

WO 2025/179058 **PCT/US2025/016654**
PYRIDOPYRIMIDINE DERIVATIVE AS KRAS G12C INHIBITOR FOR
THE TREATMENT OF BRAIN METASTASIS

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to and benefit of U.S. Provisional Patent Application No. 63/556,346, filed February 21, 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 or preventing central nervous system (CNS) metastases with a KRAS inhibitor, and more specifically to treating CNS metastases with a pyridopyrimidine derivative.

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.

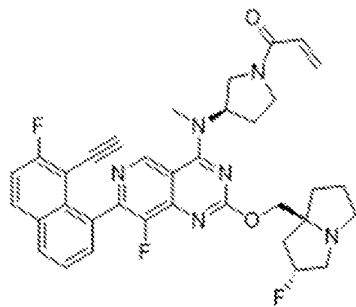
[0007] What is needed is a compound useful in the treatment of cancer, such as cancers characterized by KRAS G12C. What is further needed is a compound useful in the treatment of cancers characterized by KRAS G12C, wherein the compounds bind to and inhibit both the inactive GDP- and activated GTP-bound 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.

[0008] At diagnosis, a significant portion of patients with cancers such as KRAS G12C non-small cell lung cancer (NSCLC) will present with central nervous system (CNS) metastases. Patients with KRAS-mutated cancer such as KRAS-mutated NSCLC with CNS metastases have worse outcomes, showing low overall survival period. What is needed is a compound useful in the treatment of CNS metastases. What is further needed is a compound useful for the treatment of CNS metastases from cancers characterized by KRAS G12C. What is further needed is a compound useful in the treatment of CNS metastases from cancers characterized by KRAS G12C, wherein the compound binds to and inhibits both the inactive GDP- and activated GTP-bound forms of KRAS. What is further needed is a compound useful in the treatment of CNS metastases from cancers characterized by KRAS G12C, wherein the compound has improved inhibition of the GTP-bound form of KRAS G12C.

BRIEF SUMMARY

[0009] In one aspect, provided is a method of treating or preventing central nervous system (CNS) metastasis 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, to the subject.

In some embodiments, the method is for treating CNS metastasis. In some embodiments, the method is for preventing CNS metastasis. In some embodiments, the CNS metastasis is brain metastasis. In some embodiments, the CNS metastasis is spinal metastasis.

[0010] In some embodiments, the CNS metastasis is a CNS metastasis from a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the CNS metastasis is a CNS metastasis from 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, 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, 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 CNS metastasis is a CNS metastasis from a non-small cell lung cancer (NSCLC).

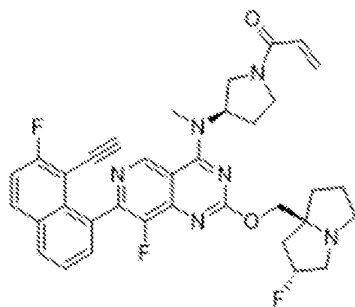
[0011] In some embodiments, the CNS metastasis is a CNS metastasis from a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0012] In some embodiments, the method further comprises administering a therapeutically effective amount of an additional anticancer agent. In some embodiments, the additional anticancer agent is a chemotherapeutic agent.

[0013] In some embodiments, there is at least about a 90% reduction in the CNS metastasis.

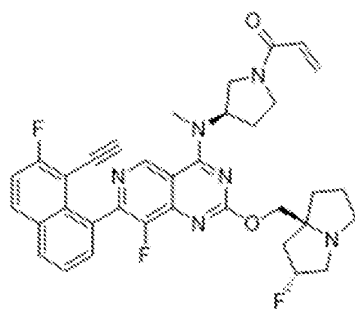
[0014] In some embodiments, the method reduces one or more symptoms of the CNS metastasis. In some embodiments, the one or more symptoms are selected from the group consisting of headache, mental changes, seizures, and weakness or numbness on one side of the body.

[0015] In one aspect, provided is a method of increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in a subject in need thereof. In some embodiments, the



method comprises administering Compound 1, or a pharmaceutically acceptable salt thereof, to the subject.

[0016] In one aspect, provided is a method of treating or preventing central nervous system (CNS) metastasis in a subject in need thereof, the method comprising increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in the subject by administering



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

[0017] In some embodiments, the subject is human.

DESCRIPTION OF THE FIGURES

[0018] The present application can be understood by reference to the following description taken in conjunction with the accompanying figures.

[0019] **FIG. 1** depicts bioluminescence imaging of mice, five treated with the vehicle (vehicle group) and the other five treated with Compound 1 (treatment group), over treatment days 0, 3, 7, 10, 14, 17, and 21.

[0020] **FIG. 2** depicts average bioluminescence as a function of treatment days for the vehicle group and the treatment group.

