymphoma, desmoplastic small round cell tumor, endometrial cancer, ependymoma, esophageal cancer, Ewing's sarcoma, germ cell tumors, gallbladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor, gliomas, hairy cell leukemia, head and neck cancer, heart cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, Hypopharyngeal cancer, intraocular melanoma, islet cell carcinoma, Kaposi sarcoma, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liposarcoma, liver cancer, lung cancers, such as non-small cell and small cell lung cancer, lymphomas, leukemias, macroglobulinemia, malignant fibrous histiocytoma of bone, medulloblastoma, melanomas, mesothelioma, metastatic squamous neck cancer with occult primary, mouth cancer, multiple endocrine neoplasia syndrome, myelodysplastic syndromes, myeloid leukemia, nasal cavity and paranasal sinus cancer, nasopharyngeal carcinoma, neuroblastoma, non-Hodgkin lymphoma, non-small cell lung cancer, oral cancer, oropharyngeal cancer, osteosarcoma, ovarian cancer, high-grade serous ovarian cancer, ovarian cancer with homologous recombination deficiency, ovarian epithelial cancer, ovarian germ cell tumor, pancreatic cancer, pancreatic cancer islet cell, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineal astrocytoma, pineal germinoma, pituitary adenoma, pleuropulmonary blastoma, plasma cell neoplasia, primary central nervous system lymphoma, prostate cancer, rectal cancer, renal cell carcinoma, renal pelvis and ureter transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, sarcomas, skin cancers, skin carcinoma merkel cell, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach cancer, T-cell lymphoma, throat cancer, thymoma, thymic carcinoma, thyroid cancer, trophoblastic tumor (gestational), cancers of unknown primary site, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, Waldenström macroglobulinemia, and Wilms tumor.

13. The use of any one of claims 1-12, wherein the cancer is ovarian cancer.

14. The use of any one of claims 1-13, wherein the subject is human.

15. The use of any one of claims 1-14, wherein the compound is:

