COMBINATION OF A KRAS G12C INHIBITOR WITH AN IMMUNE CHECKPOINT INHIBITOR FOR THE TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to and benefit of U.S. Provisional Patent Application No. 63/561,193, filed March 4, 2024, the disclosure of which is hereby incorporated herein by reference in its entirety.

FIELD

[0002] The present disclosure relates generally to methods for treating cancer with a KRAS inhibitor in combination with an immune checkpoint inhibitor, and more specifically to treating cancer with a pyridopyrimidine derivative in combination with a PD-1 or PD-L1 inhibitor.

BACKGROUND

[0003] KRAS is a molecular switch. Under normal physiological conditions, the protein is bound to guanosine diphosphate (GDP) in the "off state." In response to signaling through receptor tyrosine kinases (RTKs) such as EGFR, the GDP is exchanged to guanosine triphosphate (GTP) in a process facilitated by guanine nucleotide exchange factors (GEFs) such as SOS. The GTP-bound form of KRAS is in the "on state," and interacts with proteins such as RAF and PI3K to promote downstream signaling that leads to cell proliferation and survival. KRAS can slowly hydrolyze GTP back to GDP, thus returning to the off-state, in a process facilitated by GAPs (GTPase-activating Proteins).

[0004] KRAS mutations are found in approximately 30% of all human cancers, and are highly prevalent among three of the deadliest forms of cancer: pancreatic (95%), colorectal (45%), and lung (35%). Together, these cancers occur in more than 200,000 patients annually in the US alone. One particular mutation, a glycine to cysteine substitution at position 12 (G12C), occurs in more than 40,000 patients per year. The KRAS G12C mutation impairs hydrolysis of GTP to GDP, thus trapping KRAS in the on-state and promoting cancer cell proliferation.

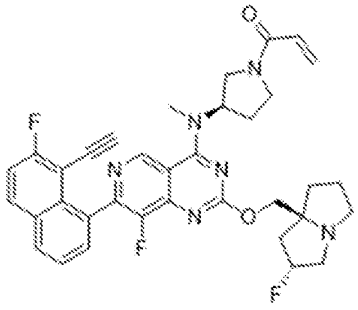
[0005] The cysteine residue of G12C provides an opportunity to develop targeted covalent drugs for this mutant KRAS. Early clinical trial results for KRAS G12C inhibitors AMG 510 and MRTX849 have shown encouraging results for non-small cell lung cancer (NSCLC), but the data are less compelling for colorectal cancer (CRC). Moreover, even in

cases where patients respond to initial treatment, there are signs that the response may be limited in duration and that resistance could arise rapidly.

[0006] Most inhibitors of KRAS mutants bind preferentially to the GDP-bound form of the protein. For example, Amgen KRAS inhibitor AMG 510 and Mirati KRAS inhibitor MRTX849 react with the GDP-bound form of KRAS G12C at least 1000-fold more rapidly than with the GTP-bound form of the protein. One form of resistance that has been observed is for cancer cells to increase signaling through RTKs, thus increasing the amount of GTP-bound KRAS, which is less affected by current inhibitors. Thus, creating a molecule that could bind to and inhibit both the GDP- and GTP-bound forms of KRAS could have substantial utility.

[0007] What is needed is a compound useful in the treatment of cancer, such as cancers characterized by KRAS G12C. What is further needed is a compound useful in the treatment of cancers characterized by KRAS G12C, wherein the compounds bind to and inhibit both the inactive GDP- and activated GTP-bound forms of KRAS. What is further needed is a compound useful in the treatment of cancers characterized by KRAS G12C, wherein the compound has improved inhibition of the GTP-bound form of KRAS G12C. What is further needed is a combination therapy for enhanced efficacy.

BRIEF SUMMARY

[0008] In one aspect, provided is a method of treating cancer in a subject in need thereof. In some embodiments, the method comprises administering a therapeutically effective amount of Compound 1  , or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor to the subject. In some embodiments, the method comprises administering a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject, wherein the subject receives an immune checkpoint inhibitor. In some embodiments, the method comprises administering a

therapeutically effective amount of an immune checkpoint inhibitor to the subject, wherein the subject receives Compound 1, or a pharmaceutically acceptable salt thereof.

[0009] In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor concurrently or separately. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor sequentially. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, before the immune checkpoint inhibitor. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, after the immune checkpoint inhibitor.

[0010] In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered concurrently or separately; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor concurrently or separately. In some embodiments, Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered sequentially; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor sequentially. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered before the immune checkpoint inhibitor is administered; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, before the immune checkpoint inhibitor. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered after the immune checkpoint inhibitor is administered; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, after the immune checkpoint inhibitor.

[0011] In some embodiments, the method further comprises administering a therapeutically effective amount of one or more additional anticancer agents. In some embodiments, the one or more additional anticancer agents comprise a chemotherapeutic agent.

[0012] In one aspect, provided is a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in treating cancer in a subject in need thereof, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered in combination with an immune checkpoint inhibitor.

[0013] In one aspect, provided is a composition comprising an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof, wherein the immune checkpoint inhibitor is administered in combination with Compound 1, or a pharmaceutically acceptable salt thereof.

[0014] In one aspect, provided is a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof.

[0015] In one aspect, provided is a combination therapeutic comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, as separate entities.

[0016] In one aspect, provided is a use of the combination therapeutic in the treatment of cancer in a subject in need thereof.

[0017] In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered concurrently or separately. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered sequentially. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered before the immune checkpoint inhibitor is administered. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered after the immune checkpoint inhibitor is administered.

[0018] In some embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Cemiplimab (Libtayo®), Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (ImfinziTM), or Dostarlimab (Jemperli). In some embodiments, the immune checkpoint inhibitor is Pembrolizumab (Keytruda®).

[0019] In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered orally. In some embodiments, the immune checkpoint inhibitor is administered intravenously or subcutaneously.

[0020] In some embodiments, the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma. In some embodiments, the cancer is a non-small cell lung cancer (NSCLC).

[0021] In some embodiments, the cancer is a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0022] In some embodiments, the subject is human.

DESCRIPTION OF THE FIGURES

[0023] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0024] **FIG. 1** depicts the average tumor volume in each group over treatment days.

[0025] **FIG. 2** depicts survival percentage in each group over treatment days.

DETAILED DESCRIPTION

[0026] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

[0027] For the avoidance of doubt, any and all disclosures of methods of treatment provided herein should also be read as disclosing Compound 1 or a pharmaceutically acceptable salt thereof, an immune checkpoint inhibitor, the combination thereof, or a pharmaceutical composition comprising the same, for use in the described methods of treatment.

[0028] The present disclosure relates generally to methods for treating cancer with a KRAS inhibitor in combination with an immune checkpoint inhibitor. The inventors have unexpectedly found that treatment with Compound 1, or a pharmaceutically acceptable salt thereof, in combination with an immune checkpoint inhibitor results in greater efficacy compared to treatment with either agent alone. The combination treatment was found to result in enhanced anti-tumor activity compared to taking either agent alone. Furthermore, the combination treatment was found to result in improved survival compared to taking either agent alone.

[0029] "Treating" a disorder with the compounds and methods discussed herein is defined as administering one or more of the compounds discussed herein, with or without additional therapeutic agents, in order to reduce or eliminate either the disorder or one or more symptoms of the disorder, or to retard the progression of the disorder or of one or more symptoms of the disorder, or to reduce the severity of the disorder or of one or more symptoms of the disorder.

[0030] A "therapeutically effective amount" of a compound is an amount of the compound, which, when administered to a subject, is sufficient to reduce or eliminate either the disorder or one or more symptoms of the disorder, or to retard the progression of the

disorder or of one or more symptoms of the disorder, or to reduce the severity of the disorder or of one or more symptoms of the disorder, or to suppress the clinical manifestation of a disorder, or to suppress the manifestation of adverse symptoms of a disorder. A therapeutically effective amount can be given in one or more administrations.

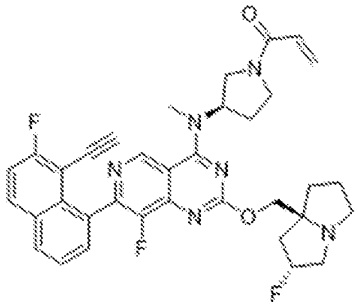
[0031] A "KRAS G12C mediated cancer" is used interchangeably herein with a "cancer characterized by KRAS G12C," and indicates that the cancer comprises cells which contain the KRAS G12C mutant.

[0032] A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable to humans and/or animals, and which, upon administration, retains at least some of the desired pharmacological activity of the parent compound. Such salts include: (a) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (b) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. Additional information on suitable pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

[0033] "In need of treatment" or "in need of prevention" as used herein means the subject is being treated by a physician or other caregiver after diagnoses of the disease, or a determination that the subject is at risk for developing the disease. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer. In some embodiments,

the subject has been determined to be at risk of developing a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a central nervous system (CNS) metastasis from a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed to be at risk of developing a central nervous system (CNS) metastasis from a KRAS G12C mediated cancer.

[0034] "Administration", "administer," and the like, as they apply to, for example, a subject, refer to contact of, for example, Compound 1 or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising same, to the subject.

[0035] In one aspect, provided is a method of treating cancer in a subject in need thereof. In some embodiments, the method comprises administering a therapeutically effective amount of Compound 1 , or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor to the subject. Compound 1 and an exemplary method of making Compound 1 are described in International Patent Application Publication No. WO 2023/081840 A1, which is incorporated herein by reference in its entirety.

[0036] In some embodiments, the method comprises administering a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject, wherein the subject receives an immune checkpoint inhibitor. In some embodiments, the method comprises administering a therapeutically effective amount of an immune checkpoint inhibitor to the subject, wherein the subject receives Compound 1, or a pharmaceutically acceptable salt thereof.

[0037] In some embodiments, the method comprises administering a therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) to the subject. In some embodiments, the method comprises administering a therapeutically effective amount of Compound 1, or a pharmaceutically

acceptable salt thereof, to the subject, wherein the subject receives Pembrolizumab (Keytruda®). In some embodiments, the method comprises administering a therapeutically effective amount of Pembrolizumab (Keytruda®) to the subject, wherein the subject receives Compound 1, or a pharmaceutically acceptable salt thereof.

[0038] In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor concurrently or separately. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor concurrently. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor separately. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor sequentially. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, before the immune checkpoint inhibitor. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, after the immune checkpoint inhibitor.

[0039] In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) concurrently or separately. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) concurrently. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) separately. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) sequentially. In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, before Pembrolizumab (Keytruda®). In some embodiments, the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, after Pembrolizumab (Keytruda®).

[0040] In some embodiments, the method further comprises administering a therapeutically effective amount of one or more additional anticancer agents. In some embodiments, the one or more additional anticancer agents comprise a chemotherapeutic agent.

[0041] In some embodiments, the method of treating cancer may result in one or more of the following: (i) a reduction in the number of cancer cells; (ii) a reduction in tumor size; (iii) inhibition of tumor growth; (iv) prolonged survival, and/or (iv) improved overall survival rates.

[0042] In one aspect, provided is a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in treating cancer in a subject in need thereof, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered in combination with an immune checkpoint inhibitor. In one aspect, provided is a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in treating cancer in a subject in need thereof, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered in combination with Pembrolizumab (Keytruda®).

[0043] In one aspect, provided is a composition comprising an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof, wherein the immune checkpoint inhibitor is administered in combination with Compound 1, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a composition comprising Pembrolizumab (Keytruda®) for use in treating cancer in a subject in need thereof, wherein Pembrolizumab (Keytruda®) is administered in combination with Compound 1, or a pharmaceutically acceptable salt thereof.

[0044] In one aspect, provided is a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof. In one aspect, provided is a composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) for use in treating cancer in a subject in need thereof.

[0045] In one aspect, provided is a combination therapeutic comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, as separate entities. In one aspect, provided is a combination therapeutic comprising Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®), as separate entities.

[0046] In one aspect, provided is a use of the combination therapeutic in the treatment of cancer in a subject in need thereof.

[0047] In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered concurrently or separately. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered concurrently. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered separately. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered sequentially. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered before the immune checkpoint inhibitor is administered. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered after the immune checkpoint inhibitor is administered.

[0048] In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) are administered concurrently or separately. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) are administered concurrently. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) are administered separately. In some embodiments, the Compound 1, or a pharmaceutically acceptable salt thereof, and Pembrolizumab (Keytruda®) are administered sequentially. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered before Pembrolizumab (Keytruda®) is administered. In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered after Pembrolizumab (Keytruda®) is administered.

[0049] In some embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor or a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a PD-1 inhibitor. In some embodiments, the immune checkpoint inhibitor is a PD-L1 inhibitor. In some embodiments, the immune checkpoint inhibitor is Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Cemiplimab (Libtayo®), Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (ImfinziTM), or Dostarlimab (Jemperli). In some embodiments, the immune checkpoint inhibitor is Pembrolizumab (Keytruda®).

[0050] In some embodiments, Compound 1, or the pharmaceutically acceptable salt thereof, is administered orally. In some embodiments, the immune checkpoint inhibitor is administered intravenously or subcutaneously.

[0051] In some embodiments, the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma. In some embodiments, the cancer is a non-small cell lung cancer (NSCLC).

[0052] In some embodiments, the cancer is a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0053] In some embodiments, the subject is human.

[0054] In some embodiments, administering Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor such as Pembrolizumab (Keytruda®) to the subject shows synergistic effect. In some embodiments, the effect of administering the combination of Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor such as Pembrolizumab (Keytruda®) to the subject is greater than the sum of the effects from administering Compound 1, or the pharmaceutically acceptable salt thereof, alone, and the effect from administering the checkpoint inhibitor such as Pembrolizumab (Keytruda®) alone. In some embodiments, the

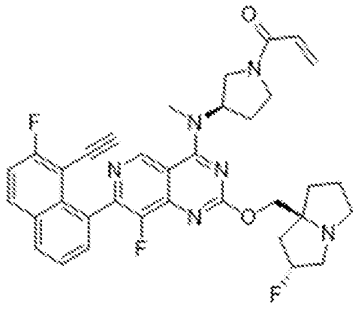
effect comprises reducing tumor volume, inhibiting growth or proliferation of cancer cells, or increasing survival of the subject, or any combination thereof.

[0055] It is to be appreciated that any one of the aspects, embodiments and/or examples described herein may be combined with one or more other aspects, embodiments and/or examples.

ENUMERATED EMBODIMENTS

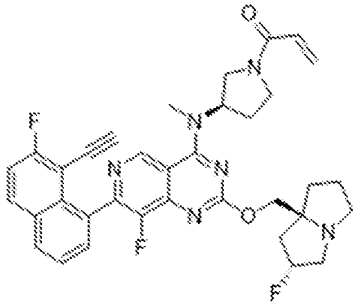
[0056] The following enumerated embodiments are representative of some aspects of the invention.

1. A method of treating cancer in a subject in need thereof, the method comprising administering a therapeutically effective amount of Compound 1



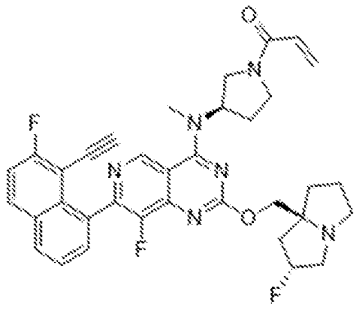
, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor to the subject.

2. A method of treating cancer in a subject in need thereof, the method comprising administering a therapeutically effective amount of Compound 1



, or a pharmaceutically acceptable salt thereof, to the subject, wherein the subject receives an immune checkpoint inhibitor.

3. A method of treating cancer in a subject in need thereof, the method comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to the



subject, wherein the subject receives Compound 1 , or a pharmaceutically acceptable salt thereof.

