

THERAPIES FOR THE TREATMENT OF CANCER

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to PCT Application PCT/CN2023/123037, filed on September 29, 2023, and PCT Application PCT/CN2024/117234, filed on September 5, 2024, the content of which is incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present application relates to therapies (e.g., combination therapies) for treating cancers with an ERK1/2 inhibitor and/or a KRAS G12C inhibitor.

BACKGROUND OF THE INVENTION

[0003] The Ras/Raf/MEK/ERK pathway is a classic mitogen activated protein kinase (MAPK) signaling cascade pathway, which is involved in the activation of various growth factors, cytokines, mitogens and hormone receptors and is one of the most important signal transduction pathways controlling cell growth, differentiation and survival.

[0004] Studies have shown that abnormal activation of the Ras/Raf/MEK/ERK pathway caused by mutation or amplification is a determinant of the occurrence of various cancers. For example, KRAS is a key regulator of cytokines that shape the tumor microenvironment. KRAS mutations play a role in many cancers. The incidence of KRAS mutations in human tumors is about 22%. The KRAS G12C mutation accounts for about 44% of all KRAS mutations. G12C is a single point mutation with a glycine-to-cysteine substitution at codon 12 of the KRAS protein that favors the active, GTP-bound conformation. This promotes constitutive activation of the signaling pathways that lead to oncogenesis.

[0005] While KRAS G12C inhibitors have recently demonstrated clinical efficacy, the overall response rates (ORR) for both sotorasib and adagrasib (MRTX849), two clinical stage KRAS G12C inhibitors, are within the 30-40% range. These data indicate a significant proportion of the KRAS G12C mutation population carry primary resistance to KRAS G12C inhibition. Use of G12C inhibitors in combination with other pathway inhibitors has been explored to further enhance the anti-tumor effect of KRAS G12C inhibition is a highly relevant strategy to overcome primary resistance and to improve overall response rate. However, the use of inhibitors at these upstream nodes can quickly lead to drug resistance problems due to mutations or pathway reactivation, which

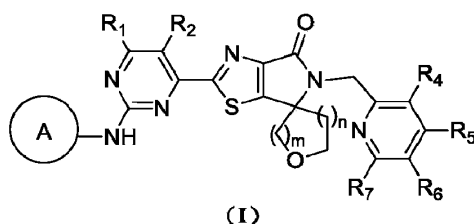
greatly limits their clinical applications. In particular, the adaptive feedback reactivation of the RAS-RAF-MEK-ERK signaling cascade is key molecular mechanisms driving primary and acquired resistance to KRAS G12C inhibitors. Achieving deeper and more durable responses in these patients remain as major challenges.

[0006] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

SUMMARY OF THE INVENTION

[0007] The present application in one aspect provides a method of treating cancer in an individual, comprising administering to the individual an effective amount of 1) an ERK1/2 inhibitor; and 2) a KRAS G12C inhibitor.

[0008] In some embodiments, the ERK1/2 inhibitor comprises an agent comprising the formula (I) or a pharmaceutically acceptable salt thereof,



wherein,

R₁ and R₂ are independently selected from H and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally substituted by 1, 2 or 3 R_a;

R₄, R₅, R₆ and R₇ are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

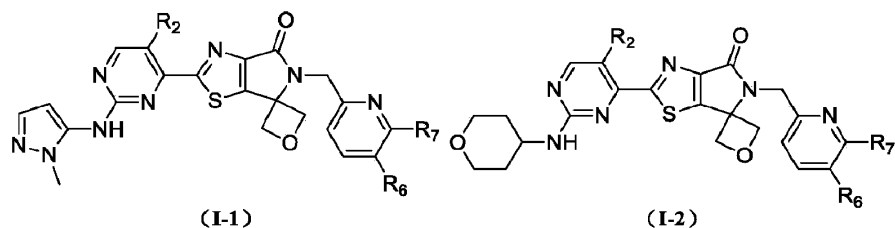
Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R;

R_a and R_c are independently selected from D, F, Cl, Br and I;

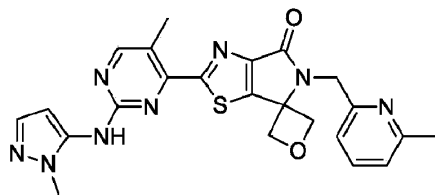
R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

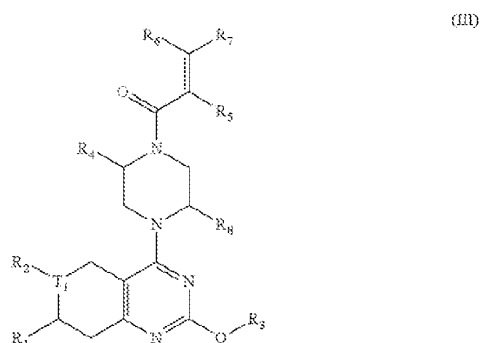
[0009] In some embodiments according to any of the methods described above, the ERK1/2 inhibitor is selected from:



[0010] In some embodiments according to any of the methods described above, the ERK1/2 inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof.



[0011] In some embodiments according to any of the methods described above, the KRAS G12C inhibitor is a small molecule. In some embodiments according to any of the methods described above, the KRAS G12C inhibitor is selected from the group consisting of: sotorasib, adagrasib, JAB-21822, GDC-6036, JDQ443, D-1553, GH35, GFH925, BPI-421286, and LY3537982, RMC-6291, RMC-8839, HBI-2438, and JNJ-74699157. In some embodiments according to any of the methods described above, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof.



wherein

T₁ is selected from O and N;

R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R₆;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R₆;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R₆;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R₆;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

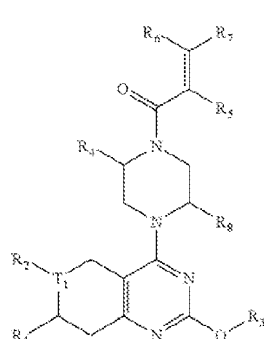
R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN;

R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C(=O)—C₁₋₃ alkylamino;

provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H.

[0012] The present application in another aspect provides a method of treating cancer in an individual, comprising administering to the individual an effective amount of 1) an ERK1/2

inhibitor; and 2) KRAS G12C inhibitor, wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T₁ is selected from O and N;

R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

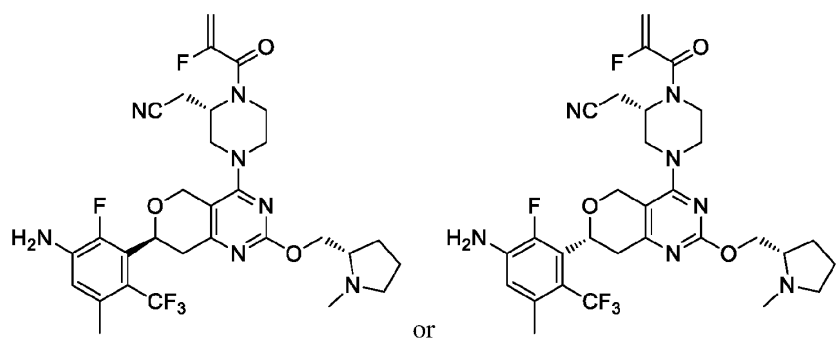
R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN;

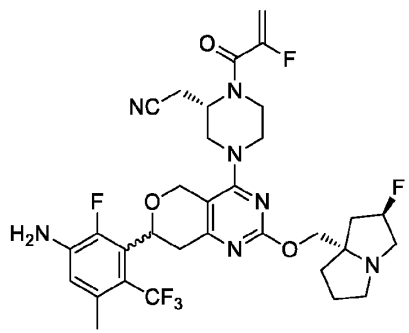
R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino;

provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H.

[0013] In some embodiments according to any of the methods described above, the KRAS G12C inhibitor comprises an agent comprising the following formula

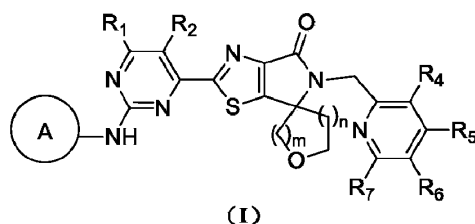


or a pharmaceutically acceptable salt thereof. In some embodiments according to any of the methods described above, the KRAS G12C inhibitor comprises an agent comprising the following formula



or a pharmaceutically acceptable salt thereof.

[0014] In some embodiments according to some of the methods described above, the ERK1/2 inhibitor is a small molecule. In some embodiments according to any of the methods described above, the ERK1/2 inhibitor is selected from the group consisting of: BVD-523 (ulixertinib), CC-90003, GDC-0994 (Ravoxertinib), KO-947, LTT462, LY3214996 (temuterkib), WX001, SCH772984, FR180204, and MK-8353. In some embodiments according to any of the methods described above, the ERK1/2 inhibitor comprises an agent comprising the formula (I) or a pharmaceutically acceptable salt thereof,



wherein,

R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ;

R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R;

R_a and R_c are independently selected from D, F, Cl, Br and I;

R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and said C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

[0015] In some embodiments according to any of the methods described above, the KRAS G12C inhibitor is administered orally. In some embodiments according to any of the methods described above, the ERK1/2 inhibitor is administered orally.

[0016] In some embodiments according to any of the methods described above, the cancer comprises one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments according to any of the methods described above, the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic

lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma, optionally wherein the cancer is selected from the group consisting of colon cancer, lung cancer and pancreatic cancer. In some embodiments according to any of the methods described above, the cancer is a solid tumor, optionally wherein the solid tumor is an advanced, unresectable, and/or metastatic solid tumor.

[0017] In some embodiments according to any of the methods described above, the cancer was previously treated with a prior KRAS G12C inhibitor, optionally wherein the cancer was previously treated with two different prior KRAS G12C inhibitors. In some embodiments according to any of the methods described above, the cancer is resistant to or has acquired resistance to a prior KRAS G12C inhibition, optionally wherein the cancer is resistant to or has acquired resistance to a prior KRAS G12C inhibitor (e.g., MRTX849, e.g., AMG510, e.g., Compound 17). In some embodiments according to any of the methods described above, the cancer is resistant to or has acquired resistance to two different prior KRAS G12C inhibitors. In some embodiments according to any of the methods described above, the individual has acquired a secondary mutation in KRAS, optionally wherein the individual has acquired a secondary KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment, further optionally the individual has acquired a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T secondary mutation after the prior KRAS inhibitor treatment, further optionally wherein the secondary mutation comprises Q61H. In some embodiments according to any of the methods described above, the cancer has an increased copy number of a mutant KRAS as compared to the cancer before the treatment of the prior KRAS G12C inhibition. In some embodiments according to any of the methods described above, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments according to any of the methods described above, the prior KRAS G12C inhibitor is or comprises sotorasib or adagrasib.

[0018] In some embodiments according to any of the methods described above, the cancer was not previously treated with a prior KRAS G12C inhibitor. In some embodiments according to any of the methods described above, the prior KRAS G12C inhibitor is or comprises sotorasib or adagrasib.

[0019] In some embodiments according to any of the methods described above, the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously or concurrently.

[0020] In some embodiments according to any of the methods described above, the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered sequentially-

[0021] In some embodiments according to any of the methods described above, optionally wherein a) the ERK1/2 inhibitor is administered prior to the KRAS G12C inhibitor or b) the KRAS G12C inhibitor is administered prior to the ERK1/2 inhibitor.

[0022] In some embodiments according to any of the methods described above, the KRAS G12C inhibitor is administered orally, intravenously, or subcutaneously. In some embodiments according to any of the methods described above, the ERK1/2 inhibitor is administered orally, intravenously, or subcutaneously.

[0023] In some embodiments according to any of the methods described above, the ERK 1/2 inhibitor is administered in one or more doses, optionally wherein the ERK 1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments according to any of the methods described above, the dose is equivalent to a dose of about 10 mg/kg to about 100 mg/kg for a mouse, optionally wherein the dose is equivalent to a dose of about 10 mg/kg to about 50 mg/kg for a mouse.

[0024] In some embodiments according to any of the methods described above, the KRAS G12C inhibitor is administered in one or more doses, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily or once every two days for at least 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments according to any of the methods described above, the dose is equivalent to a dose of about 10 mg/kg to about 100 mg/kg for a mouse, optionally wherein the dose is equivalent to a dose of about 10 mg/kg to about 50 mg/kg for a mouse.

[0025] In some embodiments according to any of the methods described above, further comprising administering to the individual an effective amount of a third therapy. In some embodiments according to any of the methods described above, wherein the third therapy comprises another anti-cancer agent. In some embodiments according to any of the methods described above, the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a

cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents, optionally wherein the anti-cancer agent is an EGFR inhibitor, further optionally wherein the EGFR inhibitor is an anti-EGFR antibody, further optionally wherein the anti-EGFR antibody is cetuximab.

[0026] In some embodiments according to any of the methods described above, the individual is a human.

[0027] In some embodiments according to any of the methods described above, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that comprises an aberration in KRAS (e.g., KRAS G12C, e.g., KRAS G12D, e.g., KRAS Q61H), optionally wherein the aberration in KRAS comprises a) a KRAS G12C mutant protein, b) a KRAS G12D mutant protein and/or c) a KRAS Q61H mutant protein.

[0028] The present application in another aspect provides a use of an ERK1/2 inhibitor and a KRAS G12C inhibitor for the manufacture of a medicament for treating cancer.

[0029] In some embodiments according to any of the methods described above, the cancer is selected from colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma. In some embodiments according to any of the methods described above, the cancer is colorectal cancer (e.g., NSCLC). In some embodiments according to any of the methods described above, the cancer is pancreatic cancer. In some embodiments according to any of the methods described above, the cancer is lung cancer.

[0030] In some embodiments according to any of the methods described above, the treatment comprises a dose that is equivalent to a dose of 25 to 50 mg/kg of the ERK 1/2 inhibitor for a mouse.

[0031] In some embodiments according to any of the methods described above, the treatment comprises a dose that is equivalent to a dose of 10 to 100 mg/kg of the KRAS G12C inhibitor.

[0032] The present application in another aspect provides a kit for treating cancer in an individual, comprising: 1) an ERK1/2 inhibitor; and 2) a KRAS G12C inhibitor.

BRIEF DESCRIPTIONS OF THE DRAWINGS

[0033] FIG. 1 shows the percentage of body weight change (%). Percentage of the body weight change of different treatment groups in female BALB/c nude mice bearing NCI-H2122 established tumors. The change was calculated based on the animal weight of the first day of dosing. Data points represent percent group mean change in BW. Error bars represent standard error of the mean (SEM).

[0034] FIG. 2 shows the tumor growth curves of different treatment groups of female BALB/c nude mice bearing NCI-H2122 xenograft tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0035] FIG. 3 shows the tumor volumes of different treatment groups of female BALB/c nude mice bearing NCI-H2122 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0036] FIG. 4 shows the weight of the tumors isolated from different treatment groups of female BALB/c nude mice bearing NCI-H2122 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0037] FIG. 5 shows the percentage body weight change of each group over time in mice bearing SW-837 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0038] FIG. 6A shows tumor growth curves of different treatment groups of mice bearing SW-837 xenograft tumors. Data points represent group mean; error bars represent the standard error of

the mean (SEM). FIGs. 6B-6C show anti-tumor effect of various treatments in mice bearing SW837 xenografts and event-free survival during and after treatment.

[0039] FIG. 7 shows the tumor volume growth curves of different treatment groups of mice bearing CR9537 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0040] FIG. 8 shows the percentage body weight change of each group over time in mice bearing CR9537 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0041] FIG. 9 shows the body weight of different groups of female BALB/c nude mice bearing AMG510-R-xMia PaCa-2 clone #2 tumors. Data points represent group mean body weight. Error bars represent standard error of the mean (SEM).

[0042] FIG. 10 shows percentage change of the body weight of different groups of female BALB/c nude mice bearing AMG510-R-xMia PaCa-2 clone #2 tumors. The change was calculated based on the animal weight of the first day of dosing. Data points represent percent group mean change in BW. Error bars represent standard error of the mean (SEM).

[0043] FIG. 11 shows the tumor growth curves of different groups of female BALB/c nude mice bearing AMG510-R-xMia PaCa-2 clone #2 tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0044] FIG. 12 shows data points represent the mouse survival curves (tumor size exceeding 1,000 mm³ as an event) of different treatment groups of BALB/c nude mice bearing AMG510-R-xMia PaCa-2 clone #2 tumors.

[0045] FIG. 13 shows overall properties of WX001.

[0046] FIG. 14A shows that in overall Kinome selectivity profiling, WX001 demonstrated favorable selectivity in Eurofins Kinome panel of 430 kinases. FIG. 14B and FIG. 14C show that in follow-up IC₅₀ analysis, potential off-target kinases (>80% inhibition at 1μM concentration from Kinome profiling) were tested by dose-titration biochemical assays. WX001 demonstrated >9.5 folds selectivity over GSK3α and >10 folds selectivity over all other potential off-target kinases.

[0047] FIG. 15A shows inhibitory effect of WX001 on downstream signaling pathway determined by phosphorylated RSK assay in BRAF or KRAS mutant cancer cell lines. FIG. 15B shows anti-proliferation effect of WX001 determined by Cell Titer-Glo method in BRAF or KRAS mutant cancer cell lines.

[0048] FIG. 16A. shows tumor growth over time in NCI-H358 NSCLC cancer model treated with WX001 or BVD523, a reference ERK1/2 inhibitor. FIG. 16B shows tumor growth over time in HCT-116 colorectal cancer model treated with WX001 or reference ERK1/2 inhibitors BVD523 and LY3214996.

[0049] FIG. 17A shows that NCI-H358 NSCLC tumor growth after treatment with KRAS G12C inhibitor monotherapy of MRTX849, AMG510 and Compound 17, or combination of Compound 17 and WX001. FIG. 17B shows a summary of complete tumor remission rate in each treatment group.

[0050] FIG. 18 shows percentage of the body weight change of different treatment groups in female BALB/c nude mice bearing NCI-H1373 established tumors. The change was calculated based on the animal weight of the first day of dosing. Data points represent percent group mean change in BW. Error bars represent standard error of the mean (SEM).

[0051] FIG. 19 shows body weight of different treatment groups in female BALB/c nude mice bearing NCI-H1373 established tumors. Data points represent group mean BW. Error bars represent standard error of the mean (SEM).

[0052] FIG. 20 shows tumor growth curves of different treatment groups female BALB/c nude mice bearing NCI-H1373 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

[0053] FIG. 21 shows tumor growth curves of different treatment groups female BALB/c nude mice bearing NCI-H1373 established tumors. Data points represent group mean; error bars represent standard error of the mean (SEM).

DETAILED DESCRIPTION OF THE INVENTION

[0054] The present application provides combination therapies for treating KRAS mutant cancer (e.g., KRAS G12C cancer) that comprises an ERK1/2 inhibitor and a KRAS inhibitor (e.g., KRAS G12C inhibitor). As shown in the Examples, the combination therapies provide advantageous and efficacious effects of treating KRAS mutant cancers (e.g., KRAS G12C cancers) while being safely tolerated.

Definitions

[0055] Before describing the embodiments in detail, it is to be understood that the present disclosure is not limited to particular compositions or biological systems, which can, of course,

vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only and is not intended to be limiting.

[0056] As used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a molecule” optionally includes a combination of two or more such molecules, and the like.

[0057] The term “about” as used herein refers to the usual error range for the respective value readily known to the skilled person in this technical field. Reference to “about” a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se.

[0058] It is understood that aspects and embodiments of the present disclosure include “comprising,” “consisting,” and “consisting essentially of” aspects and embodiments.

[0059] As used herein, the term “treatment” refers to clinical intervention designed to alter the natural course of the individual or cell being treated during the course of clinical pathology. Desirable effects of treatment include decreasing the rate of disease progression, ameliorating or palliating the disease state, and remission or improved prognosis. For example, an individual is successfully “treated” if one or more symptoms associated with cancer are mitigated or eliminated, including, but are not limited to, reducing the proliferation of (or destroying) cancerous cells, decreasing symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, and/or prolonging survival of individuals. In some embodiments, “treating” a disease such as cancer refers to delaying progression of the disease, i.e., deferring, hindering, slowing, retarding, stabilizing, and/or postponing development of the disease (such as cancer or a KRAS G12C cancer). This delay can be of varying lengths of time, depending on the history of the disease and/or individual being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop the disease. For example, a late-stage cancer, such as development of metastasis, may be delayed.

[0060] An “effective amount” is at least the minimum amount required to effect a measurable improvement or prevention of a particular disease (e.g., cancer). An effective amount herein may vary according to factors such as the disease state, age, sex, and weight of the patient, and the ability of a therapeutic agent (or combination of therapeutic agents) to elicit a desired response in

the individual. An effective amount is also one in which any toxic or detrimental effects of the treatment are outweighed by the therapeutically beneficial effects. For therapeutic use, beneficial or desired results include clinical results such as decreasing one or more symptoms resulting from the disease, increasing the quality of life of those suffering from the disease, decreasing the dose of other medications required to treat the disease, enhancing effect of another medication such as via targeting, delaying the progression of the disease, and/or prolonging survival. In the case of cancer or tumor, an effective amount of the drug may have the effect in reducing the number of cancer cells; reducing the tumor size; inhibiting (i.e., slow to some extent or desirably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and desirably stop) tumor metastasis; inhibiting to some extent tumor growth; and/or relieving to some extent one or more of the symptoms associated with the disorder. An effective amount can be administered in one or more administrations. For purposes of this disclosure, an effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to accomplish therapeutic treatment either directly or indirectly. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an “effective amount” may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

[0061] As used herein, the term “subject” for purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, horses, cats, cows, etc. Preferably, the mammal is human.

[0062] The terms “subject” and “patient” are used interchangeably and include mammals such as humans and non-human primates, as well as rabbits, rats, mice, goats, pigs, and other mammalian species. The term does not necessarily indicate that the subject has been diagnosed with a particular disease, but typically refers to an individual under medical supervision.

[0063] The term “prevent”, “preventing”, or “prevention”, as used herein in the context of preventing a condition, refers generally to preventing or delaying the onset of the disease, or preventing the manifestation of clinical or subclinical symptoms thereof in a subject (whether a human or animal), for example, preventing the disease from occurring in a subject predisposed to the condition or disease but has not yet been diagnosed as having it.

[0064] The term “pharmaceutically acceptable,” as used herein, means that the vehicle, diluent, excipient and/or salts thereof, are chemically and/or physically is compatible with other ingredients in the formulation, and the physiologically compatible with the recipient.

[0065] As used herein, the term “a pharmaceutically acceptable carrier and/or excipient” refers to a carrier and/or excipient pharmacologically and/or physiologically compatible with a subject and an active agent, which is well known in the art (see, e.g., Remington's Pharmaceutical Sciences. Edited by Gennaro AR, 19th ed. Pennsylvania: Mack Publishing Company, 1995), and includes, but is not limited to pH adjuster, surfactant, adjuvant and ionic strength enhancer. For example, the pH adjuster includes, but is not limited to, phosphate buffer; the surfactant includes, but is not limited to, cationic, anionic, or non-ionic surfactant, e.g., Tween-80; the ionic strength enhancer includes, but is not limited to, sodium chloride.

[0066] As used herein, the term “adjuvant” refers to a non-specific immunopotentiator, which can enhance immune response to an antigen or change the type of immune response in an organism when it is delivered together with the antigen to the organism or is delivered to the organism in advance. There are a variety of adjuvants, including, but not limited to, aluminium adjuvants (for example, aluminum hydroxide), Freund's adjuvants (for example, Freund's complete adjuvant and Freund's incomplete adjuvant), coryne bacterium parvum, lipopolysaccharide, cytokines, and the like. Freund's adjuvant is the most commonly used adjuvant in animal experiments now. Aluminum hydroxide adjuvant is more commonly used in clinical trials.