[0021] **FIG. 3** depicts average bioluminescence on treatment day 21 for the vehicle group and the treatment group.

DETAILED DESCRIPTION

[0022] 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. Where individual embodiments are disclosed, it should be appreciated that this disclosure is not limiting and that all embodiments may be combined. It should also be noted that references to methods of

treatment herein should be read as equivalent to compounds and/or compositions for use in said methods of treatment.

[0023] “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.

[0024] 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.

[0025] 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.

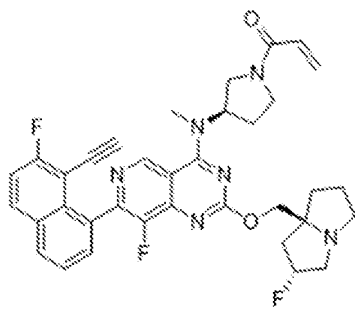
[0026] A “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable to humans and/or animals, and which, upon administration, retains at least some of the desired pharmacological activity of the parent compound. Such salts include: (a) acid addition salts, formed 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.

[0027] "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.

[0028] "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.

[0029] In one aspect, provided is a method of treating or preventing central nervous system (CNS) metastasis 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, 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.

[0030] In some embodiments, the method is for treating CNS metastasis. In some embodiments, the method is for preventing CNS metastasis. In some embodiments, the CNS metastasis is brain metastasis. In some embodiments, the CNS metastasis is spinal metastasis. In some embodiments, the CNS metastasis is both brain metastasis and spinal metastasis.

[0031] In some embodiments, the CNS metastasis is a CNS metastasis from a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer. In some embodiments, the CNS metastasis is a CNS metastasis from 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, 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, 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 CNS metastasis is a CNS metastasis from a non-small cell lung cancer (NSCLC).

[0032] In some embodiments, the CNS metastasis is a CNS metastasis from a KRAS G12C mediated cancer. In some embodiments, the subject has been diagnosed as having a KRAS G12C mediated cancer.

[0033] In some embodiments, the method further comprises administering a therapeutically effective amount of an additional anticancer agent. In some embodiments, the additional anticancer agent is a chemotherapeutic agent.

[0034] In some embodiments, the therapeutically effective amount of Compound 1, or a pharmaceutically acceptable salt thereof, and/or the therapeutically effective amount of an additional anticancer agent, are administered by any of the accepted modes of administration. In some embodiments, administration is oral, systemic (e.g. transdermal, intranasal, or by suppository), or parenteral (e.g. intramuscular, intravenous, or subcutaneous). In some embodiments, administration is preferably oral.

[0035] In some embodiments, there is at least about a 90% reduction in the CNS metastasis. In some embodiments, there is at least about a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% reduction in the CNS metastasis. In some embodiments, there is about a 100% reduction in the CNS metastasis. In some embodiments, the CNS metastasis is completely eliminated.

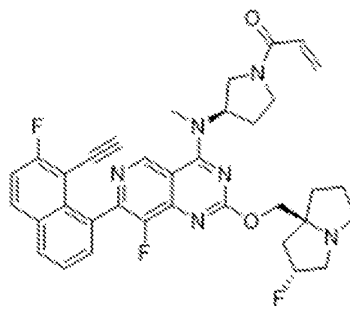
[0036] In some embodiments, there is at least about a 90% reduction in the size of the CNS metastasis. In some embodiments, there is at least about a 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% reduction in the size of the CNS metastasis. In some embodiments, there is about a 100% reduction in the size of the CNS metastasis. In some embodiments, reduction in the size of the CNS metastasis is measured by a reduction in length, area, or volume of brain lesions. In some embodiments, the reduction in the size of the CNS metastasis is measured as the % change in the sum of the longest diameters of measurable brain lesions. In some embodiments, the reduction in the size of the CNS metastasis is measured as the % change in the sum of measurable brain lesion volume.

[0037] In some embodiments, the method reduces one or more symptoms of the CNS metastasis. In some embodiments, the one or more symptoms are selected from the group consisting of headache, mental changes, seizures, and weakness or numbness on one side of the body.

[0038] In some embodiments, the subject receiving the treatment has one or more symptoms associated with CNS metastasis. In some embodiments, the one or more symptoms

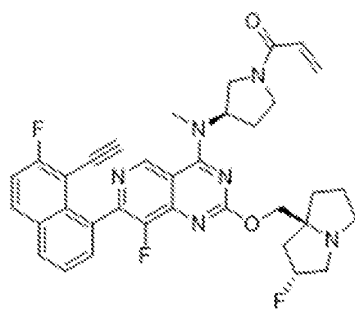
are selected from the group consisting of headache, mental changes, seizures, and weakness or numbness on one side of the body.

[0039] In one aspect, provided is a method of increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in a subject in need thereof. In some embodiments, the



method comprises administering Compound 1, or a pharmaceutically acceptable salt thereof, to the subject.