4. The method of embodiment 2 or 3, wherein the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor concurrently or separately.
5. The method of embodiment 2 or 3, wherein the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor sequentially.
6. The method of embodiment 2 or 3, wherein the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, before the immune checkpoint inhibitor.
7. The method of embodiment 2 or 3, wherein the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, after the immune checkpoint inhibitor.
8. The method of any one of embodiments 1-7, further comprising administering a therapeutically effective amount of one or more additional anticancer agents.
9. The method of embodiment 8, wherein the one or more additional anticancer agents comprise a chemotherapeutic agent.
10. A composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in treating cancer in a subject in need thereof, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered in combination with an immune checkpoint inhibitor.
11. A composition comprising an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof, wherein the immune checkpoint inhibitor is administered in combination with Compound 1, or a pharmaceutically acceptable salt thereof.
12. A composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof.
13. A combination therapeutic comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, as separate entities.

14. Use of the combination therapeutic of embodiment 13 in the treatment of cancer in a subject in need thereof.
15. The method, composition for use, or the use of any one of embodiments 1, 8-12, and 14, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered concurrently or separately.
16. The composition for use or the use of any one of embodiments 1, 8-12, and 14, wherein the Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered sequentially.
17. The composition for use or the use of any one of embodiments 1, 8-12, and 14, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered before the immune checkpoint inhibitor is administered.
18. The composition for use or the use of any one of embodiments 1, 8-12, and 14, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered after the immune checkpoint inhibitor is administered.
19. The method, the composition for use, the combination therapeutic, or the use of any one of embodiments 1-18, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.
20. The method, the composition for use, the combination therapeutic, or the use of any one of embodiments 1-18, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.
21. The method, the composition for use, the combination therapeutic, or the use of any one of embodiments 1-18, wherein the immune checkpoint inhibitor is Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Cemiplimab (Libtayo®), Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (ImfinziTM), or Dostarlimab (Jemperli).
22. The method, the composition for use, the combination therapeutic, or the use of any one of embodiments 1-18, wherein the immune checkpoint inhibitor is Pembrolizumab (Keytruda®).
23. The method, the composition for use, the combination therapeutic, or the use of any one of embodiments 1-22, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered orally.
24. The method, the composition for use, the combination therapeutic, or the use of any one of embodiments 1-22, wherein the immune checkpoint inhibitor is administered intravenously or subcutaneously.

25. The method, the composition for use, or the use of any one of embodiments 1-12 and 14-24, wherein the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer.
26. The method, the composition for use, or the use of any one of embodiments 1-12 and 14-24, wherein the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma, metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma.
27. The method, the composition for use, or the use of any one of embodiments 1-12 and 14-24, wherein the cancer is a non-small cell lung cancer (NSCLC).
28. The method, the composition, or the use of any one of embodiments 1-12 and 14-27, wherein the cancer is a KRAS G12C mediated cancer.
29. The method, the composition for use, or the use of any one of embodiments 1-12 and 14-28, wherein the subject has been diagnosed as having a KRAS G12C mediated cancer.
30. The method, the composition for use, or the use of any one of embodiments 1-12 and 14-29, wherein the subject is human.

EXAMPLES

[0057] The presently disclosed subject matter will be better understood by reference to the following Examples, which are provided as exemplary of the invention, and not by way of limitation.