[0067] The pharmaceutically acceptable salt disclosed herein can be prepared from the parent compound that contains an acidic or basic moiety by conventional chemical methods. Generally, such salt can be prepared by reacting the free acid or base form of the compound with a stoichiometric amount of an appropriate base or acid in water or an organic solvent or a mixture thereof.

[0068] Compounds disclosed herein may be present in a specific geometric or stereoisomeric form. The present disclosure contemplates all such compounds, including cis and trans isomers, (-)- and (+)-enantiomers, (R)- and (S)-enantiomers, diastereoisomer, (D)-isomer, (L)-isomer, and a racemic mixture and other mixtures, for example, a mixture enriched in enantiomer or diastereoisomer, all of which are encompassed within the scope disclosed herein. The substituent such as alkyl may have an additional asymmetric carbon atom. All these isomers and mixtures thereof are encompassed within the scope disclosed herein.

[0069] Compounds disclosed herein may contain an unnatural proportion of atomic isotopes at one or more of the atoms that make up the compounds. For example, a compound may be labeled with a radioisotope such as tritium (^3H), iodine-125 (^{125}I) or C-14(^{14}C). For another example, hydrogen can be replaced by heavy hydrogen to form a deuterated drug. The bond between deuterium and carbon is stronger than that between ordinary hydrogen and carbon. Compared with undeuterated drugs, deuterated drugs have advantages of reduced toxic side effects, increased drug stability, enhanced efficacy, and prolonged biological half-life of drugs. All changes in the isotopic composition of compounds disclosed herein, regardless of radioactivity, are included within the scope of the present disclosure.

[0070] The term "optional" or "optionally" means that the subsequent event or condition may occur but not requisite, that the term includes the instance in which the event or condition occurs and the instance in which the event or condition does not occur.

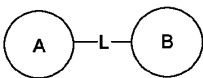
[0071] The term "substituted" means that one or more than one hydrogen atoms on a specific atom are substituted by a substituent, including deuterium and hydrogen variants, as long as the valence of the specific atom is normal and the substituted compound is stable. When the substituent is oxo (i.e., $=\text{O}$), it means two hydrogen atoms are substituted. Positions on an aromatic ring cannot be substituted by oxo. The term "optionally substituted" means an atom can be substituted by a substituent or not, unless otherwise specified, the species and number of the substituent may be arbitrary so long as being chemically achievable.

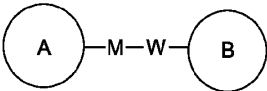
[0072] When any variable (such as R) occurs in the constitution or structure of the compound more than once, the definition of the variable at each occurrence is independent. Thus, for example, if a group is substituted by 0-2 R, the group can be optionally substituted by up to two R, wherein the definition of R at each occurrence is independent. Moreover, a combination of the substituent and/or the variant thereof is allowed only when the combination results in a stable compound.

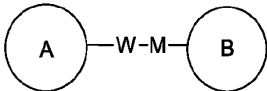
[0073] When the number of a linking group is 0, such as $-(\text{CRR})_0-$, it means that the linking group is a single bond.

[0074] When one of variables is a single bond, it means that the two groups linked by the single bond are connected directly. For example, when L in A-L-Z represents a single bond, the structure of A-L-Z is actually A-Z.

[0075] When an enumerated linking group does not indicate its linking direction, its linking

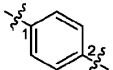
direction is arbitrary. For example, when the linking group L in  is -M-W-, the -M-W- can be linked to the ring A and the ring B in the same direction as the reading order from left

to right to constitute , or can be linked to the ring A and the ring B in the

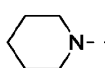
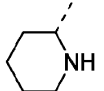
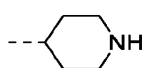
reverse direction as the reading order from left to right to constitute . A

combination of the linking groups, substituents and/or variants thereof is allowed only when such combination can result in a stable compound.

[0076] Unless otherwise specified, when a group has one or more connectable sites, any one or more sites of the group can be connected to other groups through chemical bonds. Where the connection position of the chemical bond is variable, and there is H atom(s) at a connectable site(s), when the connectable site(s) having H atom(s) is connected to the chemical bond, the number of H atom(s) at this site will correspondingly decrease as the number of the connected chemical bond increases, and the group will become a group of corresponding valence. The chemical bond between the site and other groups can be represented by a straight solid bond () , a straight dashed bond () , or a wavy line (). For example, the straight solid bond in -OCH₃ indicates that the group is connected to other groups through the oxygen atom in the group; the straight dashed bond in  indicates that the group is connected to other groups through two ends of the nitrogen atom

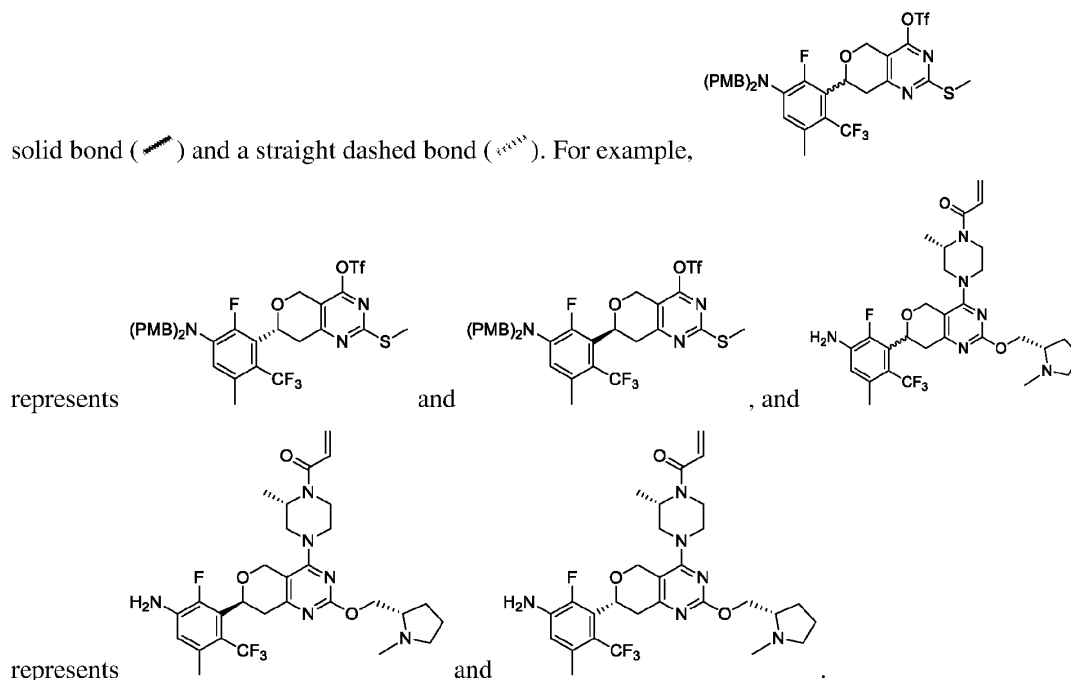
in the group; the wavy line in  indicates that the group is connected to other groups

through the 1- and 2-carbon atoms in the phenyl group;  indicates that any connectable site on the piperidinyl group can be connected to other groups through one chemical bond, including at

least four connection ways, , ,  and ; even if a H atom is

drawn on -N-,  still includes the connection way of ; it's just that when one chemical bond is connected, the H at this site will be reduced by one, and the group will become the corresponding monovalent piperidinyl group.

[0077] Unless otherwise specified, a wedged solid bond () and a wedged dashed bond () indicate the absolute configuration of a stereocenter; a straight solid bond () and a straight dashed bond () indicate the relative configuration of a stereocenter; a wavy line () indicates a wedged solid bond () or a wedged dashed bond () ; or a wavy line () indicates a straight



[0078] Unless otherwise specified, the term "enriched in one isomer", "isomer enriched", "enriched in one enantiomer" or "enantiomeric enriched" means that the content of one isomer or enantiomer is less than 100%, and the content of the isomer or enantiomer is 60% or more, or 70% or more, or 80% or more, or 90% or more, or 95% or more, or 96% or more, or 97% or more, or 98% or more, or 99% or more, or 99.5% or more, or 99.6% or more, or 99.7% or more, or 99.8% or more, or 99.9% or more.

[0079] Optically active (R)- and (S)-isomer, or D and L isomer can be prepared using chiral synthesis or chiral reagents or other conventional techniques. If one kind of enantiomer of certain compound disclosed herein is to be obtained, the pure desired enantiomer can be obtained by asymmetric synthesis or derivative action of chiral auxiliary followed by separating the resulting

diastereomeric mixture and cleaving the auxiliary group. Alternatively, when the molecule contains a basic functional group (such as amino) or an acidic functional group (such as carboxyl), the compound reacts with an appropriate optically active acid or base to form a salt of the diastereomeric isomer which is then subjected to diastereomeric resolution through the conventional method in the art to afford the pure enantiomer. In addition, the enantiomer and the diastereoisomer are generally isolated through chromatography which uses a chiral stationary phase and optionally combines with a chemical derivative method (for example, carbamate generated from amine).

[0080] Unless otherwise specified, the term "C1-6 alkyl" is used to represent a linear or branched saturated hydrocarbon group composed of 1 to 6 carbon atoms. The C1-6 alkyl includes C1-5, C1-4, C1-3, C1-2, C2-6, C2-4, C6, and C5 alkyl, etc. It may be monovalent (such as methyl), divalent (such as methylene) or multivalent (such as methenyl). Examples of the C1-6 alkyl include, but are not limited to, methyl (Me), ethyl (Et), propyl (including n-propyl and isopropyl), butyl (including n-butyl, isobutyl, s-butyl and t-butyl), pentyl (including n-pentyl, isopentyl and neopentyl), hexyl, and the like.

[0081] Unless otherwise specified, the term "C1-3 alkyl" is used to represent a linear or branched saturated hydrocarbon group composed of 1 to 3 carbon atoms. The C1-3 alkyl includes C1-2 alkyl, C2-3 alkyl, etc. It may be monovalent (such as methyl), divalent (such as methylene) or multivalent (such as methenyl). Examples of the C1-3 alkyl include, but are not limited to, methyl (Me), ethyl (Et), propyl (including n-propyl and isopropyl), and the like.

[0082] Unless otherwise specified, the term "C1-3 alkoxy" means alkyl groups containing 1 to 3 carbon atoms and attached to the remainder of a molecule by an oxygen atom. The C1-3 alkoxy group includes C1-2, C2-3, C3, and C2 alkoxy groups, and the like. Examples of C1-3 alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (including n-propoxy and isopropoxy), and the like.

[0083] Unless otherwise specified, the term "C1-3 alkylamino" means alkyl groups containing 1 to 3 carbon atoms and attached to the remainder of a molecule by an amino group. The C1-3 alkylamino group includes C1-2, C3 and C2 alkylamino groups and the like. Examples of C1-3 alkylamino groups include, but are not limited to -NHCH₃, -N(CH₃)₂, -NHCH₂CH₃, -N(CH₃)CH₂CH₃, -NHCH₂CH₂CH₃, -NHCH₂(CH₃)₂, and the like.

[0084] Unless otherwise specified, "C2-3 alkenyl" is used to represent a linear or branched hydrocarbon group composed of 2 to 3 carbon atoms containing at least one carbon-carbon double

bond, wherein the carbon-carbon double bond can be located at any position of the group. The C2-3 alkenyl includes C3 and C2 alkenyl. The C2-3 alkenyl may be monovalent, divalent or multivalent. Examples of the C2-3 alkenyl include, but are not limited to, vinyl, propenyl, and the like.

[0085] Unless otherwise specified, "C2-3 alkynyl" is used to represent a linear or branched hydrocarbon group composed of 2 to 3 carbon atoms containing at least one carbon-carbon triple bond, wherein the carbon-carbon triple bond can be located at any position of the group. The C2-3 alkynyl includes C3 and C2 alkynyl. Examples of the C2-3 alkynyl include, but are not limited to, ethynyl, propynyl, and the like.

[0086] Unless otherwise specified, the terms "C6-10 aromatic ring" and "C6-10 aryl" may be used interchangeably in this disclosure. The term "C6-10 aromatic ring" or "C6-10 aryl" means a cyclic hydrocarbon group having a conjugated pi electron system and composed of 6 to 10 carbon atoms. It may be a monocyclic, fused bicyclic or fused tricyclic ring system, wherein each ring is aromatic. It may be monovalent, divalent or multivalent. The C6-10 aryl includes C6-9, C9, C10 and C6 aryl, etc. Examples of C6-10 aryl include, but are not limited to, phenyl, naphthyl (including 1-naphthyl and 2-naphthyl, etc.).

[0087] Unless otherwise specified, the terms "5- to 10-membered heteroaromatic ring" and "5- to 10-membered heteroaryl" may be used interchangeably. The term "5- to 10-membered heteroaryl" means a cyclic group having a conjugated pi electron system and composed of 5 to 10 ring atoms, in which 1, 2, 3 or 4 ring atoms are heteroatoms independently selected from O, S and N, and the remainder is carbon atoms. It may be a monocyclic, fused bicyclic or fused tricyclic ring system, wherein each ring is aromatic, and wherein the nitrogen atom is optionally quaternized and the nitrogen and sulfur heteroatoms are optionally oxidized (i.e., NO and S(O)_p, p is 1 or 2). A 5- to 10-membered heteroaryl can be attached to the remainder of the molecule through a heteroatom or a carbon atom. The 5- to 10-membered heteroaryl group includes 5- to 8-membered, 5- to 7-membered, 5- to 6-membered, 5-membered and 6-membered heteroaryl groups. Examples of the 5- to 10 membered heteroaryl include, but are not limited to, pyrrolyl (including N-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, and the like), pyrazolyl (including 2-pyrazolyl and 3-pyrazolyl, and the like), imidazolyl (including N-imidazolyl, 2-imidazolyl, 4-imidazolyl, and 5-imidazolyl, and the like), oxazolyl (including 2-oxazolyl, 4-oxazolyl, and 5-oxazolyl, and the like), triazolyl (1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, 1H-1,2,4-triazolyl and 4H-1,2,4-triazolyl, and the like), tetrazolyl, isoxazolyl (3-isoxazolyl, 4-isoxazolyl and 5-isoxazolyl, and the like), thiazolyl (including 2-thiazolyl, 4-thiazolyl

and 5-thiazolyl, and the like), furyl (including 2-furyl and 3-furyl, and the like), thienyl (including 2-thienyl and 3-thienyl, and the like), pyridyl (including 2-pyridyl, 3-pyridyl and 4-pyridyl, and the like), pyrazinyl or pyrimidinyl (including 2-pyrimidinyl and 4-pyrimidinyl, and the like), benzothiazolyl (including 5-benzothiazolyl, and the like), purinyl, benzimidazolyl (including 2-benzimidazolyl, and the like), benzoxazolyl, indolyl (including 5-indolyl, and the like), isoquinolyl (including 1-isoquinolyl, 5-isoquinolyl, and the like), quinoxalinyl (including 2-quinoxalinyl, 5-quinoxalinyl, and the like) or quinolyl (including 3-quinolyl, 6-quinolyl, and the like).

[0088] Unless otherwise specified, the term "4- to 8-membered heterocycloalkyl" alone or in combination with other terms respectively represents a saturated cyclic group composed of 4 to 8 ring atoms, in which 1, 2, 3 or 4 ring atoms are heteroatoms independently selected from O, S and N, and the remainder is carbon atoms, wherein the nitrogen atom is optionally quaternized, and the nitrogen and sulfur heteroatoms are optionally oxidized (i.e., NO and S(O)_p, p is 1 or 2). The ring comprises monocyclic and bicyclic ring systems, wherein the bicyclic ring systems comprise spiro, fused, and bridged cyclic rings. In addition, with respect to the "4- to 8-membered heterocycloalkyl", the heteroatom may be present on the position of attachment of the heterocycloalkyl group to the remainder of a molecule. The 4- to 8-membered heterocycloalkyl includes 4-6 membered, 5-6 membered, 4 membered, 5 membered, and 6 membered heterocycloalkyl, etc. Examples of the 4- to 8-membered heterocycloalkyl include, but are not limited to, azetidiny, oxetanyl, thietanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrothienyl (including tetrahydrothien-2-yl and tetrahydrothien-3-yl and the like), tetrahydrofuranly (including tetrahydrofuran-2-yl and the like), tetrahydropyranyl, piperidinyl (including 1-piperidinyl, 2-piperidinyl and 3-piperidinyl and the like), piperazinyl (including 1-piperazinyl and 2-piperazinyl and the like), morpholinyl (including 3-morpholinyl and 4-morpholinyl and the like), dioxanyl, dithianyl, isoxazolidinyl, isothiazolidinyl, 1,2-oxazinyl, 1,2-thiazinyl, hexahydropyridazinyl, homopiperazinyl, homopiperidinyl or dioxepanyl, and the like.

[0089] Unless otherwise specified, C_n-n+m or C_n-C_{n+m} includes any specific case of n to n+m carbons, for example, C₁-12 includes C₁, C₂, C₃, C₄, C₅, C₆, C₇, C₈, C₉, C₁₀, C₁₁ and C₁₂, also includes any range from n to n+m, for example, C₁-12 includes C₁-3, C₁-6, C₁-9, C₃-6, C₃-9, C₃-12, C₆-9, C₆-12 and C₉-12, etc.; similarly, n membered to n+m membered indicates that the number of atoms on a ring is n to n+m, for example, 3-12 membered ring includes 3 membered ring, 4 membered ring, 5 membered ring, 6 membered ring, 7 membered ring, 8 membered ring, 9

membered ring, 10 membered ring, 11 membered ring, and 12 membered ring, also includes any range from n to n+m, for example, 3-12 membered ring includes 3-6 membered ring, 3-9 membered ring, 5-6 membered ring, 5-7 membered ring, 6-7 membered ring, 6-8 membered ring, and 6-10 membered ring, and the like.

[0090] Compounds disclosed herein can be prepared by a variety of synthetic methods well known to those skilled in the art, including the following enumerated embodiment, the embodiment formed by the following enumerated embodiment in combination with other chemical synthesis methods, and equivalent replacement well known to those skilled in the art. Alternative embodiments include, but are not limited to the embodiment disclosed herein.

[0091] The structures of compounds disclosed herein can be confirmed by conventional methods well known to those skilled in the art. If the present disclosure relates to an absolute configuration of a compound, the absolute configuration can be confirmed by conventional techniques in the art, such as single crystal X-Ray diffraction (SXRD). In the single crystal X-Ray diffraction (SXRD), the diffraction intensity data of the cultivated single crystal is collected using a Bruker D8 venture diffractometer with a light source of CuK α radiation in a scanning mode of ϕ/ω scan; after collecting the relevant data, the crystal structure is further analyzed by the direct method (Shelxs97) to confirm the absolute configuration.

[0092] Solvents used in the present disclosure are commercially available.

[0093] Compounds are named according to general naming principles in the art or by ChemDraw® software, and commercially available compounds are named with their vendor directory names.

[0094] The pharmaceutically acceptable salt disclosed herein can be prepared from the parent compound that contains an acidic or basic moiety by conventional chemical methods. Generally, such salt can be prepared by reacting the free acid or base form of the compound with a stoichiometric amount of an appropriate base or acid in water or an organic solvent or a mixture thereof.

[0095] All references cited herein, including patent applications, patent publications, and UniProtKB/Swiss-Prot Accession numbers are herein incorporated by reference in their entirety, as if each individual reference were specifically and individually indicated to be incorporated by reference.

Methods of Treating Cancer

[0096] Provided herein are methods of treating cancer harboring a KRAS G12C mutation (*i.e.*, a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein) in a subject, comprising administering to the subject an effective amount of (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the ERK1/2 inhibitor is used for the manufacture of a medicament for treating cancer, wherein the treatment is in combination with a KRAS G12C inhibitor.

[0097] In some embodiments, the ERK 1/2 inhibitor is, e.g., a small molecule, a polypeptide (such as an antibody), a peptide, an antisense oligonucleotide that inhibits the activity of the ERK1 and/or ERK2 protein. Exemplary small molecule ERK 1/2 inhibitors that find use with the methods provided herein include, without limitation, e.g., BVD-523 (ulixertinib), CC-90003, GDC-0994 (Ravoxertinib), KO-947, LTT462, LY3214996 (temuterkib), WX001, SCH772984, FR180204, MK-8353. In some embodiments, the KRAS G12C inhibitor is a small molecule. Exemplary small molecule KRAS G12C inhibitors that find use with the methods provided herein include, without limitation, e.g., Compound 17, sotorasib, adagrasib, JAB-21822, GDC-6036, JDQ443, D-1553, GH35, GFH925, BPI-421286, and LY3537982, RMC-6291, HBI-2438, and JNJ-74699157. In some embodiments, the KRAS G12C inhibitor is Compound 17. Additional details regarding these and other exemplary small molecule KRAS G12C inhibitors are described in further detail below.

[0098] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the ERK 1/2 inhibitor is a small molecule. In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is a small molecule. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma. In some

embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is naïve to KRAS G12C inhibition treatment. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method further comprises administering to the individual an effective amount of a third therapy comprising another anti-cancer agent, optionally wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein.

[0099] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the ERK 1/2 inhibitor is a small molecule. In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is a small molecule. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced,

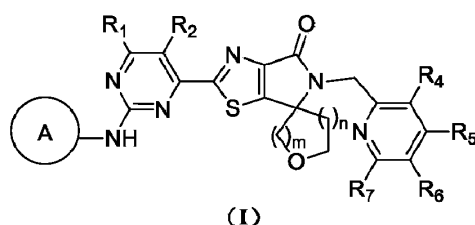
unresectable, and/or metastatic solid tumor. In some embodiment, the cancer (e.g., cancer cells) is only partially responding to the prior KRAS treatment. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method further comprises administering to the individual an effective amount of a third therapy comprising another anti-cancer agent, optionally wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein.