[0040] In one aspect, provided is a method of treating or preventing central nervous system (CNS) metastasis in a subject in need thereof, the method comprising increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in the subject by administering



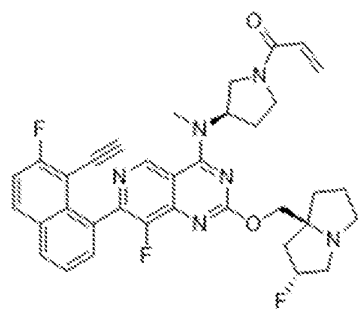
Compound 1, or a pharmaceutically acceptable salt thereof, to the subject.

[0041] In some embodiments, the subject is human.

ENUMERATED EMBODIMENTS

[0042] The following enumerated embodiments are representative of some aspects of the invention.

1. A method of treating or preventing central nervous system (CNS) metastasis in a subject, the method comprising administering a therapeutically effective amount of Compound 1



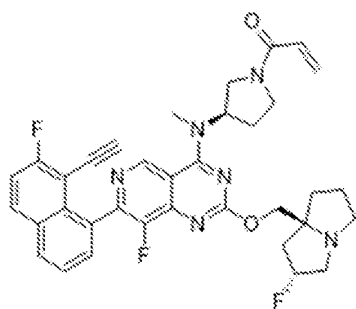
, or a pharmaceutically acceptable salt thereof, to the

subject.

2. The method of embodiment 1, wherein the method is for treating CNS metastasis.
3. The method of embodiment 1, wherein the method is for preventing CNS metastasis.
4. The method of any one of embodiments 1-3, wherein the CNS metastasis is brain metastasis.
5. The method of any one of embodiments 1-3, wherein the CNS metastasis is spinal metastasis.
6. The method of any one of embodiments 1-5, wherein the CNS metastasis is a CNS metastasis from a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer.
7. The method of any one of embodiments 1-6, wherein the CNS metastasis is a CNS metastasis from 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, 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, esophageal/stomach cancer, pediatric

Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma.

8. The method of any one of embodiments 1-7, wherein the CNS metastasis is a CNS metastasis from a non-small cell lung cancer (NSCLC).
9. The method of any one of embodiments 1-8, wherein the CNS metastasis is a CNS metastasis from a KRAS G12C mediated cancer.
10. The method of any one of embodiments 1-9, wherein the subject has been diagnosed as having a KRAS G12C mediated cancer.
11. The method of any one of embodiments 1-10, further comprising administering a therapeutically effective amount of an additional anticancer agent.
12. The method of embodiment 11, wherein the additional anticancer agent is a chemotherapeutic agent.
13. The method of any one of embodiments 1-12, wherein there is at least about a 90% reduction in the CNS metastasis.
14. The method of any one of embodiments 1-13, wherein the method reduces one or more symptoms of the CNS metastasis.
15. The method of embodiment 14, wherein the one or more symptoms are selected from the group consisting of headache, mental changes, seizures, and weakness or numbness on one side of the body.
16. A method of increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in a subject, the method comprising administering Compound 1



, or a pharmaceutically acceptable salt thereof, to the

17. The method of any one of embodiments 1-16, wherein the subject is human.

EXAMPLES

[0043] 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: Intracranial NCI-H1373-Luc NSCLC CDX (KRAS G12C; TP53)

[0044] NCI-H1373-Luc tumor cells which carry the firefly luciferase gene were inoculated intracranially with 0.3×10^6 tumor cells in 3 μ L PBS mixed with Matrigel (80:20) at the right frontal lobe of the mice using stereotaxic intracranial injection technique.

[0045] Animal health was monitored daily after intracranial inoculation. Bioluminescence intensity from the intracranially implanted NCI-H1373-luc cells measured by Xenogen machine (PerkinElmer IVIS Lumina III) is an indicator of the BM tumor burden. When bioluminescence signals reached approximately $4.513\text{E}+08$ photons/second on Day 13 after inoculation, tumor-bearing mice were randomized into vehicle or treatment group (n = 5 mice per group). The randomization date was denoted as treatment Day 0. Treatment started on the day after randomization. The treatment start day was denoted as treatment Day 1.

[0046] At each imaging time point of Days 3, 7, 10, 14, 17 and 21, the surgically inoculated mice were weighed and intraperitoneally administered luciferin at a dose of 150 mg/kg. Ten minutes after the luciferin injection, the animals were pre-anesthetized with a mixture of oxygen and isoflurane. When the animals were in a complete anesthetic state, the mice were moved into the imaging chamber for bioluminescence measurements with an IVIS (Lumina III) imaging system, as provided in FIG. 1. Tumor growth curve was plotted with bioluminescence intensity (photons/sec). The bioluminescence was measured and recorded twice per week.