Example 1: Tumor growth in different mice treatment groups

[0058] Forty female BALB/c mice (6-8 weeks old) were inoculated subcutaneously at the right flank with 0.3×10^6 CT26KRASG12C cells. The animals were randomized into four groups, each consisting of 10 mice: Group A received one oral (PO) dose of the vehicle on each of 25 consecutive treatment days, and one intraperitoneal (IP) dose of an isotype on each of treatment days 1, 4, and 7; Group B received one IP dose of Anti-mPD-1 (Clone: 29F.1A12) on each of treatment days 1, 4, and 7; Group C received one PO dose of Compound 1 on each of 25 consecutive treatment days; and Group D received what Groups B and C received. Treatment started when the average tumor volume reached approximately 100-120 mm^3. Tumor volume was measured three times a week. Tumor volume reaching 1,500 mm^3 was used as a surrogate endpoint for survival. Table 1 below summarizes the treatment for each group. FIG. 1 shows the average tumor volume in each group, and FIG. 2 shows survival percentage in each group over time. On day 16, more than 50% (70%) of the mice in Group A had tumor volume of greater than 1500 mm^3. On day 21, more than 50% (60%) of the mice in Group B had tumor volume of greater than 1500 mm^3. On day 32, more than 50% (70%) of the mice in Group C had tumor volume of greater than 1500 mm^3. On day 37, only 1 mouse in Group D had tumor volume greater than 1500 mm^3, and five mice in Group D showed complete tumor regression (i.e., showed no measurable tumor volume).

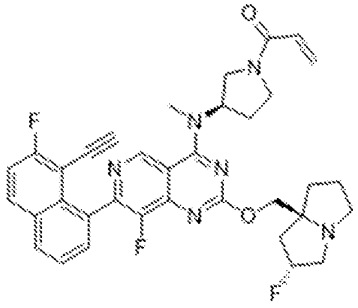
Table 1.

Group	Treatment description	Dose (mg/kg)	Dose volume (mL/kg)	Dose route	Schedule
A	Isotype	10	10	IP	One dose per day on treatment days 1, 4, and 7
	Vehicle	-	10	PO	One dose daily for 25 treatment days
B	Anti-mPD-1	10	10	IP	One dose per day on treatment days 1, 4, and 7
C	Compound 1	100	10	PO	One dose daily for 25 treatment days
D	Anti-mPD-1	10	10	IP	One dose per day on treatment days 1, 4, and 7
	Compound 1	100	10	PO	One dose daily for 25 treatment days

CLAIMS

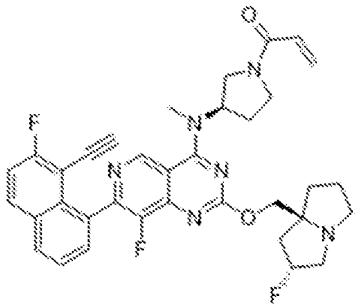
What is claimed is:

1. A method of treating cancer in a subject in need thereof, the method comprising administering a therapeutically effective amount of Compound 1



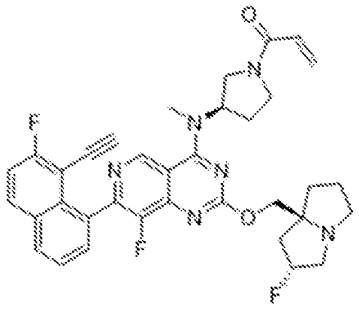
, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor to the subject.

2. A method of treating cancer in a subject in need thereof, the method comprising administering a therapeutically effective amount of Compound 1



, or a pharmaceutically acceptable salt thereof, to the subject, wherein the subject receives an immune checkpoint inhibitor.

3. A method of treating cancer in a subject in need thereof, the method comprising administering a therapeutically effective amount of an immune checkpoint inhibitor to the subject, wherein the subject receives Compound 1



, or a pharmaceutically acceptable salt thereof.

4. The method of any one of claims 1-3, further comprising administering a therapeutically effective amount of one or more additional anticancer agents.