[0100] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the ERK 1/2 inhibitor is a small molecule. In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is a small molecule. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g.,

has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer was previously treated with a KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method further comprises administering to the individual an effective amount of a third therapy comprising another anti-cancer agent, optionally wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents. In some embodiments, the method comprises selecting the

individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the cancer further comprises a KRAS Q61H mutation. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

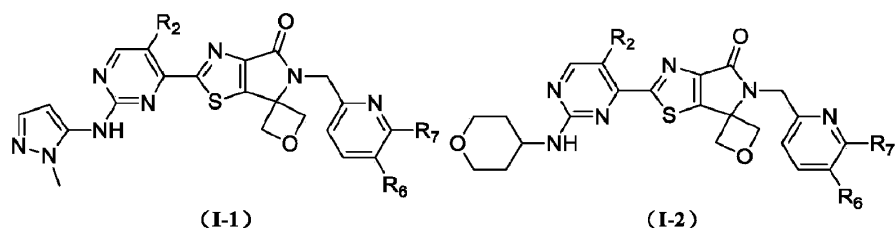
[0101] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK1/2 inhibitor; and (2) KRAS G12C inhibitor, wherein the ERK 1/2 inhibitor comprises an agent comprising formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and said C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant (e.g., has acquired resistance to) to KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after

the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

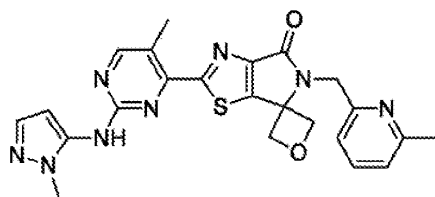
[0102] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK1/2 inhibitor; and (2) KRAS G12C inhibitor, wherein the ERK 1/2 inhibitor is selected from the following formulas or a pharmaceutically acceptable salt thereof,



In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second

KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

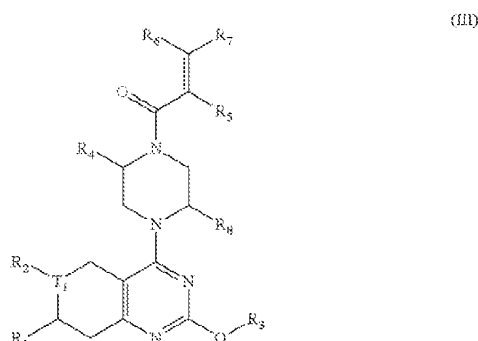
[0103] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK1/2 inhibitor; and (2) KRAS G12C inhibitor, wherein the ERK 1/2 inhibitor is the following formula or a pharmaceutically acceptable salt thereof,



In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS

inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0104] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK1/2 inhibitor; and (2) KRAS G12C inhibitor, wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



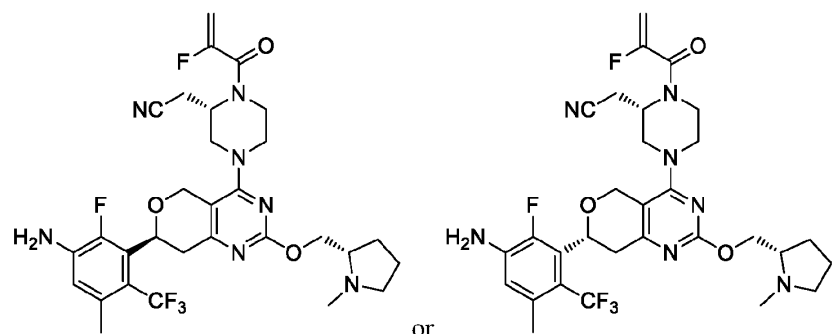
wherein T_1 is selected from O and N; R_1 is selected from C6-10 aryl and 5- to 10-membered heteroaryl, wherein the C6-10 aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c ; R_4 is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d ; R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R_8 is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R_5 , R_6 and R_7 are each independently H.

In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor.

In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0105] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK1/2 inhibitor; and (2) KRAS G12C inhibitor, wherein the KRAS G12C

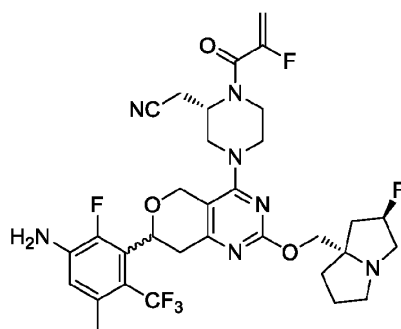
inhibitor comprises an agent comprising the following formulas or a pharmaceutically acceptable salt thereof,



In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same

individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

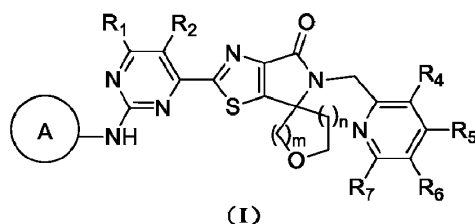
[0106] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK1/2 inhibitor; and (2) KRAS G12C inhibitor, wherein the KRAS G12C inhibitor comprises an agent comprising formula or a pharmaceutically acceptable salt thereof,



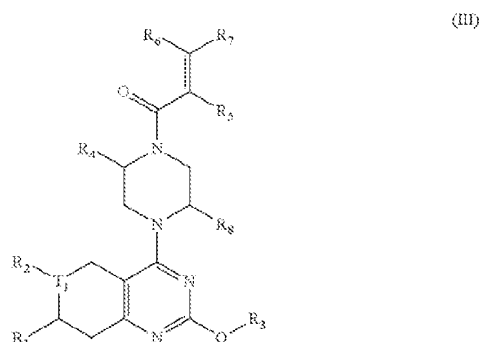
In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS

inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0107] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual, comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor, wherein the ERK 1/2 inhibitor comprises an agent comprising formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R₁ and R₂ are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a; R₄, R₅, R₆ and R₇ are independently selected from H, F, Cl, Br, I and C1-3 alkyl, and the C1-3 alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C1-3 alkyl and C1-3 alkoxy, and said C1-3 alkyl and C1-3 alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I; and wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



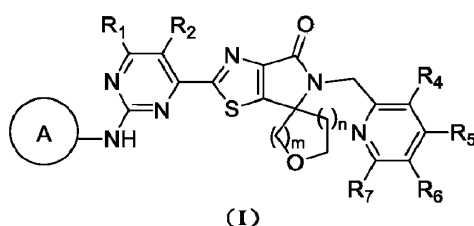
wherein T₁ is selected from O and N; R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a; when T₁ is O, R₂ is not present; when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b; R₃ is C1-3 alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c; R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d; R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R₈ is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃

alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H.

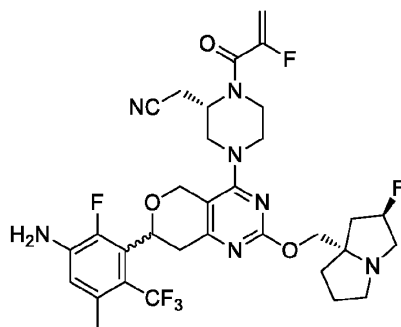
In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS

comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0108] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, ERK 1/2 inhibitor comprises an agent comprising formula (I) or a pharmaceutically acceptable salt thereof,



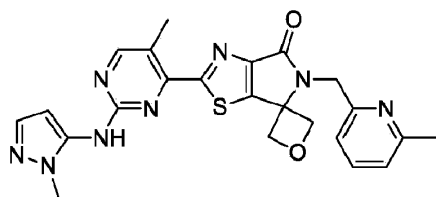
wherein, R_1 and R_2 are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I; and wherein the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



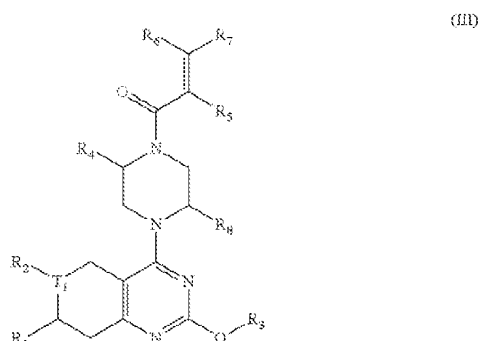
In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS

comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method further comprises administering to the individual an effective amount of a third therapy comprising another anti-cancer agent, optionally wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0109] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor, wherein the ERK 1/2 inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



; and wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



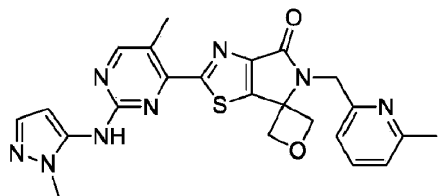
wherein T_1 is selected from O and N; R_1 is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c ; R_4 is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d ; R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R_8 is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R_5 , R_6 and R_7 are each independently H.

In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor.

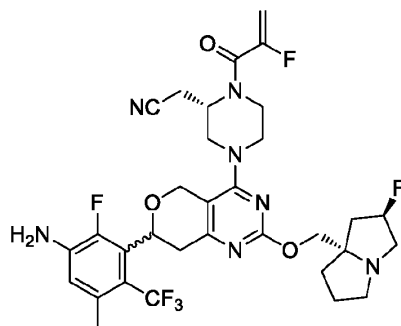
In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0110] In some embodiments, there is provided a method of treating cancer (e.g., a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein, e.g., a cancer resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor, wherein

the ERK 1/2 inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



; wherein the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,

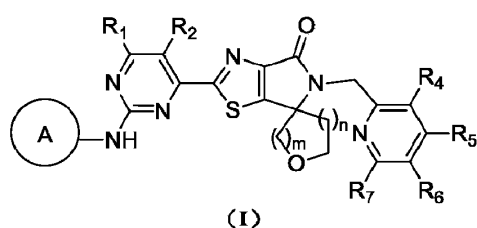


In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer

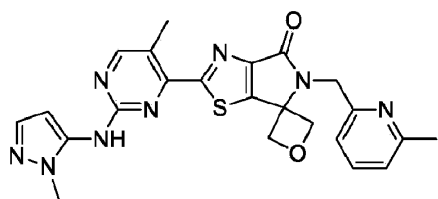
comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the KRAS Q61H mutation is acquired after a prior therapy (e.g., a KRAS G12C therapy).

[0111] In some embodiments, there is provided a method of treating a lung cancer (e.g., a NSCLC comprising a KRAS G12C mutation, e.g., a NSCLC cancer with a KRAS G12C mutation that is sensitive to an anti-EGFR therapy) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, there is provided a method of treating a lung cancer (e.g., a lung cancer that is resistant to a KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the dose of KRAS G12C inhibitor is equivalent to a dose of 30-100 mg/kg (e.g., no more than 50 mg/kg, 40 mg/kg or 30 mg/kg) for a mouse, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the dose of an ERK 1/2 inhibitor is equivalent to a dose of about 25-50 mg/kg (e.g., a daily dose of about or at least about 50 mg/kg) for a mouse, optionally wherein the ERK1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120,

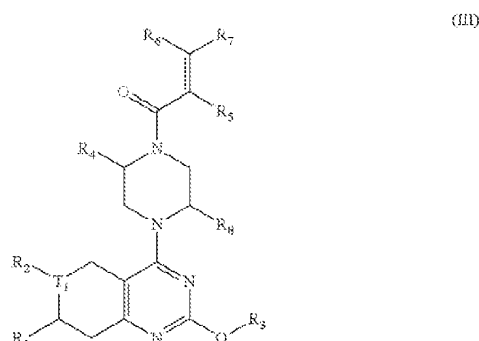
150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the ERK 1/2 inhibitor formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R_1 and R_2 are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof,

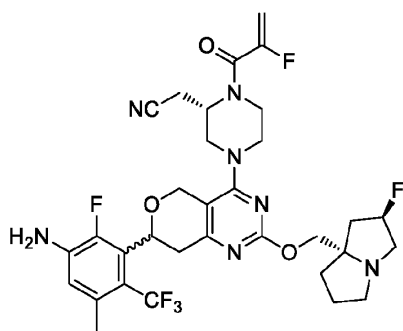


. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein T_1 is selected from O and N; R_1 is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c ; R_4 is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d ; R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R_8 is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R_5 , R_6 and R_7 are each independently H.

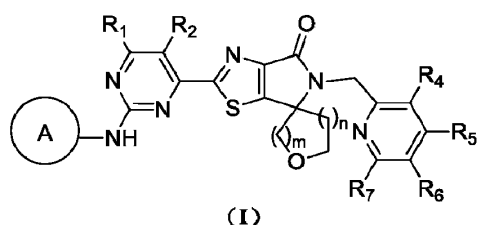
In some embodiments, the KRAS G12C inhibitor is selected from the group consisting of Compound 17, MRTX849, and AMG510. In some embodiments, the KRAS G12C inhibitor comprises an agent (Compound 17) comprising the following formula or a pharmaceutically acceptable salt thereof,



. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway.

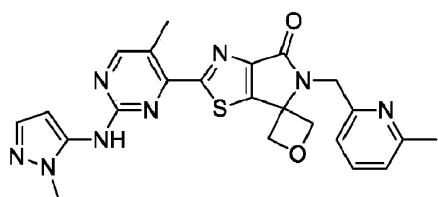
[0112] In some embodiments, there is provided a method of treating a colorectal cancer (e.g., a colorectal cancer comprising a KRAS G12C mutation, e.g., a colorectal cancer with a KRAS G12C mutation that is resistant to a prior KRAS G12C therapy) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C

inhibitor. In some embodiments, the dose of KRAS G12C inhibitor is equivalent to a dose of 10-100 mg/kg (e.g., no more than 30 mg/kg, 20 mg/kg or 10 mg/kg) for a mouse, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the dose of an ERK 1/2 inhibitor is equivalent to a dose of about 25-50 mg/kg (e.g., a daily dose of about or at least about 50 mg/kg or 25 mg/kg) for a mouse, optionally wherein the ERK1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the method further comprises administering an EGFR inhibitor (e.g., an anti-EGFR antibody, e.g., cetuximab). In some embodiments, the dose of the EGFR inhibitor is equivalent to about 30 mg/kg for a mouse. In some embodiments, the EGFR inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor, the KRAS G12C inhibitor, and/or the EGFR inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the ERK 1/2 inhibitor is administered prior to the EGFR inhibitor. In some embodiments, the EGFR inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the EGFR inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the EGFR inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the ERK 1/2 inhibitor formula (I) or a pharmaceutically acceptable salt thereof,

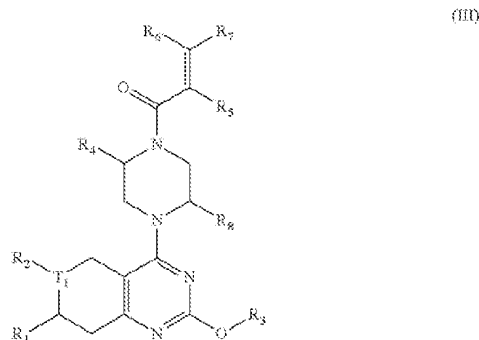


wherein, R₁ and R₂ are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a; R₄, R₅, R₆ and R₇ are independently selected from H, F, Cl,

Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof,

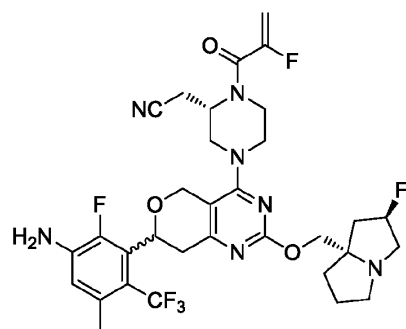


. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein T₁ is selected from O and N; R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a; when T₁ is O, R₂ is not present; when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b; R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c; R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d; R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R₈ is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered

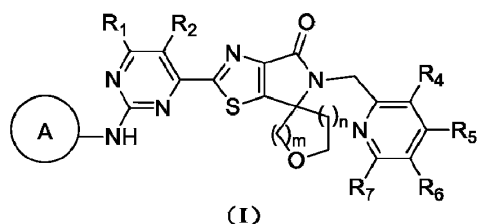
heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H. In some embodiments, the KRAS G12C inhibitor is selected from the group consisting of Compound 17, MRTX849, and AMG510. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



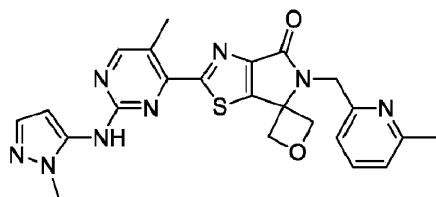
. In some embodiments, the cancer has acquired resistance to KRAS G12C inhibition (e.g., has acquired resistance to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same

individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway.

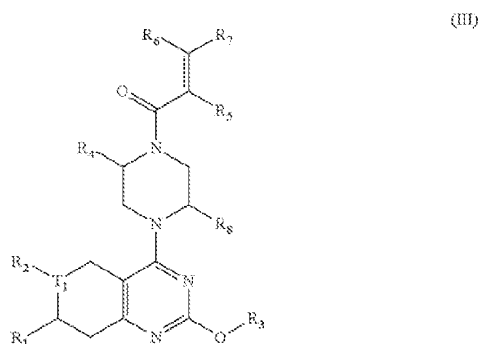
[0113] In some embodiments, there is provided a method of treating a colorectal cancer (e.g., a colorectal cancer comprising a KRAS G12C mutation and a Q61H mutation) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor (e.g., WX001); and (2) a KRAS G12C inhibitor (e.g., MRTX849, e.g., Compound 17). In some embodiments, there is provided a method of treating a colorectal cancer (e.g., a colorectal cancer comprising a KRAS G12C mutation and a Q61H mutation) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor (e.g., WX001); and (2) MRTX849. In some embodiments, there is provided a method of treating a colorectal cancer (e.g., a colorectal cancer comprising a KRAS G12C mutation and a Q61H mutation) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor (e.g., WX001); and (2) Compound 17. In some embodiments, the Q61H mutation is acquired after resistance to a prior KRAS inhibitor (e.g., a prior KRAS G12C inhibitor). In some embodiments, the dose of KRAS G12C inhibitor is equivalent to a dose of 30-100 mg/kg (e.g., no more than 50 mg/kg, 40 mg/kg or 30 mg/kg) for a mouse, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the dose of an ERK 1/2 inhibitor is equivalent to a dose of about 25-50 mg/kg (e.g., a daily dose of about or at least about 50 mg/kg) for a mouse, optionally wherein the ERK1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the ERK 1/2 inhibitor formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R_1 and R_2 are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof,

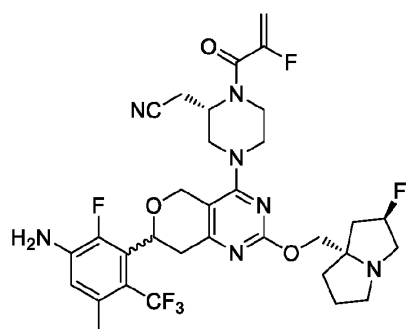


. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein T_1 is selected from O and N; R_1 is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C₁₋₃ alkyl, wherein the C₁₋₃

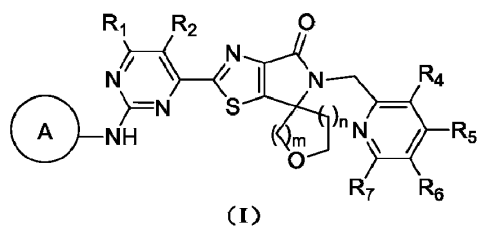
alkyl is optionally substituted with 1, 2 or 3 R_c; R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d; R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R₈ is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H. In some embodiments, the KRAS G12C inhibitor is selected from the group consisting of Compound 17, MRTX849, and AMG510. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



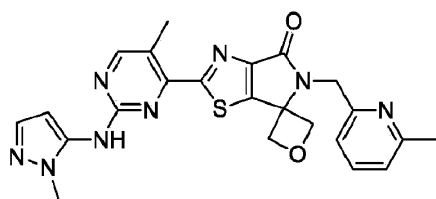
. In some embodiments, the cancer has acquired resistance to KRAS G12C inhibition (e.g., has acquired resistance to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a

R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway.

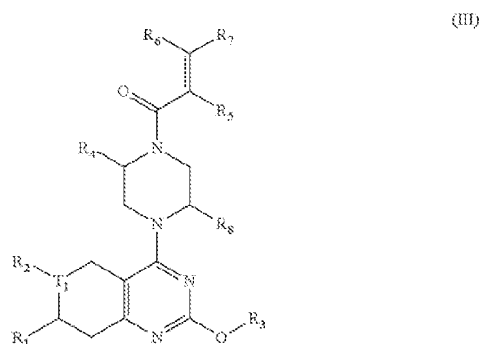
[0114] In some embodiments, there is provided a method of treating a pancreatic cancer (e.g., a pancreatic cancer comprising a KRAS G12C mutation, e.g., a pancreatic cancer with a KRAS G12C mutation that is resistant to a prior KRAS G12C inhibitor) in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor (e.g., WX001); and (2) a KRAS G12C inhibitor (e.g., MRTX849, e.g., Compound 17). In some embodiments, the dose of KRAS G12C inhibitor is equivalent to a dose of 30-100 mg/kg (e.g., no more than 50 mg/kg, 40 mg/kg or 30 mg/kg) for a mouse, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the dose of an ERK 1/2 inhibitor is equivalent to a dose of about 25-50 mg/kg (e.g., a daily dose of about or at least about 50 mg/kg) for a mouse, optionally wherein the ERK1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the ERK 1/2 inhibitor formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R_1 and R_2 are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof,

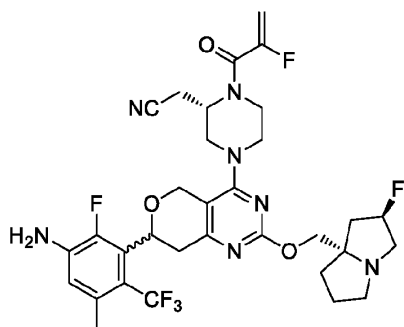


. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein T_1 is selected from O and N; R_1 is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C₁₋₃ alkyl, wherein the C₁₋₃

alkyl is optionally substituted with 1, 2 or 3 R_c; R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d; R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R₈ is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H. In some embodiments, the KRAS G12C inhibitor is selected from the group consisting of Compound 17, MRTX849, and AMG510. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,

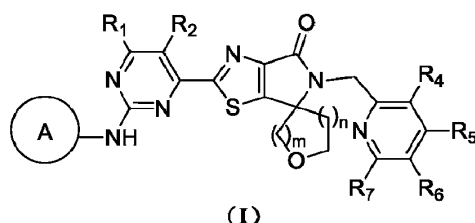


. In some embodiments, the cancer has acquired resistance to KRAS G12C inhibition (e.g., has acquired resistance to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a

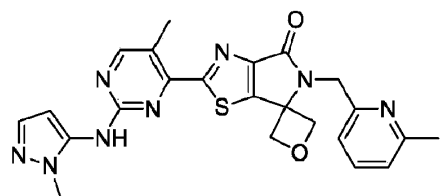
R68, Y96, or A59 mutation in KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway.

[0115] In some embodiments, there is provided a method of treating a cancer harboring a KRAS G12C mutation in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; (2) a KRAS G12C inhibitor and (3) an EGFR inhibitor. In some embodiments, the cancer does not have any additional KRAS mutation or aberration. In some embodiments, the cancer does not have any acquired secondary KRAS mutation. In some embodiments, the EGFR inhibitor is an EGFR antibody (e.g., cetuximab). In some embodiments, the cancer is a lung cancer, a colorectal cancer, or a pancreatic cancer. In some embodiments, the dose of KRAS G12C inhibitor is equivalent to a dose of 30-100 mg/kg (e.g., no more than 50 mg/kg, 40 mg/kg or 30 mg/kg) for a mouse, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the dose of an ERK 1/2 inhibitor is equivalent to a dose of about 25-50 mg/kg (e.g., a daily dose of about or at least about 50 mg/kg) for a mouse, optionally wherein the ERK1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more

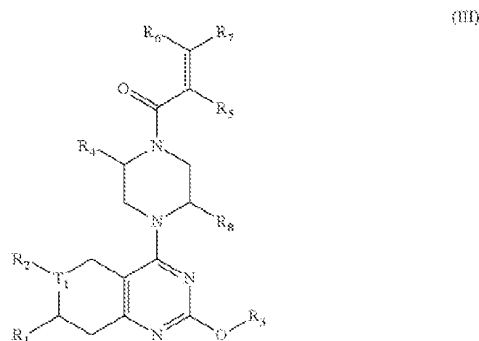
cancer cells that express a KRAS G12C mutant protein. In some embodiments, the ERK 1/2 inhibitor formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R_1 and R_2 are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof,



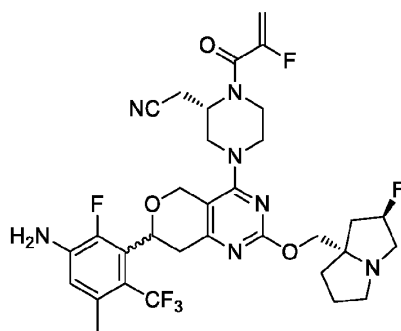
. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein T_1 is selected from O and N; R_1 is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with

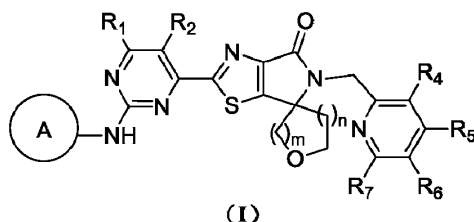
1, 2, 3, 4 or 5 R_d ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C_{1-3} alkyl, $—C(=O)—C_{1-3}$ alkyl and $—S(=O)_2—C_{1-3}$ alkyl, wherein the C_{1-3} alkyl, $—C(=O)—C_{1-3}$ alkyl and $—S(=O)_2—C_{1-3}$ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_c ; R_4 is selected from H and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d ; R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 F; R_8 is selected from H and CH_3 ; R_a is each independently selected from F, Cl, Br, I, OH, NH_2 , CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{2-3} alkynyl and C_{2-3} alkenyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{2-3} alkynyl and C_{2-3} alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH_2 ; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C_{1-3} alkyl, C_{1-3} alkoxy and $—C_{1-3}$ alkyl-O- $C(=O)—C_{1-3}$ alkylamino; provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH_2 , CF_3 , CH_2CH_3 and $—C\equiv CH$, and R_5 , R_6 and R_7 are each independently H.