[0047] Summary statistics, including mean and the SEM, are provided for the bioluminescence and relative tumor growth of each group at each time point, as summarized in Table 1 below and in FIG. 2. The treatment with Compound 1 at 100 mg/kg resulted in a significant reduction in bioluminescence signal compared to baseline suggesting robust tumor regression. FIG. 3 compares the bioluminescence on treatment day 21.

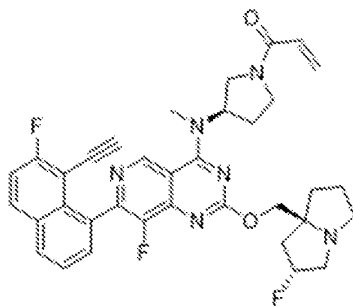
Table 1.

	Vehicle (PO, QD)		Compound 1 (100 mg/kg, PO, QD)	
Treatment day	Mean	SEM	Mean	SEM
0	4.51E+08	1.14E+08	4.52E+08	1.24E+08
3	5.84E+08	1.44E+08	2.78E+08	1.16E+08
7	1.14E+09	5.00E+08	6.77E+07	2.20E+07
10	1.56E+09	6.24E+08	2.27E+07	9.16E+06
14	3.23E+09	1.49E+09	1.44E+07	5.28E+06
17	3.89E+09	1.59E+09	1.23E+07	4.40E+06
21	4.49E+09	1.52E+09	9.15E+06	3.17E+06

CLAIMS

What is claimed is:

1. A method of treating or preventing central nervous system (CNS) metastasis in a subject in need thereof, the method comprising administering a therapeutically effective amount



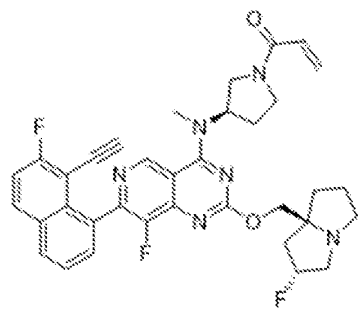
of Compound 1, or a pharmaceutically acceptable salt thereof, to the subject.

2. The method of claim 1, wherein the method is for treating CNS metastasis.
3. The method of claim 1, wherein the method is for preventing CNS metastasis.
4. The method of any one of claims 1-3, wherein the CNS metastasis is brain metastasis.
5. The method of any one of claims 1-3, wherein the CNS metastasis is spinal metastasis.
6. The method of any one of claims 1-5, wherein the CNS metastasis is a CNS metastasis from a lung, colorectal, pancreatic, bile duct, thyroid, gall bladder, uterine, mesothelioma, cervical, or bladder cancer.
7. The method of any one of claims 1-6, wherein the CNS metastasis is a CNS metastasis from 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, 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, esophageal/stomach cancer, pediatric Wilms' tumor, pediatric acute lymphoid leukemia, chronic lymphocytic leukemia, mature B-cell malignancies, pediatric neuroblastoma, or melanoma.

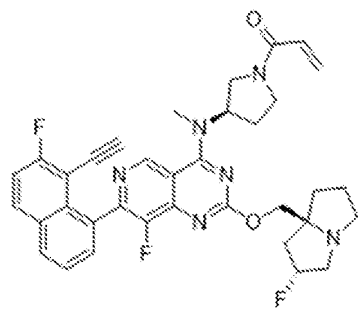
8. The method of any one of claims 1-7, wherein the CNS metastasis is a CNS metastasis from a non-small cell lung cancer (NSCLC).
9. The method of any one of claims 1-8, wherein the CNS metastasis is a CNS metastasis from a KRAS G12C mediated cancer.
10. The method of any one of claims 1-9, wherein the subject has been diagnosed as having a KRAS G12C mediated cancer.
11. The method of any one of claims 1-10, further comprising administering a therapeutically effective amount of an additional anticancer agent.
12. The method of claim 11, wherein the additional anticancer agent is a chemotherapeutic agent.
13. The method of any one of claims 1-12, wherein there is at least about a 90% reduction in the CNS metastasis.
14. The method of any one of claims 1-13, wherein the method reduces one or more symptoms of the CNS metastasis.
15. The method of claim 14, wherein the one or more symptoms are selected from the group consisting of headache, mental changes, seizures, and weakness or numbness on one side of the body.

16. A method of increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in a subject in need thereof, the method comprising administering Compound 1



, or a pharmaceutically acceptable salt thereof, to the subject.

17. A method of treating or preventing central nervous system (CNS) metastasis in a subject in need thereof, the method comprising increasing cerebrospinal fluid (CSF) exposure to an anticancer agent in the subject by administering Compound 1



, or a pharmaceutically acceptable salt thereof, to the subject.

18. The method of any one of claims 1-17, wherein the subject is human.