5. The method of claim 4, wherein the one or more additional anticancer agents comprise a chemotherapeutic agent.
6. A composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, for use in treating cancer in a subject in need thereof, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered in combination with an immune checkpoint inhibitor.
7. A composition comprising an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof, wherein the immune checkpoint inhibitor is administered in combination with Compound 1, or a pharmaceutically acceptable salt thereof.
8. A composition comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor for use in treating cancer in a subject in need thereof.
9. A combination therapeutic comprising Compound 1, or a pharmaceutically acceptable salt thereof, and an immune checkpoint inhibitor, as separate entities.
10. Use of the combination therapeutic of claim 9 in the treatment of cancer in a subject in need thereof.
11. The method, composition for use, or the use of any one of claims 1-8 and 10, wherein Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered concurrently or separately; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor concurrently or separately.
12. The composition for use or the use of any one of claims 1-8 and 10, wherein Compound 1, or a pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor are administered sequentially; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, and the immune checkpoint inhibitor sequentially.
13. The composition for use or the use of any one of claims 1-8 and 10, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered before the immune checkpoint inhibitor is administered; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, before the immune checkpoint inhibitor.
14. The composition for use or the use of any one of claims 1-8 and 10, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered after the immune checkpoint inhibitor is administered; and/or the subject receives Compound 1, or the pharmaceutically acceptable salt thereof, after the immune checkpoint inhibitor.

15. The method, the composition for use, the combination therapeutic, or the use of any one of claims 1-14, wherein the immune checkpoint inhibitor is a PD-1 inhibitor.
16. The method, the composition for use, the combination therapeutic, or the use of any one of claims 1-14, wherein the immune checkpoint inhibitor is a PD-L1 inhibitor.
17. The method, the composition for use, the combination therapeutic, or the use of any one of claims 1-14, wherein the immune checkpoint inhibitor is Pembrolizumab (Keytruda®), Nivolumab (Opdivo®), Cemiplimab (Libtayo®), Atezolizumab (Tecentriq®), Avelumab (Bavencio®), Durvalumab (ImfinziTM), or Dostarlimab (Jemperli).
18. The method, the composition for use, the combination therapeutic, or the use of any one of claims 1-14, wherein the immune checkpoint inhibitor is Pembrolizumab (Keytruda®).
19. The method, the composition for use, the combination therapeutic, or the use of any one of claims 1-18, wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered orally.
20. The method, the composition for use, the combination therapeutic, or the use of any one of claims 1-18, wherein the immune checkpoint inhibitor is administered intravenously or subcutaneously.
21. The method, the composition for use, or the use of any one of claims 1-8 and 10-20, wherein the cancer is a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer.
22. The method, the composition for use, or the use of any one of claims 1-8 and 14-20, wherein the cancer is glioblastoma multiforme, lower grade glioma, head and neck squamous cell carcinoma, papillary thyroid carcinoma, anaplastic thyroid carcinoma, follicular thyroid carcinoma, lung adenocarcinoma, lung squamous cell carcinoma, breast invasive carcinoma, esophageal carcinoma, stomach adenocarcinoma, small intestine adenocarcinoma, colon adenocarcinoma, rectal adenocarcinoma, liver hepatocellular carcinoma, cholangiocarcinoma, gallbladder carcinoma, pancreatic adenocarcinoma, kidney renal clear cell carcinoma, bladder urothelial carcinoma, prostate adenocarcinoma, ovarian serous cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous carcinoma and endocervical adenocarcinoma, skin cutaneous melanoma, acute lymphoblastic leukemia, acute myeloid leukemia, chronic myeloid leukemia, plasma cell myeloma, uterine carcinosarcoma, mesothelioma, adrenocortical carcinoma, brain lower grade glioma, diffuse large B-cell lymphoma, esophageal adenocarcinoma, kidney chromophobe, kidney renal papillary cell carcinoma, pheochromocytoma and paraganglioma, sarcoma, testicular germ cell tumors, thymoma, uveal melanoma,

metastatic colorectal cancer, bladder cancer, adenoid cystic carcinoma, myelodysplastic, breast cancer, thyroid carcinoma, glioma, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma.

23. The method, the composition for use, or the use of any one of claims 1-8 and 10-20, wherein the cancer is a non-small cell lung cancer (NSCLC).
24. The method, the composition, or the use of any one of claims 1-8 and 10-23, wherein the cancer is a KRAS G12C mediated cancer.
25. The method, the composition for use, or the use of any one of claims 1-8 and 10-24, wherein the subject has been diagnosed as having a KRAS G12C mediated cancer.
26. The method, the composition for use, or the use of any one of claims 1-8 and 10-25, wherein the subject is human.