In some embodiments, the KRAS G12C inhibitor is selected from the group consisting of Compound 17, MRTX849, and AMG510. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



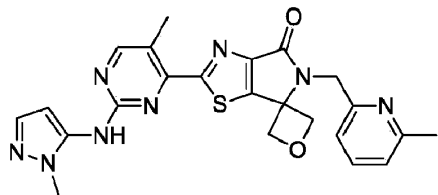
[0116] In some embodiments, there is provided a method of treating a cancer harboring a KRAS G12C mutation in an individual (e.g., a human patient), comprising administering to the individual (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor, wherein the cancer has at least one additional KRAS aberration other than G12C mutation. In some embodiments, the additional KRAS aberration is an acquired secondary aberration after a prior therapy (e.g., a prior KRAS G12C inhibitor described here). In some embodiments, the additional KRAS aberration is a

germline aberration or mutation. In some embodiment, the additional KRAS aberration is selected from the group consisting of a G12D, G12R, G12V, G12W, G13D, A59T, Q61H, R68S, R68M, H95D, H95Q, H95R, Y96C, Y96D, and high-level amplification of the KRASG12C allele. In some embodiments, the cancer is a lung cancer, a colorectal cancer, or a pancreatic cancer. In some embodiments, the dose of KRAS G12C inhibitor is equivalent to a dose of 30-100 mg/kg (e.g., no more than 50 mg/kg, 40 mg/kg or 30 mg/kg) for a mouse, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the dose of an ERK 1/2 inhibitor is equivalent to a dose of about 25-50 mg/kg (e.g., a daily dose of about or at least about 50 mg/kg) for a mouse, optionally wherein the ERK1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that express a KRAS G12C mutant protein. In some embodiments, the ERK 1/2 inhibitor formula (I) or a pharmaceutically acceptable salt thereof,

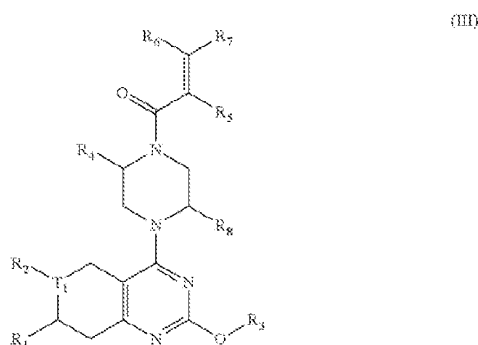


wherein, R₁ and R₂ are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a; R₄, R₅, R₆ and R₇ are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor

comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof.

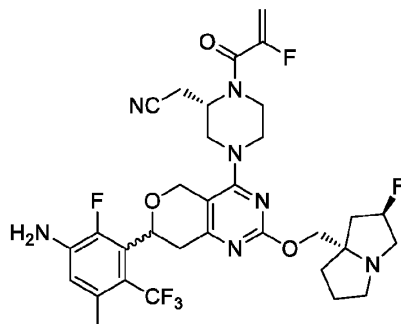


. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof.



wherein T₁ is selected from O and N; R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a; when T₁ is O, R₂ is not present; when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b; R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c; R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d; R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R₈ is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H.

In some embodiments, the KRAS G12C inhibitor is selected from the group consisting of Compound 17, MRTX849, and AMG510. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



[0117] In some embodiments, the subject is a human (e.g. a human patient). Cancer described herein include any kind of cancer that has a KRAS G12C mutation. A cancer (or a population of cancer cells) that comprises one or more cancer cells that express a KRAS G12C mutant protein is alternatively referred to herein as “a KRAS G12C mutant cancer.” In some embodiments, the cancer (such as the KRAS G12C mutant cancer) is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is an advanced, unresectable, and/or metastatic solid tumor.

[0118] In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally.

[0119] In some embodiments, the construct and the KRAS G12C inhibitor are administered simultaneously. In some embodiments, “simultaneous administration” means that the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered with a time separation of no more than about 15 minute(s), such as no more than about any of 10, 5, or 1 minutes. In some embodiments, simultaneous administration of the ERK 1/2 inhibitor and the KRAS G12C inhibitor can be

combined with supplemental doses of the ERK 1/2 inhibitor and/or the KRAS G12C inhibitor. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered sequentially. In some embodiments, “sequential administration” means that the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered with a time separation of more than about 15 minutes, such as more than about any of 20, 30, 40, 50, 60 or more minutes. For example, in some embodiments, the ERK 1/2 inhibitor is administered prior to the small molecule KRAS G12C inhibitor. In some embodiments, the small molecule KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the administration of the ERK 1/2 inhibitor and the KRAS G12C inhibitor are concurrent, i.e., the administration period of the ERK 1/2 inhibitor and the KRAS G12C inhibitor overlap with each other. In some embodiments, the administration of the ERK 1/2 inhibitor and the KRAS G12C inhibitor are non-concurrent.

[0120] In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor.

[0121] In some embodiments, the methods disclosed herein further comprise administering an effective amount of a third therapy. In some embodiments, the third therapy is another anti-cancer agent. The term “anti-cancer agent” or “anti-proliferative agent” means any agent that can be used to treat a cell proliferative disorder such as cancer, and includes, but is not limited to, cytotoxic agents, cytostatic agents, anti-angiogenic agents, debulking agents, chemotherapeutic agents, radiotherapy and radiotherapeutic agents, targeted anti-cancer agents, BRMs, therapeutic antibodies, cancer vaccines, cytokines, hormone therapies, radiation therapy and anti-metastatic agents and immunotherapeutic agents. It will be appreciated that, in selected embodiments as discussed above, such anti-cancer agents may comprise conjugates and may be associated with the disclosed antibodies prior to administration. More specifically, in certain embodiments selected anti-cancer agents will be linked to the unpaired cysteines of the engineered antibodies to provide engineered conjugates as set forth herein. Accordingly, such engineered conjugates are expressly contemplated as being within the scope of the present disclosure. In other embodiments, the disclosed anti-cancer agents will be given in combination with site-specific conjugates comprising a different therapeutic agent as set forth above.

[0122] Also provided herein is the use of an effective amount of (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor to treat cancer harboring a KRAS G12C mutation (*i.e.*, a cancer

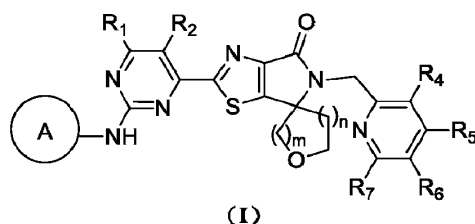
comprising one or more cancer cells that express a KRAS G12C mutant protein) in a subject, comprising administering to the subject an effective amount of (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the ERK1/2 inhibitor is used for the manufacture of a medicament for treating cancer, wherein the treatment is in combination with a KRAS G12C inhibitor. In some embodiments, the ERK1/2 inhibitor and the KRAS G12C inhibitor are used for the manufacture of a medicament for treating cancer, wherein the treatment is in combination with a KRAS G12C inhibitor. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is pancreatic cancer.

[0123] Also provided herein is the use of any of the methods as described herein for the treatment of a cancer harboring a KRAS G12C mutation (*i.e.*, a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein) in a subject, comprising administering to the subject an effective amount of (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. ERK1/2 and ERK1/2 inhibitors.

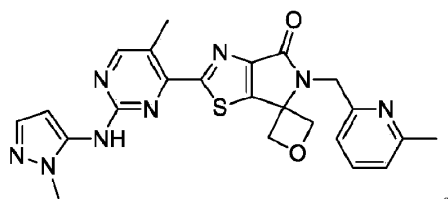
[0124] In some embodiments, the methods and uses of the present disclosure may be combined with an additional therapeutic agent, such as an anti-cancer agent, including an anti-cancer small molecule inhibitor. The additional therapeutic agent may also be an antagonist or an inhibitor of a kinase. In some embodiments, the kinase is involved in the RAS/RAF/MEK/ERK pathway. In some embodiments, the kinase is an extracellular signal-regulated kinase (ERK). In some embodiments, the ERK is ERK1. In some embodiments, the ERK kinase is ERK2 (also known as MAPK1). The ERK kinases are terminal kinases of phosphorelay signaling pathways that govern growth and mitogenic signals. The ERK kinases phosphorylate substrates that are involved in regulating cell proliferation, survival, growth, metabolism, migration and differentiation.

[0125] In some embodiments, the treatment results in a tumor growth inhibitor of at least more than about 70%, 75%, 80%, 85%, 90%, 95% or 97%. In some embodiments, the treatment results in a tumor regression. In some embodiments, the treatment results in a prolonged or sustainable tumor inhibition, regression or eradication effect for more than 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, or 140 days as compared to a monotherapy of a G12C inhibitor or a monotherapy of an ERK 1/2 inhibitor. In some embodiments, the treatment results in a sustainable tumor inhibition, regression or eradication effect for more than 5, 10, 15, 20, 25, or 30 days after the treatment is stopped.

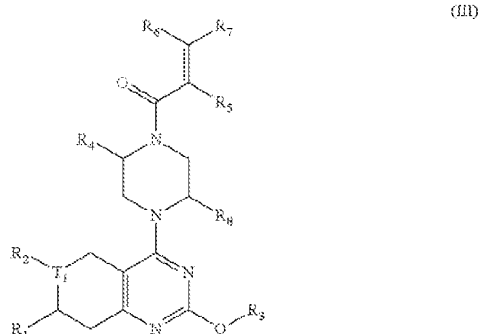
[0126] The present application also provides use of any of the ERK1/2 inhibitors described herein for treating a cancer with a *BRAF* aberration (e.g., V600E) or a *KRAS* aberration (e.g., any of the mutant *KRAS* described in the “mutant *KRAS*” section, e.g., *KRAS* G12C, e.g., *KRAS* G12D). See e.g., FIG. 15A and 15B. In some embodiments, the ERK 1/2 inhibitor comprises an agent comprising a formula (I) or a pharmaceutically acceptable salt thereof,



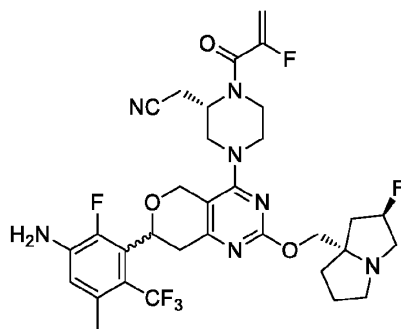
wherein, R_1 and R_2 are independently selected from H and C 1-3 alkyl, and the C 1-3 alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I. In some embodiments, the ERK 1/2 inhibitor comprises a molecule comprising the following formula or a pharmaceutically acceptable salt thereof,



[0127] The present application also provides use of any of the G12C inhibitors described herein for treating a cancer with *KRAS* G12C mutation in combination with an EGFR inhibitor (e.g., an anti-EGFR antibody, e.g., cetuximab). In some embodiments, the cancer is a pancreatic cancer, a lung cancer or a colorectal cancer. In some embodiments, the *KRAS* G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



[1] wherein T_1 is selected from O and N; R_1 is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ; when T_1 is O, R_2 is not present; when T_1 is N, R_2 is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b ; R_3 is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c ; R_4 is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d ; R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R_8 is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R_5 , R_6 and R_7 are each independently H. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



[0128] The present application also provides a composition (e.g., a pharmaceutical composition) comprising both a KRAS G12C inhibitor (e.g., Compound 17) and a ERK 1/2 inhibitor (e.g., WX001). In some embodiments, the composition further comprises a pharmaceutical carrier.

KRAS and KRAS Inhibitors

A. KRAS

[0129] Kirsten rat sarcoma (KRAS) gene belongs to a member of the RAS family and its mutations are genetic drivers of multiple cancer types, especially colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and non-small cell lung cancer (NSCLC). KRAS-G12 mutations (89%) predominate in human cancers, followed by G13 (9%) and Q61 (1%) mutations. Furthermore, the G12D mutation is the most common mutation among three common G12C (14%), G12D (36%), and G12V (23%) mutations. Compared with G12D which plays a major role in PDAC, G12C is the most common mutation subtype in NSCLC (13%). Identifying specific types of KRAS mutations in combination with other gene mutations may provide information about disease aggressiveness or drug sensitivity, which is the basis of precision medicine or personalized care. *See e.g.*, Liu et al., *Cancer Gene Ther* 29, 875–878 (2022).

[0130] KRAS protein is a signaling GTPase that switches between the active GTP-bound and inactive GDP-bound conformations. Guanine nucleotide exchange factors (GEF) promote the exchange of GDP to GTP on KRAS, whereas GTPase-activating proteins (GAP) favor the exchange of GTP to GDP. The activation of receptor tyrosine kinases (RTKs) on the plasma membrane, such as epidermal growth factor receptor (EGFR) family, initiates KRAS activation and subsequent multiple effector pathways, especially mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) pathways. As the downstream of RTKs, SOS Ras/Rac guanine

nucleotide exchange factor 1 (SOS1) and protein tyrosine phosphatase non-receptor type 11 (PTPN11, best known as SHP2) promote the ratio of GDP-GTP exchange, leading to KRAS activation. Comparing the GTP- and GDP-bound structures of KRAS identified two regions, called switch-I and switch-II. The mutant cysteine 12 is located next to the pocket (P2) in the switch-II region. Compared with the wild-type, the KRAS mutation disrupts the guanine exchange cycle, thereby locking it in an inactive GDP-bound form that drives pro-tumorigenic signals. The oncogenic KRAS signal establishes the main signal axis of tumor cell proliferation and survival, providing a key target for cancer treatment. *See e.g.*, Liu et al., Cancer Gene Ther 29, 875–878 (2022).

B. KRAS G12C inhibitor

[0131] Although it has long been deemed “undruggable”, with the development of drugs specifically binding the KRAS-G12C mutant protein, clinical trials that directly inhibit oncogenic RAS have recently made promising improvements. In particular, the covalent KRAS-G12C inhibitors sotorasib and adagrasib are used to treat patients with advanced non-small cell lung cancer (NSCLC) carrying KRAS-G12C mutations. Unfortunately, the vast majority of patients do not completely respond to KRAS-G12C inhibitor therapy, mainly due to intrinsic or acquired resistance caused by cellular, molecular, and genetic mechanisms. Improving the understanding of drug response in the tumor microenvironment may continue to promote the design, testing, and clinical application of KRAS-G12C inhibitors. *See e.g.*, Liu et al., Cancer Gene Ther 29, 875–878 (2022).

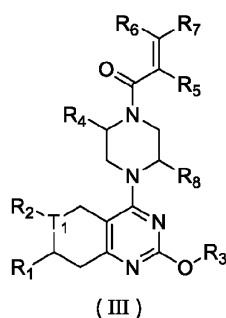
[0132] In some embodiments, the KRAS inhibitor is an inhibitor that inhibits the G12C variant of KRAS (i.e., KRAS G12C). In some embodiments, the term “KRAS G12C inhibitor” refers to any agent, *e.g.*, polypeptide, fusion polypeptide, antibody, peptide, antisense oligonucleotide, or small molecule drug, that inhibits the activity of the KRAS G12C mutant protein. In some embodiments, the KRAS G12C inhibitor interacts directly with the KRAS G12C mutant protein to inhibit the protein’s activity.

[0133] In some embodiments, the KRAS G12C inhibitor is a small molecule drug. In some embodiments, the KRAS G12C inhibitor is a small molecule (*e.g.*, an irreversible small molecule inhibitor) that inhibit KRAS activity by forming irreversible covalent bonds with cysteine residues of KRAS G12C mutant protein.

a) Exemplary KRAS G12C inhibitor

[0134] Exemplary KRAS G12C inhibitors (e.g., Compound 17) discussed herein include, but are not limited to a class of KRAS G12C inhibitors. The molecular mode of action (MOA) of this class of KRAS G12C inhibitors is allosteric binding to the Switch II pocket of the GDP-bound form of the KRAS G12C protein and forming a covalent bond at the cysteine-12 position. This irreversible conjugation traps KRASG12C in its GDP-bound inactive state. This class of KRAS G12C inhibitors with the same mechanism of action (MOA) includes sotorasib, adgrasib, JDQ443, GDC-6036, etc. Thus, the anti-tumor effect observed for combination of ERK1/2 inhibitor (e.g., WX001) with the exemplary KRAS G12C inhibitor is predicted to extend to all KRAS G12C inhibitors of the same class.

[0135] In some embodiments, the KRAS G12C inhibitor comprises or is a compound represented by formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T₁ is selected from O and N;

R₁ is selected from C₆-10 aryl and 5- to 10-membered heteroaryl, wherein the C₆-10 aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, -C(=O)-C₁₋₃ alkyl and -S(=O)₂-C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, -C(=O)-C₁₋₃ alkyl and -S(=O)₂-C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN;

R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and -C₁₋₃ alkyl-O-CO-C₁₋₃ alkylamino;

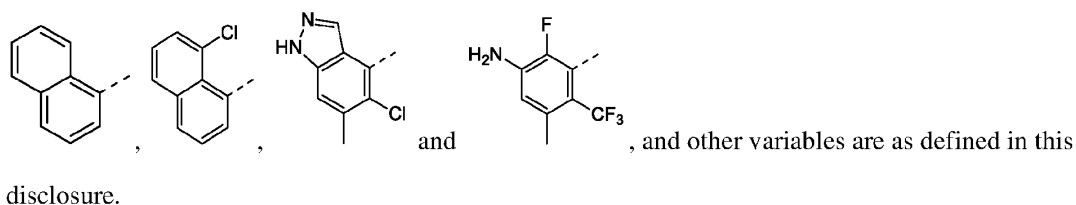
provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and -C≡CH, and R₅, R₆ and R₇ are each independently H.

[0136] In some embodiments of the present disclosure, the above R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, CH₃, CH₂CH₃, OCH₃, OCH₂CH₃, -CH=CH₂, -CH₂-CH=CH₂ and -C≡CH, wherein the CH₃, CH₂CH₃, OCH₃, OCH₂CH₃, -CH=CH₂, -CH₂-CH=CH₂ and -C≡CH are optionally substituted with 1, 2 or 3 F, and other variables are as defined in this disclosure.

[0137] In some embodiments of the present disclosure, the above R_a is each independently selected from F, OH, NH₂, CH₃, CF₃, CH₂CH₃ and -C≡CH, and other variables are as defined in this disclosure.

[0138] In some embodiments of the present disclosure, the above R₁ is selected from phenyl, naphthyl, indolyl and indazolyl, wherein the phenyl, naphthyl, indolyl and indazolyl are optionally substituted with 1, 2 or 3 R_a, and other variables are as defined in this disclosure.

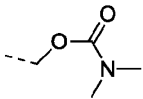
[0139] In some embodiments of the present disclosure, the above R₁ is selected from



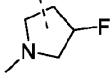
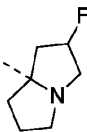
[0140] In some embodiments of the present disclosure, the above R_2 is selected from H, CH_3 , CH_2CH_3 and $CH(CH_3)_2$, wherein the CH_3 , CH_2CH_3 and $CH(CH_3)_2$ are optionally substituted with 1, 2 or 3 R_b , and other variables are as defined in this disclosure.

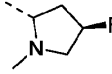
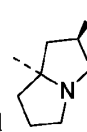
[0141] In some embodiments of the present disclosure, the above R_2 is selected from H and CH_3 , and other variables are as defined in this disclosure.

[0142] In some embodiments of the present disclosure, the above R is each independently

selected from H, F, Cl, Br, OH, CN, CH_3 , CH_2CH_3 , CH_2CF_3 , OCH_3 , OCF_3 and , and other variables are as defined in this disclosure.

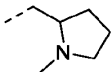
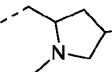
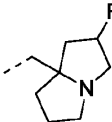
[0143] In some embodiments of the present disclosure, the above R_c is selected from tetrahydropyrrolyl and hexahydro-1H-pyrrolizynyl, wherein the tetrahydropyrrolyl and hexahydro-1H-pyrrolizynyl are optionally substituted with 1, 2 or 3 R, and other variables are as defined in this disclosure.

[0144] In some embodiments of the present disclosure, the above R_c is selected from , , , and , and other variables are as defined in this disclosure.

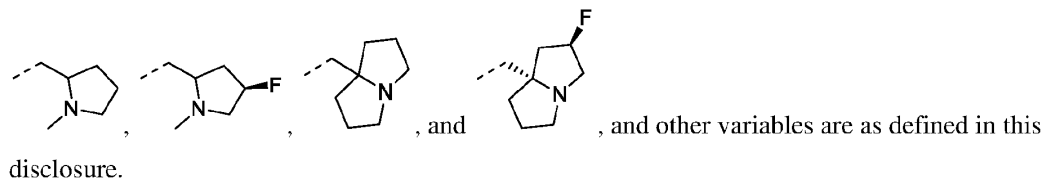
[0145] In some embodiments of the present disclosure, the above R_c is selected from , , , and , and other variables are as defined in this disclosure.

[0146] In some embodiments of the present disclosure, the above R_3 is CH_3 , wherein the CH_3 is optionally substituted with 1, 2 or 3 R_c , and other variables are as defined in this disclosure.

[0147] In some embodiments of the present disclosure, the above R_3 is selected from

, , , and , and other variables are as defined in this disclosure.

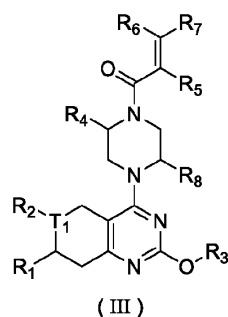
[0148] In some embodiments of the present disclosure, the above R₃ is selected from



[0149] In some embodiments of the present disclosure, the above R₄ is selected from H and CH₃, wherein the CH₃ is optionally substituted with 1, 2 or 3 R_d, and other variables are as defined in this disclosure.

[0150] In some embodiments of the present disclosure, the above R₄ is selected from H, CH₃ and CH₂CN, and other variables are as defined in this disclosure.

[0151] The present disclosure provides a compound represented by formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T₁ is selected from O and N;

R₁ is selected from phenyl, naphthyl and indazolyl, wherein the phenyl, naphthyl and indazolyl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, -C(=O)-C₁₋₃ alkyl and -S(=O)₂-C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, -C(=O)-C₁₋₃ alkyl and -S(=O)₂-C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, OH and NH₂;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, CH₃, CF₃ and OCH₃;

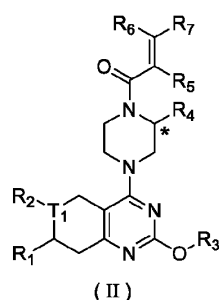
R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

R_c is each independently selected from tetrahydropyrrolyl and hexahydro-1H-pyrroliziny, wherein the tetrahydropyrrolyl and hexahydro-1H-pyrroliziny are substituted with 1, 2 or 3 R;

R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN;

R is each independently selected from H, F, Cl, Br and CH₃.

In some embodiments of the present disclosure, disclosed is the above compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from,



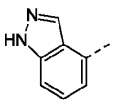
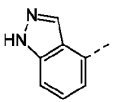
wherein

R₄ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

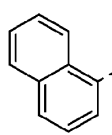
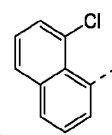
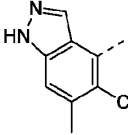
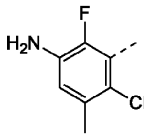
T₁, R₁, R₂, R₃, R₅, R₆, R₇ and R_d are as defined in this disclosure;

the carbon atom with “*” is a chiral carbon atom, which exists in the form of (R) or (S) single enantiomer or is enriched in one enantiomer.

[0152] In some embodiments of the present disclosure, the above R₁ is selected from phenyl,

naphthyl and , wherein the phenyl, naphthyl and  are optionally substituted with 1, 2 or 3 R_a, and other variables are as defined in this disclosure.

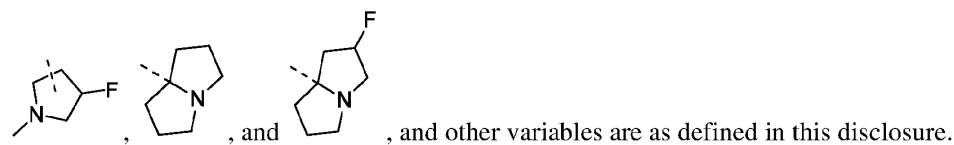
[0153] In some embodiments of the present disclosure, the above R₁ is selected from

, ,  and , and other variables are as defined in this disclosure.

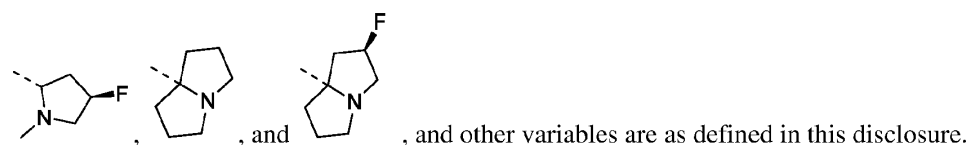
[0154] In some embodiments of the present disclosure, the above R_2 is selected from H, CH_3 , CH_2CH_3 and $CH(CH_3)_2$, wherein the CH_3 , CH_2CH_3 and $CH(CH_3)_2$ are optionally substituted with 1, 2 or 3 R_b , and other variables are as defined in this disclosure.

[0155] In some embodiments of the present disclosure, the above R_2 is selected from H and CH_3 , and other variables are as defined in this disclosure.

[0156] In some embodiments of the present disclosure, the above R_c is selected from ,

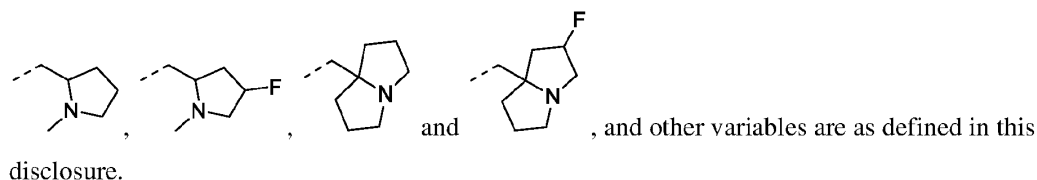


[0157] In some embodiments of the present disclosure, the above R_c is selected from ,

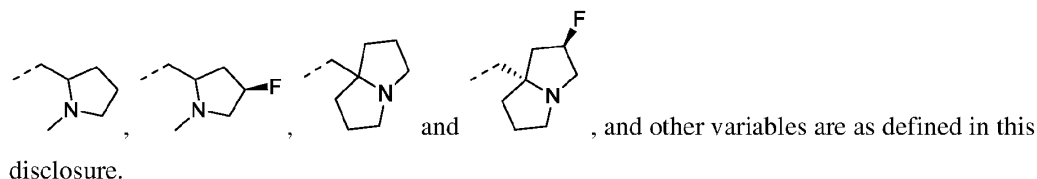


[0158] In some embodiments of the present disclosure, the above R_3 is CH_3 , wherein the CH_3 is optionally substituted with 1, 2 or 3 R_c , and other variables are as defined in this disclosure.

[0159] In some embodiments of the present disclosure, the above R_3 is selected from



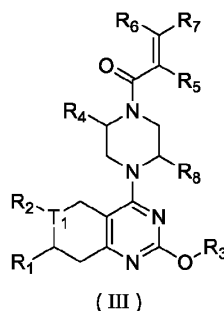
[0160] In some embodiments of the present disclosure, the above R_3 is selected from



[0161] In some embodiments of the present disclosure, the above R_4 is selected from H and CH_3 , wherein the CH_3 is optionally substituted with 1, 2 or 3 R_d , and other variables are as defined in this disclosure.

[0162] In some embodiments of the present disclosure, the above R_4 is selected from H, CH_3 and CH_2CN , and other variables are as defined in this disclosure.

[0163] The present disclosure provides a compound represented by formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T_1 is selected from O and N;

R_1 is selected from phenyl, naphthyl and indazolyl, wherein the phenyl, naphthyl and indazolyl are optionally substituted with 1, 2, 3, 4 or 5 R_a ;

when T_1 is O, R_2 is not present;

when T_1 is N, R_2 is selected from H, C_{1-3} alkyl, $-\text{C}(=\text{O})-\text{C}_{1-3}$ alkyl and $-\text{S}(=\text{O})_2-\text{C}_{1-3}$ alkyl, wherein the C_{1-3} alkyl, $-\text{C}(=\text{O})-\text{C}_{1-3}$ alkyl and $-\text{S}(=\text{O})_2-\text{C}_{1-3}$ alkyl are optionally substituted with 1, 2 or 3 R_b ;

R_3 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_c ;

R_4 is selected from H and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d ;

R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, OH and NH_2 ;

R_8 is selected from H and CH_3 ;

R_a is each independently selected from F, Cl, Br, I, OH, NH_2 , CN, CH_3 , CF_3 and OCH_3 ;

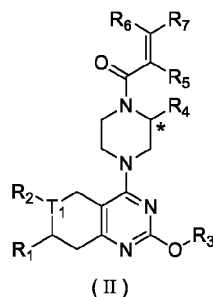
R_b is each independently selected from F, Cl, Br, I, OH, NH_2 and CH_3 ;

R_c is each independently tetrahydropyrrolyl, wherein the tetrahydropyrrolyl is substituted with 1, 2 or 3 R ;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

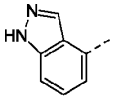
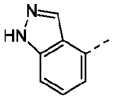
R is each independently selected from F, Cl, Br and CH_3 .

In some embodiments of the present disclosure, disclosed is the above compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from,

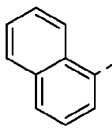
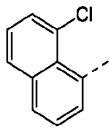
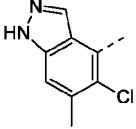
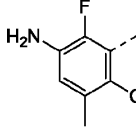


wherein T₁, R₁, R₂, R₃, R₄, R₅, R₆ and R₇ are as defined in this disclosure; the carbon atom with “*” is a chiral carbon atom, which exists in the form of (R) or (S) single enantiomer or is enriched in one enantiomer.

[0164] In some embodiments of the present disclosure, the above R₁ is selected from phenyl,

naphthyl and , wherein the phenyl, naphthyl and  are optionally substituted with 1, 2 or 3 R_a, and other variables are as defined in this disclosure.

[0165] In some embodiments of the present disclosure, the above R₁ is selected from

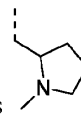
, ,  and , and other variables are as defined in this disclosure.

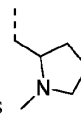
[0166] In some embodiments of the present disclosure, the above R₂ is selected from H, CH₃, CH₂CH₃ and CH(CH₃)₂, wherein the CH₃, CH₂CH₃ and CH(CH₃)₂ are optionally substituted with 1, 2 or 3 R_b, and other variables are as defined in this disclosure.

[0167] In some embodiments of the present disclosure, the above R₂ is selected from H and CH₃, and other variables are as defined in this disclosure.

[0168] In some embodiments of the present disclosure, the above R_c is , and other variables are as defined in this disclosure.

[0169] In some embodiments of the present disclosure, the above R₃ is CH₃, wherein the CH₃ is optionally substituted with 1, 2 or 3 R_c, and other variables are as defined in this disclosure.

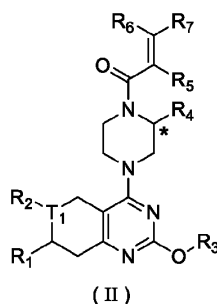


[0170] In some embodiments of the present disclosure, the above R_3 is , and other variables are as defined in this disclosure.

[0171] In some embodiments of the present disclosure, the above R_4 is CH_3 , wherein the CH_3 is optionally substituted with 1, 2 or 3 R_d , and other variables are as defined in this disclosure.

[0172] In some embodiments of the present disclosure, the above R_4 is CH_2CN , and other variables are as defined in this disclosure.

[0173] The present disclosure provides a compound represented by formula (II) or a pharmaceutically acceptable salt thereof,



wherein

T_1 is selected from O and N;

R_1 is selected from phenyl and naphthyl, wherein the phenyl and naphthyl are optionally substituted with 1, 2 or 3 R_a ;

when T_1 is O, R_2 is not present;

when T_1 is N, R_2 is selected from C_{1-3} alkyl, $-\text{C}(=\text{O})-\text{C}_{1-3}$ alkyl and $-\text{S}(=\text{O})_2-\text{C}_{1-3}$ alkyl, wherein the C_{1-3} alkyl, $-\text{C}(=\text{O})-\text{C}_{1-3}$ alkyl and $-\text{S}(=\text{O})_2-\text{C}_{1-3}$ alkyl are optionally substituted with 1, 2 or 3 R_b ;

R_3 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_c ;

R_4 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d ;

R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, OH and NH_2 ;

R_a is each independently selected from F, Cl, Br, I, OH, NH_2 , CN, CH_3 and OCH_3 ;

R_b is each independently selected from F, Cl, Br, I, OH, NH_2 and CH_3 ;

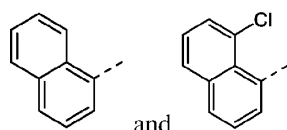
R_c is each independently tetrahydropyrrolyl, wherein the tetrahydropyrrolyl is substituted with 1, 2 or 3 R ;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

R is each independently selected from F, Cl, Br and CH_3 ; the carbon atom with "*" is a chiral carbon atom, which exists in the form of (R) or (S) single enantiomer or is enriched in one enantiomer.

[0174] In some embodiments of the present disclosure, the above R_1 is naphthyl, wherein the naphthyl is optionally substituted with 1, 2 or 3 R_a , and other variables are as defined in this disclosure.

[0175] In some embodiments of the present disclosure, the above R_1 is selected from



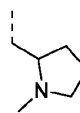
and , and other variables are as defined in this disclosure.

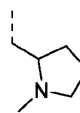
[0176] In some embodiments of the present disclosure, the above R_2 is selected from CH_3 , CH_2CH_3 and $CH(CH_3)_2$, wherein the CH_3 , CH_2CH_3 and $CH(CH_3)_2$ are optionally substituted with 1, 2 or 3 R_b , and other variables are as defined in this disclosure.

[0177] In some embodiments of the present disclosure, the above R_2 is CH_3 , and other variables are as defined in this disclosure.

[0178] In some embodiments of the present disclosure, the above R_c is , and other variables are as defined in this disclosure.

[0179] In some embodiments of the present disclosure, the above R_3 is CH_3 , wherein the CH_3 is optionally substituted with 1, 2 or 3 R_c , and other variables are as defined in this disclosure.

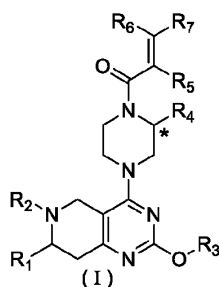


[0180] In some embodiments of the present disclosure, the above R_3 is , and other variables are as defined in this disclosure.

[0181] In some embodiments of the present disclosure, the above R_4 is CH_3 , wherein the CH_3 is optionally substituted with 1, 2 or 3 R_d , and other variables are as defined in this disclosure.

[0182] In some embodiments of the present disclosure, the above R_4 is CH_2CN , and other variables are as defined in this disclosure.

[0183] The present disclosure provides a compound represented by formula (I) or a pharmaceutically acceptable salt thereof,



wherein R_1 is selected from phenyl and naphthyl, wherein the phenyl and naphthyl are optionally substituted with 1, 2 or 3 R_a ;

R_2 is selected from C_{1-3} alkyl, $-C(=O)-C_{1-3}$ alkyl and $-S(=O)_2-C_{1-3}$ alkyl, wherein the C_{1-3} alkyl, $-C(=O)-C_{1-3}$ alkyl and $-S(=O)_2-C_{1-3}$ alkyl are optionally substituted with 1, 2 or 3 R_b ;

R_3 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_c ;

R_4 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d ;

R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, OH and NH_2 ;

R_a and R_b are each independently selected from F, Cl, Br, I, OH, NH_2 and CH_3 ;

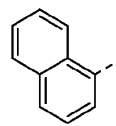
R_c is each independently tetrahydropyrrolyl, wherein the tetrahydropyrrolyl is substituted with 1, 2 or 3 R ;

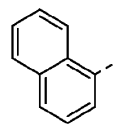
R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

R is each independently selected from F, Cl, Br and CH_3 ;

the carbon atom with “*” is a chiral carbon atom, which exists in the form of (R) or (S) single enantiomer or is enriched in one enantiomer.

[0184] In some embodiments of the present disclosure, the above R_1 is naphthyl, and other variables are as defined in this disclosure.



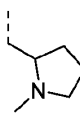
[0185] In some embodiments of the present disclosure, the above R_1 is , and other variables are as defined in this disclosure.

[0186] In some embodiments of the present disclosure, the above R_2 is selected from CH_3 , CH_2CH_3 and $CH(CH_3)_2$, wherein the CH_3 , CH_2CH_3 and $CH(CH_3)_2$ are optionally substituted with 1, 2 or 3 R_b , and other variables are as defined in this disclosure.

[0187] In some embodiments of the present disclosure, the above R_2 is CH_3 , and other variables are as defined in this disclosure.

[0188] In some embodiments of the present disclosure, the above R_c is , and other variables are as defined in this disclosure.

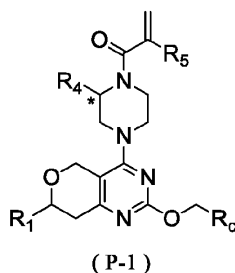
[0189] In some embodiments of the present disclosure, the above R₃ is CH₃, wherein the CH₃ is optionally substituted with 1, 2 or 3 R_c, and other variables are as defined in this disclosure.

[0190] In some embodiments of the present disclosure, the above R₃ is , and other variables are as defined in this disclosure.

[0191] In some embodiments of the present disclosure, the above R₄ is CH₃, wherein the CH₃ is optionally substituted with 1, 2 or 3 R_d, and other variables are as defined in this disclosure.

[0192] In some embodiments of the present disclosure, the above R₄ is CH₂CN, and other variables are as defined in this disclosure.

[0193] In some embodiments of the present disclosure, disclosed is the above compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from,



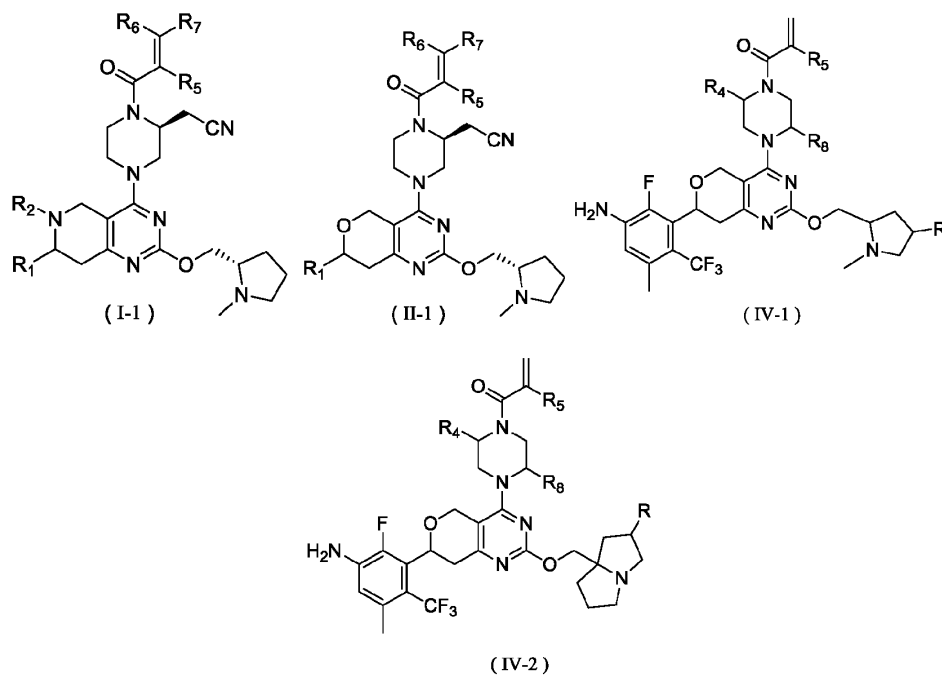
[0194] wherein R₁, R₅, and R₆ are as defined in this disclosure;

[0195] R₄ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

[0196] R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN;

[0197] the carbon atom with “*” is a chiral carbon atom, which exists in the form of (R) or (S) single enantiomer or is enriched in one enantiomer.

[0198] In some embodiments of the present disclosure, disclosed is the above compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from:

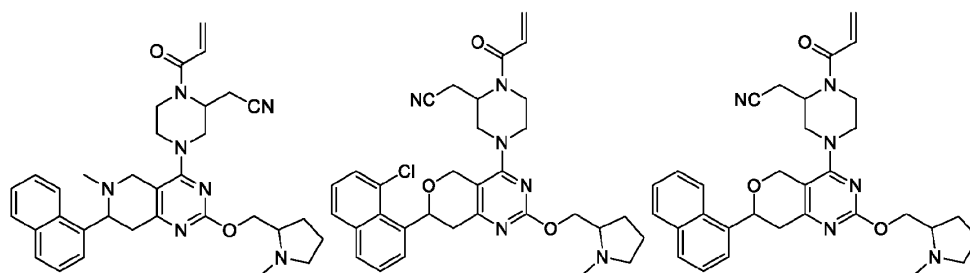


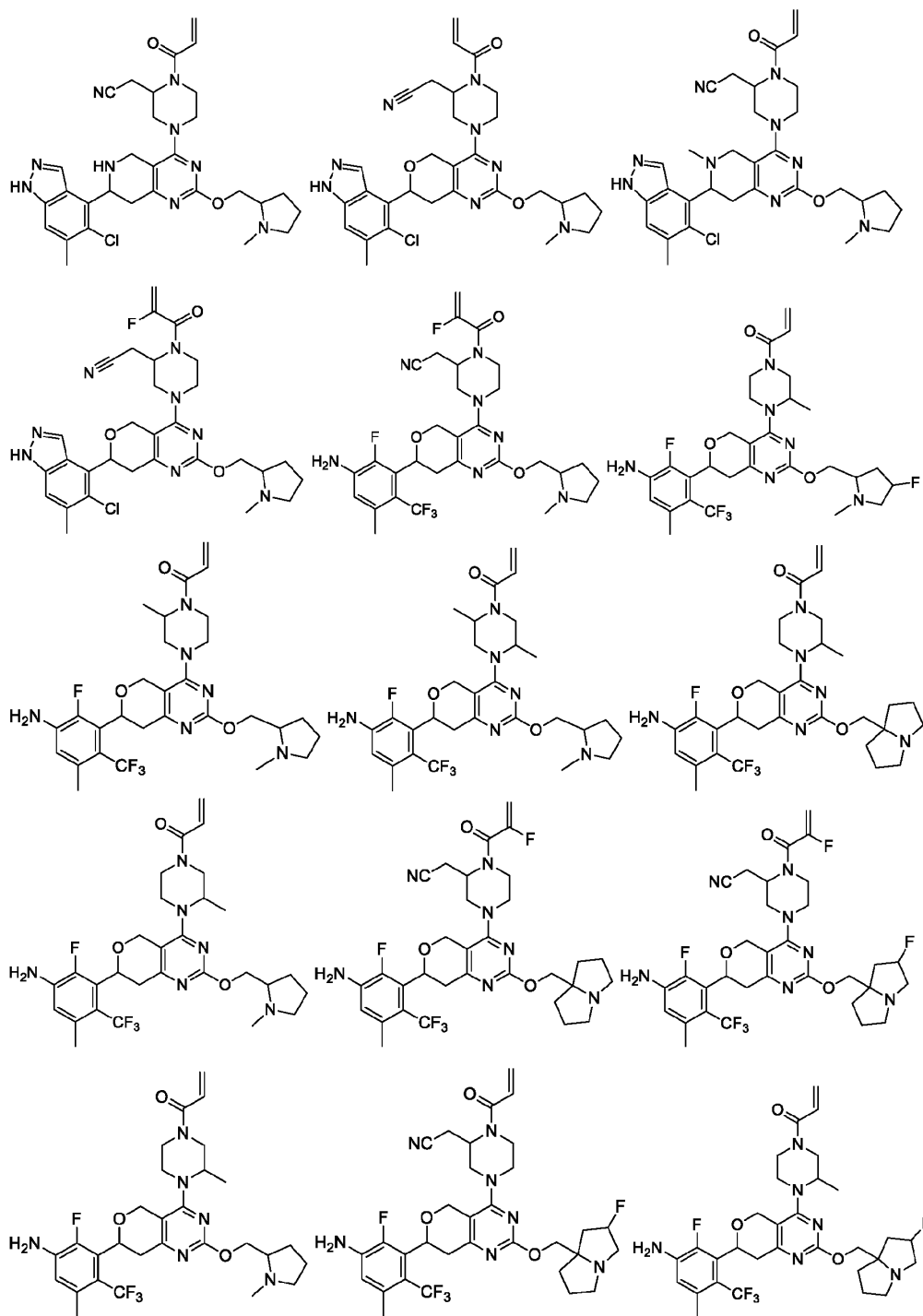
wherein

R₁, R₂, R₄, R₅, R₆, R₇, R₈ and R are as defined in this disclosure.

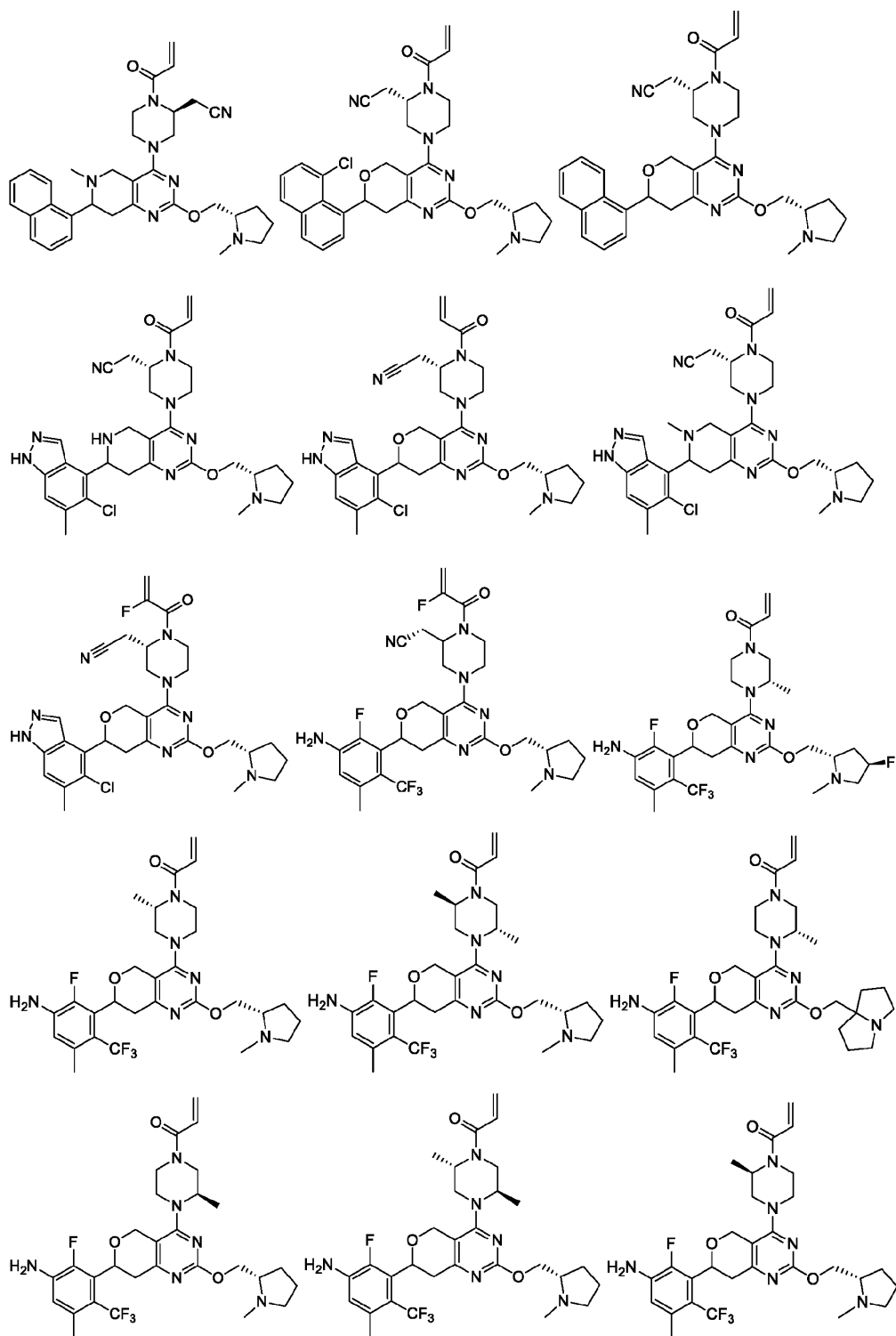
[0199] The present disclosure also includes some embodiments obtained by any combination of the above variables.

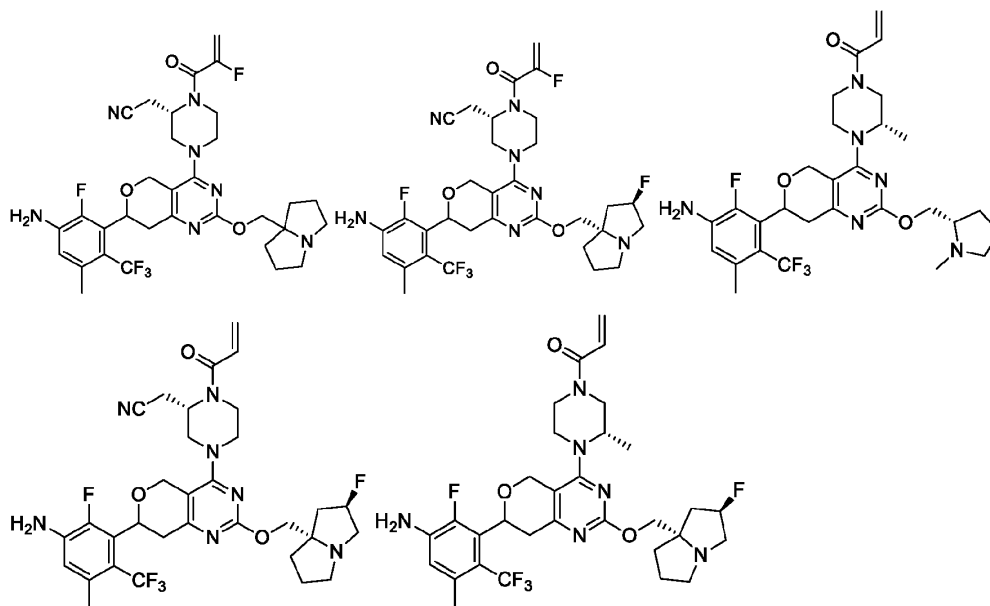
[0200] The present disclosure provides a compound of the following formula or a pharmaceutically acceptable salt thereof,



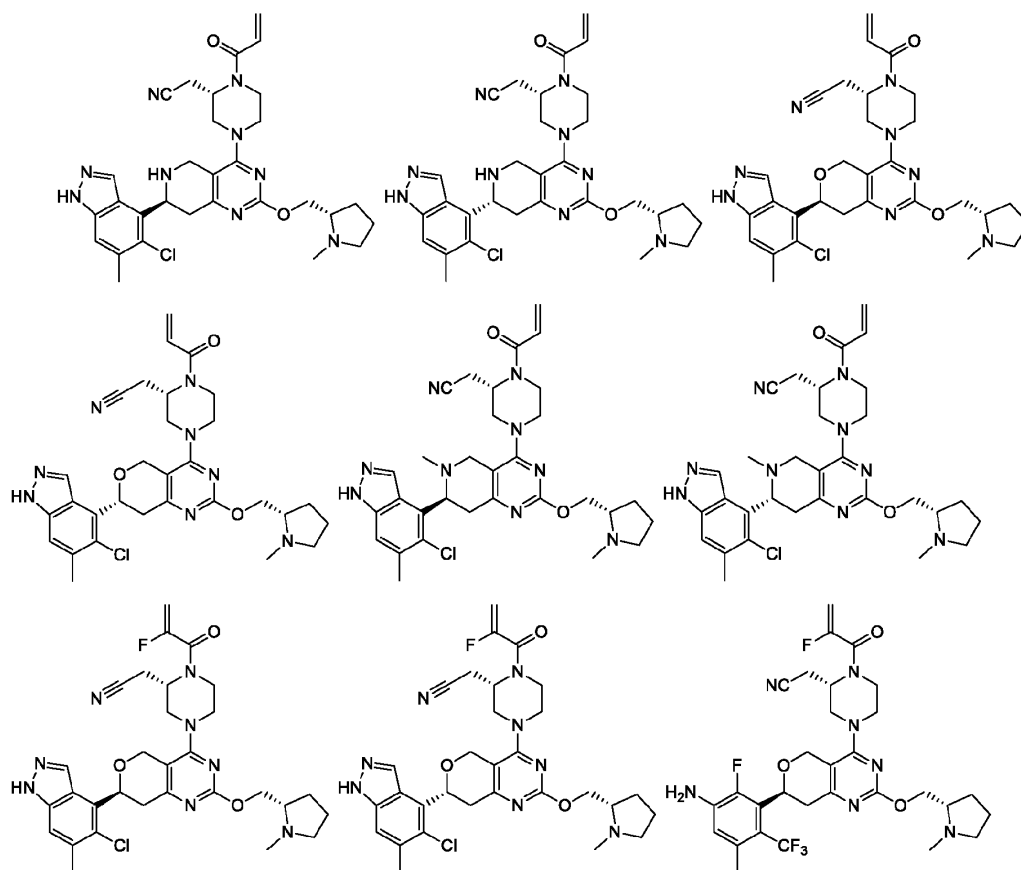


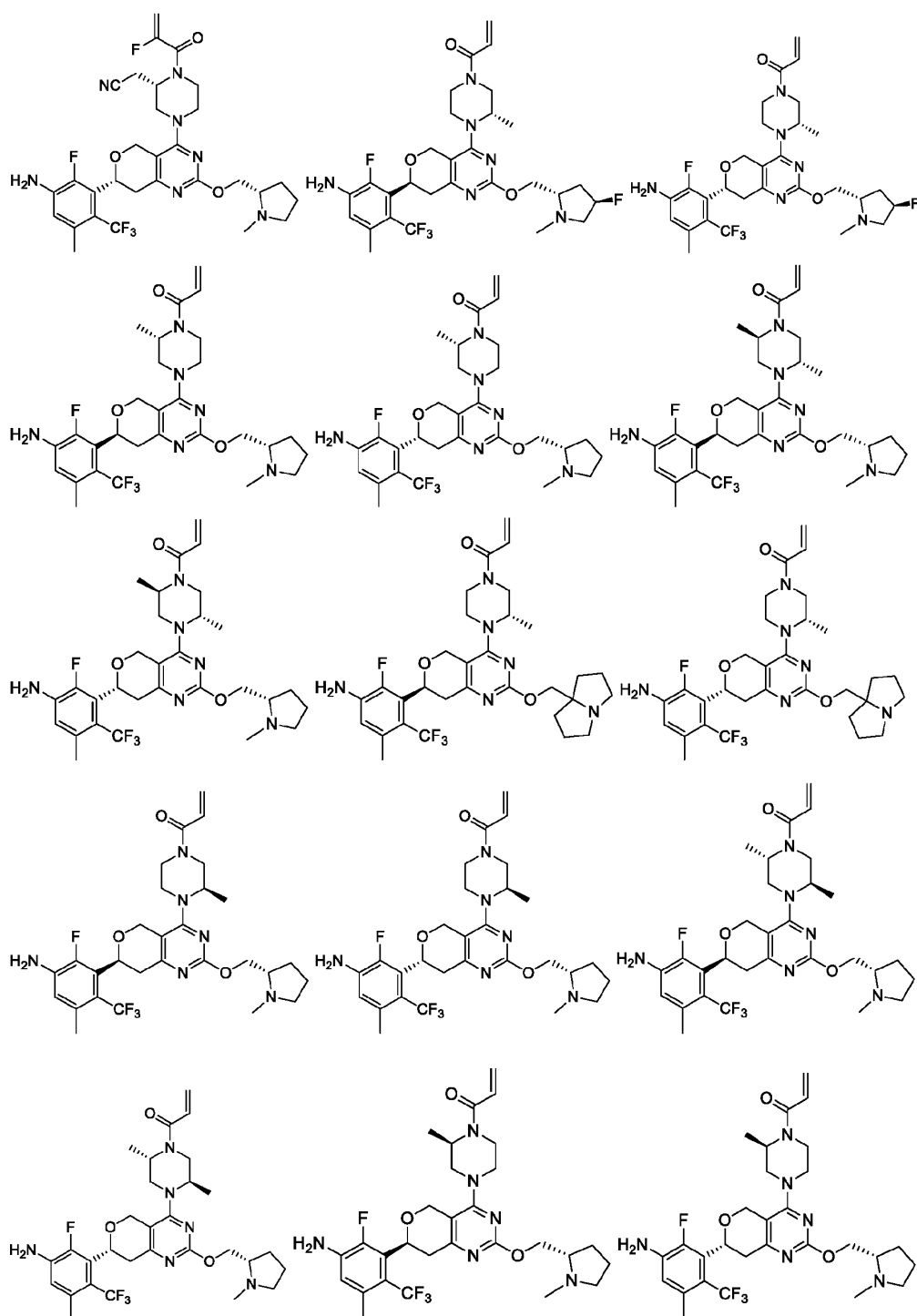
[0201] In some embodiments of the present disclosure, disclosed is the above compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from,

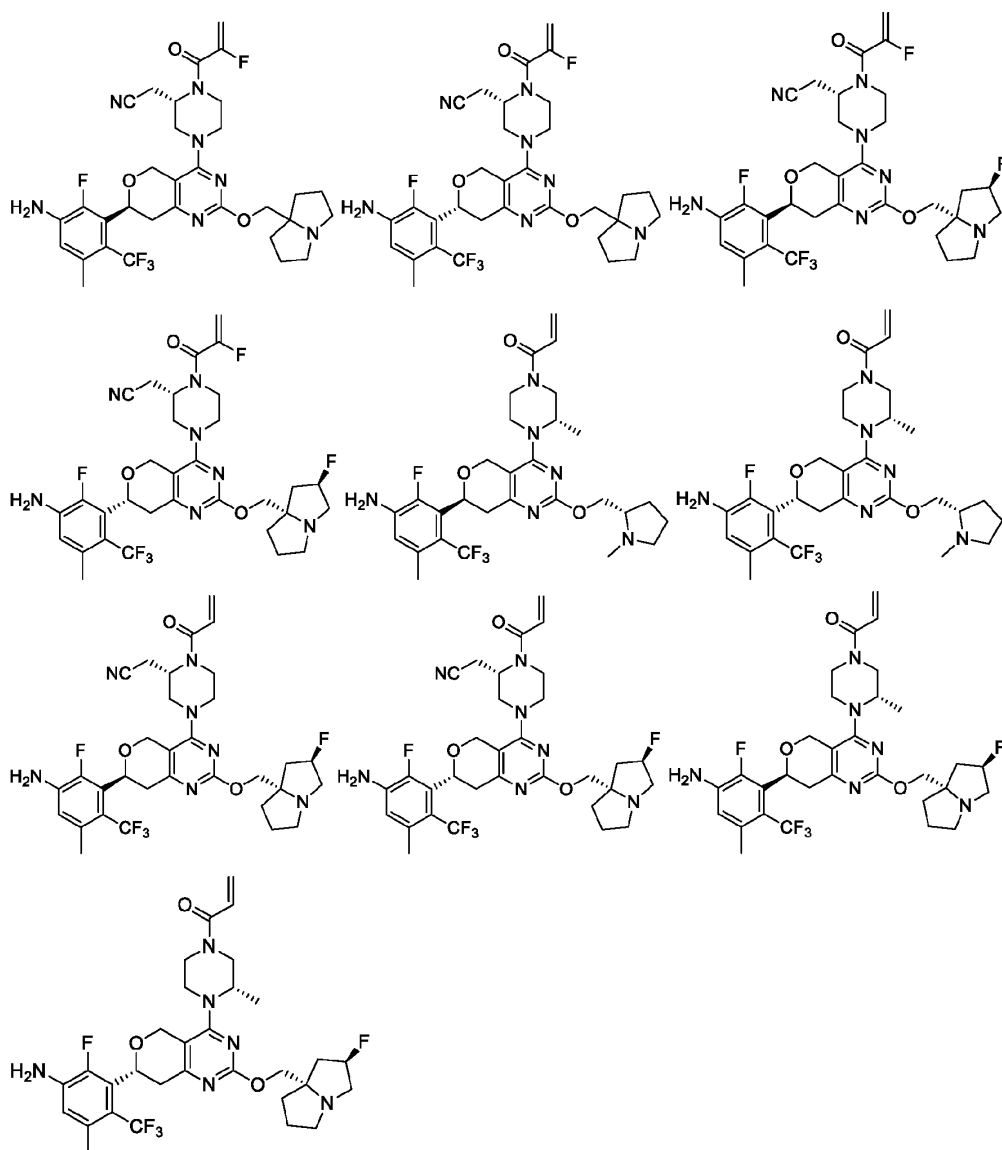




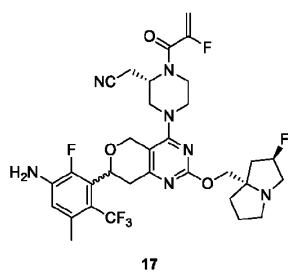
[0202] In some embodiments of the present disclosure, disclosed is the above compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from,







[0203] In some embodiments, the KRAS G12C compound is Compound 17 with the structure below, or a pharmaceutically acceptable salt thereof.



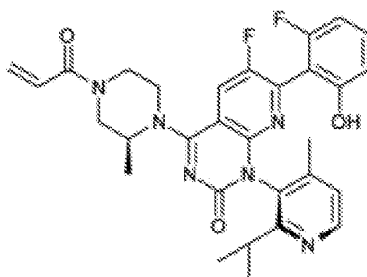
[0204] The compounds discussed above have good cell proliferation inhibitory activity on KRASG12C-mutated MIA-PA-CA-2 cell line and NCI-H358 cells. The compounds of the present disclosure have good stability in liver microsomes, hepatocytes, plasma and whole blood, as well as good PK properties and significant anti-tumor effect. *See e.g.*, US20230151004A1 and WO2023/036282 which are incorporated herein by reference by their entirety. The manufacture and/or synthesis of the compounds discussed above can be found in US20230151004A1 and/or WO2023/036282.

b) Additional exemplary KRAS G12C Inhibitors

[0205] Exemplary KRAS G12C inhibitors that find use with the methods provided herein include, without limitation, *e.g.*, sotorasib, adagrasib, JAB-21822, GDC-6036, JDQ443, D-1553, GH35, GFH925, BPI-421286, and LY3537982, RMC-6291, RMC-8839, HBI-2438, Compound 17, and JNJ-74699157, BI 1823911, MK-1084, HS-10370, JMKX001899, YL-15293, ZG19018, XNW14010, HJ891, BEBT-607, GEC-255, and JS116. Other exemplary small molecule KRAS G12C inhibitors are described in, *e.g.*, Hillig *et al.* (2019) *Proc Natl Acad Sci U S A.* 116(7): 2551–2560 and Sun *et al.* (2012) *Angew Chem Int Ed Engl.* 51(25): 6140–6143, and in WO 2020/233592, WO 2021/023247, WO 2021/083167, WO 2020/238791, WO 2021/000885, CN 112585129, CN 112552295, CN 112390818, CN 112390796, WO 2019/141250, CN 111592528, WO 2020/259432, CN 112300153, CN 112552294, WO 2020/239123, CN 110698378, CN 111377918, CN 111205286, CN 112047939, WO 2020/259513, WO 2021/023154, CN 112430234, WO 2021/063346, WO 2021/058018, CN 112225734, WO 2021/155716, CN112159405, CN 112778302, CN 112830928, WO 2020/1027943, CN 112574199, WO 2021/037018, CN 110172089, WO 2020/156285, CN 111499634, WO 2020/177629, WO 2020/216190, WO 2020/221239, WO 2020/233592, WO 2020/238791, WO 2020/239077, WO 2020/239123, CN 112047933, CN 112047937, CN 112047948, WO 2020/259513, WO 2020/259573, WO 2020/259432, WO 2021/000885, CN 112174950, CN 112300153, WO 2021/023154, WO 2021/023247, CN 112390818, WO 2021/027943, WO 2021/027911, WO 2021/031952, CN 112390796, WO 2021/037018, CN 112442029, WO 2021/043322, WO 2021/052499, CN 112538084, CN 112552295, WO 2021/058018, WO 2021/063346, WO 2021/068898, WO 2021/078285, CN 112225734, CN 112707905, CN 112745335, WO 2021/083167, CN 112778284, WO 2021/088458, CN 112851663, WO 2021/093758, WO 2021/098859, CN 112830928, CN 111377918, WO 2021/104431, WO 2021/109737, WO 2021/113595, CN 112920183, WO

2021/121371, WO 2021/121367, CN 113004269, WO 2021/129824, WO 2021/129820, CN 113061132, WO 2021/139678, WO 2021/139748, CN 111205286, WO 2021/143693, CN 113135924, WO 2021/147965, WO 2021/155716, WO 2021/168193, WO 2021/169990, WO 2021/169963, CN 113321654, WO 2021/175199, WO 2021/180181, WO 2021/185233, WO 2021/190467, WO 2021/197499, CN 112574199, CN 112300269, US20230151004, and WO2023/036282, the contents of which are incorporated herein by reference in their entireties.

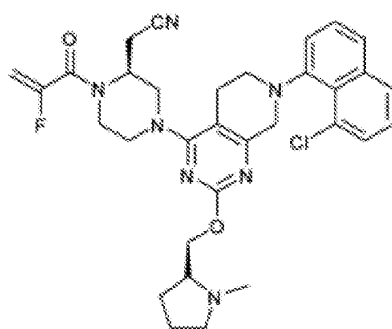
[0206] In some embodiments, the KRAS G12C inhibitor is AMG 510, which, as noted above, is also known as sotorasib, LUMAKRAS™, and LUMYKRAS™. AMG 510 is currently under development by Amgen/Beigene. AMG 510 can exist in either of two atropisomeric forms and one is more active than the other (see, e.g., [https://cen\(dot\)acs\(dot\)org/pharmaceuticals/drug\(dash\)discovery/Amgen\(dash\)unveils\(dash\)KRas\(dash\)inhibitor\(dash\)human/97/i14](https://cen(dot)acs(dot)org/pharmaceuticals/drug(dash)discovery/Amgen(dash)unveils(dash)KRas(dash)inhibitor(dash)human/97/i14)). AMG 510 selectively forms an irreversible covalent bond to the sulfur atom in the cysteine residue that is present in the G12C mutated form of the KRAS protein, but not in the wild type form. The covalent binding of AMG 150 to KRAS G12C locks the protein in its inactive GDP-bound conformation, thus inhibiting KRAS-dependent signal transduction. AMG 150 has the empirical formula C₃₀H_F₂N₆O₃ and a molecular weight of 560.606 g/mol. AMG 150 is described chemically as 6-Fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1*M*)-1-[4-methoxy-2-(propan-2-yl)pyridin-3-yl]-4-[(2*S*)-2-methyl-4-(prop-2-en-1-yl)piperazin-1-yl]pyrido[2,3-*d*]pyrimidin-2(1*H*)-one and has the following chemical structure:



[0207] The CAS Registry Number for AMG 510 is 2252403-56-6. The efficacy of AMG 510 was demonstrated in a subset of patients enrolled in a single-arm, open-label, multicenter trial (NCT03600883) and is currently being investigated in further clinical trials. Complete information about AMG 510 preparation, dispensing, dosage, and administration schedule can be found in the local package insert (for the United States, see, e.g.,

[www\(dot\)accessdata\(dot\)fda\(dot\)gov/drugsatfda_docs/label/2021/214665s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2021/214665s000lbl.pdf). Further details regarding the structure and synthesis of AMG 510 are provided in WO 2018/217651, the contents of which are incorporated herein by reference in their entirety.

[0208] In some embodiments, the KRAS G12C inhibitor is MRTX849 (also known as adagrasib). MRTX849, which is currently under development by Mirati/Zai Lab. Like AMG 510, MRTX849 selectively forms an irreversible covalent bond to the sulfur atom in the cysteine residue that is present in the G12C mutated form of the KRAS protein, but not in the wild type form. Like AMG 510, the covalent binding of MRTX849 to KRAS G12C locks the protein in its inactive GDP-bound conformation, thus inhibiting KRAS-dependent signal transduction. MRTX849 has the empirical formula $C_{32}H_{35}ClFN_7O_2$ and a molecular weight of 604.13 g/mol. MRTX849 is described chemically as 2-[(2S)-4-[7-(8-chloronaphthalen-1-yl)-2-[(2S)-1-methylpyrrolidin-2-yl]methoxy]-6,8-dihydro-5H-pyrido[3,4-d]pyrimidin-4-yl]-1-(2-fluoroprop-2-enoyl)piperazin-2-yl]acetonitrile and has the following chemical structure:



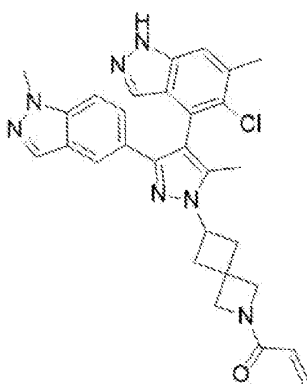
[0209] The CAS Registry Number for MRTX849 is 2326521-71-3. MRTX849 is currently being evaluated in several clinical trials, including NCT04613596, NCT04685135, NCT03785249, NCT04330664, and others. Further details regarding the structure and synthesis of MRTX849 are provided in Fell *et al.* (2020) *J. Med. Chem.* 63, 6679–6693 and WO 2017/201161, the contents of which are incorporated herein by reference in their entirety.

[0210] In some embodiments, the KRAS G12C inhibitor is JAB-21822. JAB-21822 is being developed by Jacobio Pharmaceuticals Group Co., LTD. (see, *e.g.*, [en\(dot\)jacobiopharma\(dot\)com/blank3\(dot\)html?introId=23](http://en.jacobiopharma.com/blank3.html?introId=23) and [www\(dot\)jacobiopharma\(dot\)com/news/207\(dot\)html](http://www.jacobiopharma.com/news/207.html)). JAB-21822 is currently being evaluated in several clinical trials, including NCT05009329 and NCT05002270. Further details regarding the

structure and synthesis of JAB-21822 are provided in WO 2021/057832, the contents of which are incorporated herein by reference in their entirety.

[0211] In some embodiments, the KRAS G12C inhibitor is GDC-6036. GDC-6036 is being developed by Genentech, Inc. (see, *e.g.*, [www\(dot\)genentechoncology\(dot\)com/pipeline-molecules/kras-g12c.html](http://www.genentechoncology.com/pipeline-molecules/kras-g12c.html)) and is currently being evaluated clinical trial NCT04449874. Further details regarding the structure and synthesis of GDC-6036 are provided in WO 2020/097537, the contents of which are incorporated herein by reference in their entirety.

[0212] In some embodiments, the KRAS G12C inhibitor is JDQ443. JDQ443 is an inhibitor of KRAS G12C that is being developed by Novartis. The structure of JDQ443 is:



[0213] JDQ443 is currently being evaluated in clinical trial NCT04699188. Further details regarding the synthesis of JDQ443 are provided in WO 2021/124222, the contents of which are incorporated herein by reference in their entirety.

[0214] In some embodiments, the KRAS G12C inhibitor is D-1553. D-1553 is being developed by InventisBio Co., Ltd. (see, *e.g.*, [www\(dot\)inventisbio\(dot\)com/%e4%b8%b4%e5%ba%8a%e8%af%95%e9%aa%8c/](http://www.inventisbio.com/%e4%b8%b4%e5%ba%8a%e8%af%95%e9%aa%8c/)) and is currently being evaluated in clinical trial NCT04585035 in collaboration with Merck Sharp & Dohme. Further details regarding the structure and synthesis of D-1553 are provided in WO 2020/233592, the contents of which are incorporated herein by reference in their entirety.

[0215] In some embodiments, the KRAS G12C inhibitor is GH35. GH35 is being developed by Suzhou Genhouse Bio Co., Ltd. (see, *e.g.*, [www\(dot\)genhousebio\(dot\)com/en/product/index\(dot\)html](http://www.genhousebio.com/en/product/index(dot)html)) and is being evaluated in clinical trial NCT05010694. Further details regarding the structure and synthesis of GH35 are provided in WO2020/177653, the contents of which are incorporated herein by reference in their entirety.

[0216] In some embodiments, the KRAS G12C inhibitor is GFH925. GFH925 is being developed by GenFleet Therapeutics (Zhejiang) (*see, e.g.,* [www\(dot\)genfleet\(dot\)com/en/science](http://www.genfleet.com/en/science)) and is being evaluated in clinical trial NCT05005234. Further details regarding the structure and synthesis of GFH925 are provided in WO 2020/177629, WO 2020/221239, and WO 2021/031952, the contents of which are incorporated herein by reference in their entirety.

[0217] In some embodiments, the KRAS G12C inhibitor is BPI-421286. BPI-421286 is being developed by Betta Pharmaceutical Co., Ltd (*see, e.g.,* [www\(dot\)bettapharma\(dot\)com/News/show/id/2380](http://www.bettapharma.com/News/show/id/2380)), and clinical trial applications for the evaluation of BPI-421286 (CXHL2100046 and CXHL2100047) have been accepted by the State Food and Drug Administration of the People's Republic of China. Further details regarding the structure and synthesis of BPI-421286 are provided in CN112390796, the contents of which are incorporated herein by reference in their entirety.

[0218] In some embodiments, the KRAS G12C inhibitor is LY3537982. LY3537982 is being developed by Eli Lilly and Company and Loxo Oncology, Inc. (*see, e.g.,* [www\(dot\)lillyloxooncologypipeline\(dot\)com/molecule/kras-g12c-inhibitor/](http://www.lillyloxooncologypipeline.com/molecule/kras-g12c-inhibitor/)), and is being investigated in clinical trial NCT04956640. Further details regarding the structure and synthesis of LY3537982 are provided in WO2021/118877, the contents of which are incorporated herein by reference in their entirety.

[0219] In some embodiments, the KRAS G12C inhibitor is RMC-6291. RMC-6291 is being developed Revolution Medicines.

[0220] In some embodiments, the KRAS G12C inhibitor is RMC-8839. RMC-8839 is being developed by Revolution Medicines.

[0221] In some embodiments, the KRAS G12C inhibitor is HBI-2438. HBI-2438 is being developed by Huya Bioscience and Jemin Biocare, and is being investigated in clinical trial NCT05485974.

[0222] In some embodiments, the KRAS G12C inhibitor is JNJ-74699157 (ARS-3248). JNJ-74699157 is being developed by Johnson and Johnson and Wellspring Biosciences, and was investigated in clinical trial NCT04006301.

C. ERK1/2

[0223] Extracellular Regulated Protein kinase (ERK) 1 and ERK2 are the main players and the terminal signaling kinases involved in the Ras/Raf/MEK/ERK pathway. ERK1/2 act as key

signaling nodules downstream of the Ras-Raf-MEK-ERK pathway and has been shown to be overly activated in human cancers driven by RAS or RAF mutations. Innate resistance to RAF or MEK inhibitors is, in part, due to loss of regulation via a negative feedback loop and pathway re-activation.

[0224] Dysregulation of the RAS/RAF/MAP/ERK kinase cascade has been implicated in many human cancers. Any mutation that causes dysregulated cascade signaling culminates in aberrant activation of ERK 1/2 and results in tumorigenesis. Thus, the ERKs are highly controlled by multiple spatial and temporal mechanisms due to their importance as regulators of critical pathways. ERK 1/2 are directly phosphorylated by MEK 1 and MEK 2. Phosphorylated (e.g., activated) ERK1/2 kinases subsequently phosphorylate numerous substrates which regulate cell cycle progression, differentiation, and survival (Sugiura *et al.*, Cells, 10(10): 2509 (2021)). For example, ERK 1/2 regulated transcription factors control genes that play significant roles in critical cellular processes such as cellular proliferation and cell cycle progression.

[0225] The ERK signaling cascade has also been implicated in several aspects of tumor development (Sugiura *et al.*, Cells, 10(10): 2509 (2021)). For example, ERK 1/2 mediated phosphorylation of certain protein substrates such as focal adhesion kinase promotes cancer cell migration.

D. ERK1/2 inhibitors

[0226] Because the ERK kinases are the nexus of several important signaling pathways in normal cells, limited progress has been achieved with ERK inhibitors because of their lower therapeutic index. However, tumors that are altered in the proteins that are found upstream of ERK 1/2 have been observed to be sensitive to ERK inhibitors (Chin *et al.* Jour. Imm. Pres. Onc., 2(1):10-16, (2020)). ERK 1/2 inhibitors are known to inhibit the ERK kinases through one of two major mechanisms. ERK inhibitors can inhibit ERK catalytic activity through competition for the ATP binding site. These inhibitors are known as catalytic ERKi or catERKi, are reversible inhibitors, and largely result in accumulation of phosphorylated ERK 1/2 in the nucleus (Kidger *et al.*, Mol. Cancer Ther. 19(2): 525-539 (2020)). Dual mechanism ERK inhibitors (dmERKi) prevent ERK activation by blocking MEK 1/2 mediated phosphorylation at the T-E-Y motif (Kidger *et al.*, 2020).

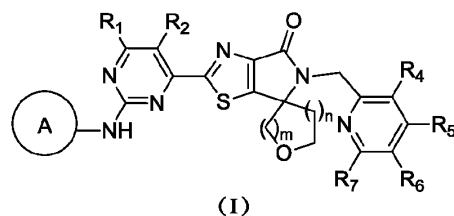
[0227] In some embodiments, the ERK1/2 inhibitor is an inhibitor that inhibits ERK1/2. In some embodiments, the term “ERK1/2” refers to any agent, e.g., polypeptide, fusion polypeptide,

antibody, peptide, antisense oligonucleotide, or small molecule drug, that inhibits the activity of the ERK 1/2 proteins (e.g., the ERK 1/2 kinases). In some embodiments, the ERK1/2 inhibitor interacts directly with the ERK1/2 protein to inhibit the protein's activity.

[0228] In some embodiments, the ERK1/2 inhibitor is a small molecule drug. In some embodiments, the ERK1/2 inhibitor is a small molecule (e.g., a reversible, small molecule catalytic ERK1/2 inhibitor) that inhibits ERK1/2 catalytic activity by competing with ATP for binding to the ERK1/2 protein. In some embodiments, the ERK1/2 inhibitor is a small molecule (e.g., a dual mechanism ERK1/2 inhibitor) that inhibits ERK1/2 activity preventing the formation of the active conformation of ERK1/2. In some embodiments, the ERK1/2 inhibitor prevents phosphorylation of ERK 1/2. In some embodiments, the ERK1/2 inhibitor is a thiazolactam spiroheterocyclic compound, such as the ERK1/2 inhibitor disclosed in WO2023274256, which is herein incorporated by reference. The manufacture and/or synthesis of the ERK1/2 inhibitor can be found in WO2023274256.

a) Exemplary ERK1/2 inhibitor

[0229] In some embodiments, the ERK1/2 inhibitor is a compound represented by formula (I) or a pharmaceutically acceptable salt thereof,



in,

R₁ and R₂ are independently selected from H and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally substituted by 1, 2 or 3 R_a;

R₄, R₅, R₆ and R₇ are independently selected from H, F, Cl, Br, I and C₁₋₃ alkyl, and the C₁₋₃ alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R;

R_a and R_c are independently selected from D, F, Cl, Br and I;

R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and the C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

[0230] In some embodiments of the present disclosure, R_1 and R_2 are independently selected from H, CH_3 and CH_2CH_3 , and said CH_3 and CH_2CH_3 are either is optionally substituted by 1, 2 or 3 R_a .

[0231] In some embodiments of the present disclosure, R_1 and R_2 are independently selected from H, CH_3 , CHF_2 , CD_3 and CH_2CH_3 .

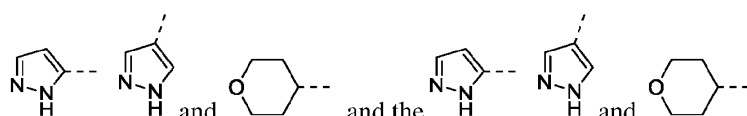
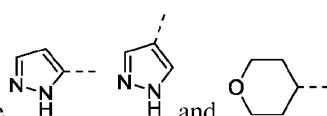
[0232] In some embodiments of the present disclosure, R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and CH_3 , and the CH_3 is optionally substituted by 1, 2 or 3 R_c .

[0233] In some embodiments of the present disclosure, R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and CH_3 .

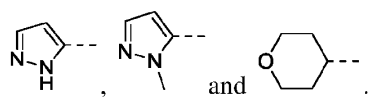
[0234] In some embodiments of the present disclosure, R is selected from F, Cl, Br, I, CH_3 and OCH_3 , and the CH_3 and OCH_3 are optionally replaced by 1, 2 or 3 R substitutions.

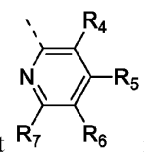
[0235] In some embodiments of the present disclosure, the R_d is selected from CH_3 and OCH_3 .

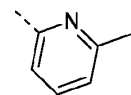
[0236] In some embodiments of the present disclosure, the ring A is selected from the group

consisting of , and the  are optionally substituted by 1, 2 or 3 R_d .

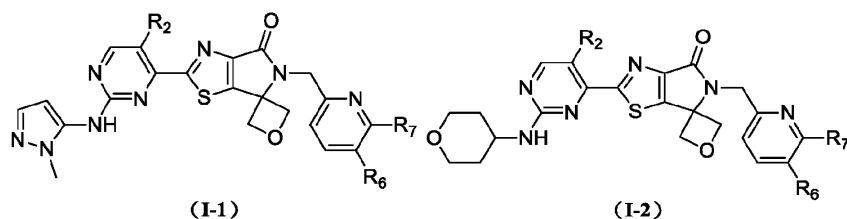
[0237] In some embodiments of the present disclosure, the Ring A is selected from the group

consisting of .

[0238] In some embodiments of the present disclosure, the structural unit  is



[0239] In some embodiments of the present disclosure, the compound or pharmaceutically acceptable salt thereof is selected from

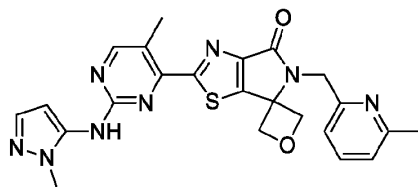


in,

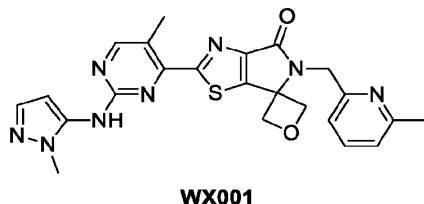
R₂ is as defined in any one of claims 1 to 3;

R₆ and R₇ are as defined in any one of claims 1, 4 or 5.

[0240] In some embodiments of the present disclosure, the ERK1/2 inhibitor comprises an agent comprising WX001 with the following formula or pharmaceutically acceptable salt thereof,



[0241] In some embodiments of the present disclosure, the compound is Form A of WX001, characterized in that its X-ray powder diffraction pattern has characteristic diffraction peaks at the following 2 θ angles: 10.2080 $\pm$ 0.2000 $^\circ$, 18.8429 $\pm$ 0.2000 $^\circ$, 20.6217 $\pm$ 0.2000 $^\circ$;



[0242] In some embodiments of the present disclosure, the ERK1/2 inhibitor has a X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2 θ angles:

 $10.2080 \pm 0.2000^\circ, 18.8429 \pm 0.2000^\circ, 20.6217 \pm 0.2000^\circ, 25.0767 \pm 0.2000^\circ, 25.4797 \pm 0.2000^\circ.$

[0243] In some embodiments of the present disclosure, the ERK1/2 inhibitor has a X-ray powder diffraction pattern with characteristic diffraction peaks at the following 2θ angles:

10.2080 $\pm$ 0.2000 $^{\circ}$, 15.2687 $\pm$ 0.2000 $^{\circ}$, 17.6747 $\pm$ 0.2000 $^{\circ}$, 18.8429 $\pm$ 0.2000 $^{\circ}$, 20.6217 $\pm$ 0.2000 $^{\circ}$,
21.0531 $\pm$ 0.2000 $^{\circ}$, 25.0767 $\pm$ 0.2000 $^{\circ}$, 25.4797 $\pm$ 0.2000 $^{\circ}$.

[0244] In some embodiments of the present disclosure, the ERK1/2 inhibitor has a X-ray powder diffraction spectrum has characteristic diffraction peaks at the following 2θ angles: 10.2080±0.2000°, 14.4684±0.2000°, 15.2687±0.2000°, 17.6747±0.2000°, 18.8429 ± 0.2000 °,

$20.6217 \pm 0.2000^\circ$, $21.0531 \pm 0.2000^\circ$, $21.5713 \pm 0.2000^\circ$, $22.0420 \pm 0.2000^\circ$, $22.4540 \pm 0.2000^\circ$, $25.0767 \pm 0.2000^\circ$, $25.4797 \pm 0.2000^\circ$.

[0245] In some embodiments of the present disclosure, the ERK1/2 inhibitor has a X-ray powder diffraction pattern has characteristic diffraction peaks at the following 2θ angles: 10.2080° , 10.4856° , 14.4684° , 15.0133° , 15.2687° , 15.9518° , 16.6214° , 17.6747° , 17.9514° , 18.4703° , 18.8429° , 19.1531° , 20.6217° , 21.0531° , 21.2894° , 21.5713° , 22.0420° , 22.4540° , 25.0767° , 25.4797° , 26.3255° , 26.9544° .

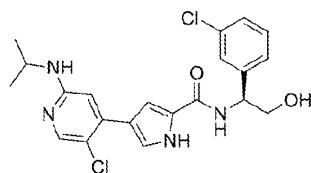
[0246] In some embodiments of the present disclosure, the ERK1/2 inhibitor has a differential scanning calorimetry curve that has an endothermic starting point at $241.0 \pm 3.0^\circ\text{C}$.

[0247] In some embodiments, the ERK1/2 inhibitor has a thermogravimetric analysis curve that has a weight loss of 0.83% at $150.0 \pm 3.0^\circ\text{C}$.

b) Other exemplary ERK 1/2 inhibitors

[0248] Exemplary small molecule ERK 1/2 inhibitors that find use with the methods provided herein include, without limitation, e.g., BVD-523 (ulixertinib), CC-90003, GDC-0994 (Ravoxertinib), KO-947, LTT462, LY3214996 (temuterkib), SCH772984, ERA007, ASN007, FR180204, and MK-8353.

[0249] In some embodiments, the ERK 1/2 inhibitor is BVD-523, which is also known as ulixertinib and VRT752271. BVD-523 is currently under development by BioMed Valley. BVD-523 is a reversible, ATP- competitive oral inhibitor. BVD-523 has an empirical formula of $\text{C}_{21}\text{H}_{22}\text{Cl}_2\text{N}_4\text{O}_2$ and a molecular weight of 433.33 g/mol. BVD-523 is described chemically as (S)-4- (5-chloro-2- (isopropylamino)pyridin-4-yl)-N- (1- (3-chlorophenyl)-2-hydroxyethyl)-1H-pyrrole-2-carboxamide hydrochloride and has the following chemical structure:



[0250] The CAS Registry Number for BVD-523 is 869886-67-9. The efficacy of BVD-523 was demonstrated in a subset of patients enrolled in a multicenter, dose escalation trial (NCT01781429) and is currently being investigated in further clinical trials.

[0251] In some embodiments, the ERK 1/2 inhibitor is CC-90003. CC-90003 is a covalent inhibitor of ERK 1/2 that was developed by Celgene.

[0252] In some embodiments, the ERK 1/2 inhibitor is GDC-0994, which is also known as raxoxertinib. GDC-0994 was developed by Array and Genentech. GDC-0994 has a CAS number of 1453848-26-4, and is also known as 1-[(1S)-1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl]-4-[2-[(2-methylpyrazol-3-yl)amino]pyrimidin-4-yl]pyridin-2-one. The molecular formula is C₂₁H₁₈ClFN₆O₂ and has a molecular weight of 440.863 g/mol. Efficacy of GDC-0994 was demonstrated in a subset of patients enrolled in an open label, multicenter, dose escalation trial (NCT01875705). Further details regarding the structure and synthesis of GDC-0994 is provided in WO2013/130976, the contents of which are incorporated herein by reference in their entirety.

[0253] In some embodiments, the ERK 1/2 inhibitor is KO-947 developed by Araxes Pharma and Kura Oncology. Further details regarding the structure and synthesis of KO-947 is provided in WO2015/051341, the contents of which are incorporated herein by reference in their entirety.

[0254] In some embodiments, the ERK 1/2 inhibitor is LTT462, which is also known as rineterkib and was developed by Novartis. LTT462 has a chemical formula of C₂₆H₂₇BrF₃N₅O₂.

[0255] In some embodiments, the ERK 1/2 inhibitor is LY3214996, which is also known as temuterkib. LY3214996 is being developed by Eli Lilly. The efficacy of temuterkib is currently being investigated in clinical trials.

[0256] In some embodiments, the ERK 1/2 inhibitor is SCH772984. SCH772984 is under development by Merck. SCH772984 has a CAS number of 942183-80-4, a molecular formula of C₃₃H₃₃N₉O₂, and a molecular weight of 587.67 g/mol.

[0257] In some embodiments, the ERK 1/2 inhibitor is FR180204. FR180204 is also known as 5-(2-phenylpyrazolo[1,5-a]pyridin-3-yl)-1H-pyrazolo[3,4-c]pyridazin-3-amine. The CAS number is 865362-74-9, has a molecular formula of C₁₈H₁₃N₇, and a molecular weight of 327.3 g/mol.

[0258] In some embodiments, the ERK 1/2 inhibitor is MK-8353 (SCH 900353). MK-8353 is under development by Merck. MK-8353 has a CAS number of 1184173-73-6, a molecular weight of 691.84 g/mol, and has the formula C₃₇H₄₁N₉O₃S.

E. KRAS-G12C resistance

[0259] In some embodiments, the cancer is resistant to a prior KRAS treatment (e.g., a treatment involves a KRAS-G12C inhibitor, e.g., cancer has acquired resistance to a KRAS G12C inhibition, e.g., cancer being resistant or acquired resistant to a KRAS inhibitor such as MRTX849, AMG510, or Compound 17).). In some embodiment, the cancer (e.g., cancer cells) is only partially responding to the prior KRAS treatment. In some embodiments, the partial response is determined by the absence of tumor regression. In some embodiments, the partial response is determined by no more than about 90%, 80%, 70%, 60%, 50%, 40%, 30%, or 20% of tumor growth inhibition (e.g., as calculated by methods described herein).

[0260] A series of strategies try to indirectly target KRAS, such as inhibiting farnesyltransferase by blocking KRAS post-translational modification or by inhibiting downstream KRAS effectors. Amgen and Mirati Therapeutics have developed two direct KRAS-G12C inhibitors, namely sotorasib (also known as AMG 510 or Lumakras) and adagrasib (also known as MRTX849), which act by selectively forming a covalent bond with cysteine 12 within the switch-II pocket of KRAS-G12C protein, thereby locking KRAS in the inactive state to arrest cell proliferation. Preclinical studies have shown that sotorasib and adagrasib selectively impair the viability of KRAS-G12C mutant cell lines, but do not affect cell lines with other KRAS mutations in vitro and in vivo. Both sotorasib and adagrasib have long half-life (5.5–24 h) and extensive tissue distribution in human. Unexpectedly, neither sotorasib nor adagrasib affects PI3K signaling, indicating that the upstream pathway independent of KRAS-G12C facilitates the activation of PI3K, which provides an explanation for the formation of KRAS-G12C inhibitor resistance.

[0261] Emerging preclinical and clinical evidence shows that the biggest obstacle to KRAS-G12C inhibitor treatment is the inevitable emergence of drug resistance. Although the problem of resistance to therapy is multifaceted, intercellular variability or intratumoral heterogeneity is considered to be the main factor leading to KRAS-G12C inhibitor resistance. Single-cell RNA sequencing analysis of KRAS-G12C mutant NSCLC cell line treated with KRAS-G12C inhibitor ARS1620 demonstrated that the subpopulation of cells synthesizing the new KRAS-G12C protein, rather than the wild-type KRAS protein, is the cause of adaptive resistance. *See e.g.*, Nature. 2020 Jan;577(7790):421-425. Further analysis revealed that the EGFR or aurora kinase A (AURKA) signals can maintain the newly expressed KRAS-G12C protein in the active GTP-bound form, thereby evading KRAS-G12C inhibitor treatment. However, another study suggests that wild-type RAS activation mediated by multiple RTKs, rather than a single RTK, is responsible for the

acquired resistance of KRAS-G12C inhibitors (ARS-1620 and sotorasib) in various types of cancer cell lines. *See Clin Cancer Res.* 2020;26:1633–43. Regardless, many independent studies demonstrate the importance of PTPN11/SHP2 as a common downstream of RTKs to activate the wild-type or mutant KRAS protein in mediating acquired drug resistance. Clinical trials (NCT04330664) are ongoing to test the combination with TNO155 (SHP2 inhibitor) and adagrasib in patients with advanced solid tumors carrying KRAS-G12C mutation. In addition, the activation of the PI3K-AKT-mTOR pathway contributes to the development of sotorasib resistance in human PDAC cell line in vitro and in xenograft mouse models. Gene set enrichment analysis and mass spectrometry-based phosphoproteomics analysis found that induction of epithelial-to-mesenchymal transition (EMT) promotes resistance to sotorasib or ARS-1620 through activation of PI3K or ERK pathway in NSCLC cells in a cell type-dependent manner. Nuclear factor, erythroid 2 like 2 (NFE2L2, best known as NRF2) regulated by kelch like ECH associated protein 1 (KEAP1) is a key transcription factor in cellular antioxidant response. KEAP1 or NFE2L2 mutations that predict poor response to checkpoint inhibitor immunotherapy may also be related to resistance to adagrasib. These findings provide a kinase- or transcription factor-targeted therapy approach for overcoming resistance to KRAS-G12C inhibitors. *See e.g., Cancer Gene Ther* 29, 875–878 (2022).

[0262] In addition, intrinsic or adaptive resistance may be caused by concurrent genetic changes, such as secondary KRAS mutations and other genetic mutations, which are not targeted by KRAS-G12C inhibitors. Indeed, a recent clinical study used next-generation sequencing and deep mutation scanning to characterize genetic variations in tissue samples or circulating tumor DNA from patients resistant to adagrasib. Among 38 patients with KRAS-G12C mutation cancer (27 patients with NSCLC, 10 with colorectal cancer, and 1 with appendix cancer) received adagrasib monotherapy, 45% patients are found a putative resistance mechanism to adagrasib. Moreover, 18% of them have multiple overlapping genetic mechanisms: acquired KRAS mutations of G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, and Y96C; high-level amplification of the KRAS-G12C allele; acquired bypass resistance mechanisms including MET amplification; activating mutations in NRAS, BRAF, MAP2K1, RETALK, RET, RAF1, FGFR3, NF1, and PTEN; oncogenic fusions involving ALK, RET, BRAF, RAF1, and FGFR3; and loss-of-function mutations in NF1 and PTEN. This information could finally be synthesized for each tumor cell at any decision point and used to adapt treatment. Similarly, acquired resistance to adagrasib has been reported in an NSCLC patient, which is related to the reactivation of the RAS-MAPK signaling by 10

secondary gene mutations on the RAS-RAF-MEK-ERK pathway. Among them, KRAS-Y96D mutation directly affects the binding of adagrasib to the P2 pocket, thereby conferring resistance to sotorasib, adagrasib, or ARS-1620 in multiple cancer cell lines (H358, MIA PaCa2, and BaF3). In contrast, RM-018, a representative KRAS-G12C-selective inhibitor from Revolution Medicines' new class of RAS(ON) inhibitors, retains potent inhibitory activity against tumor cells harboring dual KRAS-G12C/Y92D mutations. In addition to KRAS-Y96D, KRAS-Y96S and KRAS-Y96C also contribute to the resistance to sotorasib or adagrasib in BaF3 cells, and this process can be reversed by the combined use of SOS1 inhibitors (BI-3406). Altogether, these findings highlight the complexity of the genetic mechanism of KRAS-G12C inhibitor resistance. *See e.g., Cancer Gene Ther* 29, 875–878 (2022).

[0263] In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment.

[0264] In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment.

[0265] In some embodiments, the individual comprises a secondary mutation in KRAS. In some embodiments, the secondary mutation comprises a R68, Y96, or A59 mutation in KRAS. In some embodiments, the individual comprises a R68M, Y96D, or A59T mutation.

[0266] In some embodiments, the cancer comprises a copy number variation in KRAS. In some embodiments, the cancer comprises a copy number in KRAS (e.g., mutant KRAS, e.g., wildtype KRAS) that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% higher than a reference copy number. In some embodiments, the cancer comprises a copy number in KRAS (e.g., mutant KRAS, e.g., wildtype KRAS) that is at least about one-fold, two-fold, three-fold, four-fold, five-fold, six-fold, seven-fold, eight-fold, nine-fold, ten-fold higher than a reference copy number in KRAS. In some embodiments, the reference copy number in KRAS is a corresponding copy number in KRAS of a reference individual (or a population of reference individual) without the disease (e.g., cancer). In some embodiments, the reference copy number in KRAS is a corresponding copy number in KRAS of the same individual prior to the prior therapy (e.g., prior KRAS G12C inhibitor treatment).

[0267] In some embodiments, the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy. In some embodiments, the cancer comprises a KRAS mRNA level and/or KRAS protein level (e.g., mutant KRAS, e.g., wildtype KRAS) that is at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% higher than a reference KRAS mRNA level and/or KRAS protein level. In some embodiments, the cancer comprises a KRAS mRNA level and/or KRAS protein level (e.g., mutant KRAS, e.g., wildtype KRAS) that is at least about one-fold, two-fold, three-fold, four-fold, five-fold, six-fold, seven-fold, eight-fold, nine-fold, ten-fold higher than a reference KRAS mRNA level and/or KRAS protein level. In some embodiments, the reference KRAS mRNA level and/or KRAS protein level is a corresponding KRAS mRNA level and/or KRAS protein level of a reference individual (or a population of reference individual) without the disease (e.g., cancer). In some embodiments, the reference KRAS mRNA level and/or KRAS protein level is a corresponding KRAS mRNA level and/or KRAS protein level of the same individual prior to the prior therapy (e.g., prior KRAS G12C inhibitor treatment).

[0268] In some embodiments, the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter.

[0269] In some embodiments, the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy. In some embodiments, the cancer has an increased level of active GTP-bound wildtype RAS. In some embodiments, the wildtype RAS comprises H-RAS and/or N-RAS.

[0270] In some embodiments, the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway (e.g., when the mRNA level or protein level of a molecule involved in MAPK pathway is not significantly changed, see e.g., Microbiol Mol Biol Rev. 2011 Mar; 75(1): 50–83).

[0271]

Prior KRAS inhibitor treatments

[0272] In some embodiments, the prior KRAS inhibitor is an inhibitor specifically targeting a mutation on codon 12.

[0273] In some embodiments, the *KRAS* inhibitor is a G12C inhibitor. Exemplary G12C inhibitors can be found in e.g., J Exp Clin Cancer Res 41, 27 (2022), which is incorporated herein in its entirety. In some embodiments, the *KRAS* inhibitor is ARS-1620, RM-018, sotorasib or adagrasib.

[0274] In some embodiments, the *KRAS* inhibitor is a G12D inhibitor. Exemplary G12D inhibitors can be found in e.g., Cell Discov 8, 5 (2022), which is incorporated herein in its entirety. In some embodiments, the G12D inhibitor is MRTX1133 or RMC-9805.

[0275] In some embodiments, the *KRAS* inhibitor is a G12V inhibitor. Exemplary G12V inhibitors can be found in e.g., Cancer Res (2021) 81 (13_Supplement): 1260, which is incorporated herein in its entirety. .

[0276] In some embodiments, the complex is administered at least about 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, or 24 months after the *KRAS* inhibitor treatment.

[0277] In some embodiments, the complex is administered no more than about 1, 2, 3, 4, 5, 6, 9, 12, 15, 18, 21, or 24 months after the *KRAS* inhibitor treatment.

Mutant KRAS (e.g., mutation on codon 12, e.g., secondary mutation post prior KRAS inhibitor treatment)

[0278] In some embodiments, the cancer tissue has a *KRAS* aberration. In some embodiments, the aberration of *KRAS* comprises a mutation on codon 12. In some embodiments, the mutation on codon 12 is a somatic mutation. In some embodiments, the mutation on codon 12 is a germline mutation. In some embodiments, the aberration of *KRAS* is G12C.

[0279] In some embodiments, the cancer tissue has a *KRAS* mutation on codon 13, 59, 61, 68, 95, or 96. In some embodiments, the cancer tissue has a G12D, G12R, G12V, G12W, G13D, A59T, Q61H, R68S, R68M, H95D, H95Q, H95R, Y96C, Y96D, or high-level amplification of the KRASG12C allele. In some embodiments, any one of the mutations on codon 13, 59, 61, 68, 95, and/or 96 are germline mutation. In some embodiments, any one of the mutations on codon 13, 59, 61, 68, 95, and/or 96 are somatic mutation.

[0280] In some embodiments, the cancer tissues have a secondary mutation in *KRAS* after the prior *KRAS* inhibitor *treatment*. In some embodiments, the cancer tissue developed a *KRAS* mutation on codon 12, 13, 59, 61, 68, 95, or 96 after the prior *KRAS* inhibitor treatment. In some embodiments, the cancer tissue has an acquired *KRAS* aberration selected from the group consisting of G12D, G12R, G12V, G12W, G13D, A59T, Q61H, R68S, R68M, H95D, H95Q, H95R,

Y96C, Y96D, and high-level amplification of the KRASG12C allele, optionally the acquired KRAS aberration is developed after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a Q61H mutation after the prior therapy (e.g., a prior KRAS inhibitor treatment).

[0281] In some embodiments, the cancer tissue has at least one (or at least two, three, four or five) additional *KRAS* aberration (e.g., one additional mutation) other than G12C. In some embodiments, the at least one (or at least two, three, four or five) additional *KRAS* aberration is selected from the group consisting of G12D, G12R, G12V, G12W, G13D, A59T, Q61H, R68S, R68M, H95D, H95Q, H95R, Y96C, Y96D, and high-level amplification of the KRASG12C allele. In some embodiments, the one additional *KRAS* aberration is Q61H.

[0282] The genetic aberrations of *KRAS* may be assessed based on a sample, such as a sample from the individual and/or reference sample. In some embodiments, the sample is a tissue sample or nucleic acids extracted from a tissue sample. In some embodiments, the sample is a cell sample (for example a CTC sample) or nucleic acids extracted from a cell sample. In some embodiments, the sample is a tumor biopsy. In some embodiments, the sample is a tumor sample or nucleic acids extracted from a tumor sample. In some embodiments, the sample is a biopsy sample or nucleic acids extracted from the biopsy sample. In some embodiments, the sample is a Formaldehyde Fixed-Paraffin Embedded (FFPE) sample or nucleic acids extracted from the FFPE sample. In some embodiments, the sample is a blood sample. In some embodiments, cell-free DNA is isolated from the blood sample. In some embodiments, the biological sample is a plasma sample or nucleic acids extracted from the plasma sample.

[0283] The genetic aberrations of *KRAS* may be determined by any method known in the art. See, for example, Dickson et al. *Int. J. Cancer*, 2013, 132(7): 1711-1717; Wagle N. *Cancer Discovery*, 2014, 4:546-553; and Cancer Genome Atlas Research Network. *Nature* 2013, 499: 43-49. Exemplary methods include, but are not limited to, genomic DNA sequencing, bisulfite sequencing or other DNA sequencing-based methods using Sanger sequencing or next generation sequencing platforms; polymerase chain reaction assays; in situ hybridization assays; and DNA microarrays. The epigenetic features (such as DNA methylation, histone binding, or chromatin modifications) of one or more genes from a sample isolated from the individual may be compared with the epigenetic features of the one or more genes from a control sample. The nucleic acid molecules extracted from the sample can be sequenced or analyzed for the presence of the genetic aberrations relative to a reference sequence, such as the wildtype sequences of *KRAS*.

[0284] In some embodiments, the genetic aberration of *KRAS* is assessed using cell-free DNA sequencing methods. In some embodiments, the genetic aberration of *KRAS* is assessed using next-generation sequencing. In some embodiments, the genetic aberration of *KRAS* isolated from a blood sample is assessed using next-generation sequencing. In some embodiments, the genetic aberration of *KRAS* is assessed using exome sequencing. In some embodiments, the genetic aberration of *KRAS* is assessed using fluorescence in-situ hybridization analysis. In some embodiments, the genetic aberration of *KRAS* is assessed prior to initiation of the methods of treatment described herein. In some embodiments, the genetic aberration of *KRAS* is assessed after initiation of the methods of treatment described herein. In some embodiments, the genetic aberration of *KRAS* is assessed prior to and after initiation of the methods of treatment described herein. An aberrant level of *KRAS* may refer to an aberrant expression level or an aberrant activity level.

[0285] In some embodiments, the individual does not develop a secondary *KRAS* mutation in exon 1 and/or 2 after the *KRAS* treatment.

Cancer

[0286] In some embodiments, the cancer is a leukemia or lymphoma. In some embodiments, the cancer is a solid tumor.

[0287] In some embodiments, the solid tumor includes, but is not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, Kaposi's sarcoma, soft tissue sarcoma, uterine sarcoma, synovial sarcoma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0288] In some embodiments, the disease is selected from the group consisting of myelodysplastic syndrome, lung cancer (*e.g.*, NSCLC, small cell lung cancer, squamous cell lung cancer), colorectal cancer, acute myeloid leukemia, pancreatic cancer, rectal cancer, esophageal squamous cell carcinoma, gastrointestinal stromal tumor, head and neck squamous cancer, pancreatic ductal adenocarcinoma, multiple myeloma, and glioma.

[0289] In some embodiments, the cancer is pancreatic cancer (*e.g.*, pancreatic ductal adenocarcinoma).

[0290] In some embodiments, the cancer is colorectal cancer.

[0291] In some embodiments, the cancer is lung cancer (*e.g.*, NSCLC).

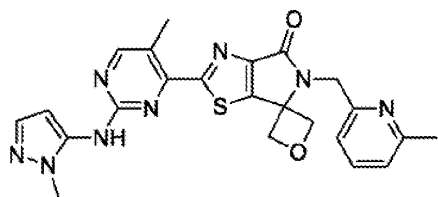
[0292] In some embodiments, the cancer is a malignant and/or advanced cancer.

Dosages

[0293] The amount of ERK 1/2 inhibitor, KRAS G12C inhibitor, and/or an EGFR inhibitor (*e.g.*, an anti-EGFR antibody, *e.g.*, cetuximab) which will be effective in the treatment, inhibition and prevention of cancer harboring a KRAS G12C mutation (*i.e.*, a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein) may be determined by standard clinical techniques. The doses of the inhibitors will also depend the concentration of each inhibitor, on the route of administration, and the seriousness of the cancer, the patient's condition, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

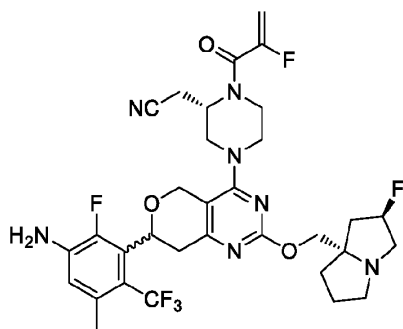
[0294] In some embodiments, provided herein are methods and/or uses for treating cancer harboring a KRAS G12C mutation (*i.e.*, a cancer comprising one or more cancer cells that express a KRAS G12C mutant protein) in a subject, comprising administering to the subject an effective amount of (1) an ERK 1/2 inhibitor; and (2) a KRAS G12C inhibitor. In some embodiments, the method further comprises administering an effective amount of an EGFR inhibitor (*e.g.*, an anti-EGFR antibody, *e.g.*, cetuximab). In some embodiments, an effective amount (*e.g.*, dosage) can result in the functionality as described below and herein.

[0295] In some embodiments, the ERK 1/2 inhibitor is the following formula or a pharmaceutically acceptable salt thereof,



In some embodiments, the amount of ERK 1/2 inhibitor administered to the subject is equivalent to a dose for a mouse which is included in any of the following ranges: about 10 mg/kg to about 100 mg/kg, about 10 to about 25 mg/kg, about 10 to about 30 mg/kg, about 10 mg/kg to about 50 mg/kg, about 20 to about 25 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25 to about 55 mg/kg, about 20 to about 25 mg/kg, about 40 to about 50 mg/kg, about 30 mg/kg to about 50 mg/kg, about 20 mg/kg to about 60 mg/kg, about 10 mg/kg to about 25 mg/kg, or about 45 mg/kg to about 55 mg/kg. In some embodiments, the amount of ERK 1/2 inhibitor administered to the subject for treating cancer is equivalent to a dose for a mouse which includes, for example, any of about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, about 32 mg/kg, about 33 mg/kg, about 34 mg/kg, about 35 mg/kg, about 36 mg/kg, about 37 mg/kg, about 38 mg/kg, about 39 mg/kg, about 40 mg/kg, about 41 mg/kg, about 42 mg/kg, about 43 mg/kg, about 44 mg/kg, about 45 mg/kg, about 46 mg/kg, about 47 mg/kg, about 48 mg/kg, about 49 mg/kg, about 50 mg/kg, about 51 mg/kg, about 52 mg/kg, about 53 mg/kg, about 54 mg/kg, about 55 mg/kg, or about 60 mg/kg. In some embodiments, the ERK 1/2 inhibitor is administered to the subject twice a day, daily, or once every two days. In some embodiments, the ERK 1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the ERK 1/2 inhibitor is administered twice a day, daily, or once every two days for at least about 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, or 52 weeks.

[0296] In some embodiments, the KRAS G12C inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



In some embodiments, the amount of KRAS G12C inhibitor administered to the subject is a dose equivalent to a dose for a mouse that is included in any of the following ranges: about 1 to about 10 mg/kg, about 10 to about 100 mg/kg, about 10 to about 25 mg/kg, about 10 to about 30 mg/kg, about 10 mg/kg to about 50 mg/kg, about 20 to about 25 mg/kg, about 20 to about 50 mg/kg, about 25 to about 50 mg/kg, about 25 to about 55 mg/kg, about 20 to about 25 mg/kg, about 40 to about 50 mg/kg, about 30 mg/kg to about 50 mg/kg, about 20 mg/kg to about 60 mg/kg, about 10 mg/kg to about 25 mg/kg, about 40 mg/kg to about 80 mg/kg, about 5 mg/kg to about 30 mg/kg, about 50 mg/kg to about 100 mg/kg, about 75 mg/kg to about 100 mg/kg, about 80 mg/kg to about 100 mg/kg, 90 mg/kg to about 100 mg/kg, or about 40 mg/kg to about 100 mg/kg. In some embodiments, the dose of the KRAS G12C inhibitor for treating cancer in a subject is a dose equivalent to a dose for a mouse that is for example any of about 3 mg/kg, about 5 mg/kg, about 10 mg/kg, about 15 mg/kg, about 20 mg/kg, about 21 mg/kg, about 22 mg/kg, about 23 mg/kg, about 24 mg/kg, about 25 mg/kg, about 26 mg/kg, about 27 mg/kg, about 28 mg/kg, about 29 mg/kg, about 30 mg/kg, about 31 mg/kg, about 32 mg/kg, about 33 mg/kg, about 34 mg/kg, about 35 mg/kg, about 36 mg/kg, about 37 mg/kg, about 38 mg/kg, about 39 mg/kg, about 40 mg/kg, about 41 mg/kg, about 42 mg/kg, about 43 mg/kg, about 44 mg/kg, about 45 mg/kg, about 46 mg/kg, about 47 mg/kg, about 48 mg/kg, about 49 mg/kg, about 50 mg/kg, about 51 mg/kg, about 52 mg/kg, about 53 mg/kg, about 54 mg/kg, about 55 mg/kg, or about 60 mg/kg, about 65 mg/kg, about 70 mg/kg, about 75 mg/kg, about 80 mg/kg, about 85 mg/kg, about 90 mg/kg, about 91 mg/kg, about 92 mg/kg, about 93 mg/kg, about 94 mg/kg, about 95 mg/kg, about 96 mg/kg, about 97 mg/kg, about 98 mg/kg, about 99 mg/kg, or about 100 mg/kg. In some embodiments, the G12C inhibitor is administered to the subject twice a day, daily, or once every two days. In some embodiments, the G12C inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In

some embodiments, the G12C inhibitor is administered twice a day, daily, or once every two days for at least about 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, or 52 weeks.

[0297] In some embodiments, the ERK 1/2 inhibitor is administered orally. In some embodiments, the KRAS G12C inhibitor is administered orally. In some embodiments, the inhibitor or inhibitors are administered twice a day, daily, or once every two days. In some embodiments, the inhibitor or inhibitors are administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days. In some embodiments, the inhibitor or inhibitors are administered twice a day, daily, or once every two days for at least about 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, or 52 weeks. In some embodiments, the inhibitor or inhibitors are administered twice a day. In some embodiments, the inhibitor or inhibitors are administered twice a day for 28 days. In some embodiments, the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma. In some embodiments, the cancer is advanced, unresectable, and/or metastatic solid tumor. In some embodiments, the cancer is resistant to (e.g., has acquired resistance to) KRAS G12C inhibition (e.g., resistant to a KRAS inhibitor, e.g., resistant to MRTX849, AMG510, or Compound 17). In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer was previously treated with a second KRAS G12C inhibitor. In some embodiments, the cancer tissues has a secondary mutation in KRAS after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T mutation after the prior KRAS inhibitor treatment. In some embodiments, the cancer tissue developed a R68M, Y96D, or A59T mutation after the prior KRAS inhibitor treatment. In some embodiments, 1) the individual comprises a secondary mutation in KRAS, optionally wherein the secondary mutation comprises a R68, Y96, or A59 mutation in

KRAS, optionally the individual comprises a R68M, Y96D, or A59T mutation; 2) the cancer comprises a copy number variation in KRAS; 3) the cancer comprises an upregulated KRAS mRNA level and/or KRAS protein relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy; 4) the cancer comprises a mutation in KRAS promoter that increases the strength of the promoter; and/or 5) the cancer comprises an increased wildtype RAS signaling relative to a corresponding tissue or organ in a reference individual, a non-cancer tissue or organ in the same individual, or the same cancer prior to a prior therapy, optionally wherein the cancer has an increased level of active GTP-bound wildtype RAS, optionally wherein the wildtype RAS comprises H-RAS and/or N-RAS. In some embodiments, the second KRAS inhibitor is sotorasib or adagrasib. In some embodiments, the ERK 1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously, concurrently, or sequentially. In some embodiments, the ERK 1/2 inhibitor is administered prior to the KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is administered prior to the ERK 1/2 inhibitor. In some embodiments, the method further comprises administering to the individual an effective amount of a third therapy comprising another anti-cancer agent, optionally wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents.

[0298] In some embodiments, the ERK1/2 inhibitor is used for the manufacture of a medicament for treating cancer, wherein the treatment is in combination with a KRAS G12C inhibitor. In some embodiments, the ERK1/2 inhibitor and the KRAS G12C inhibitor are used for the manufacture of a medicament for treating cancer, wherein the treatment is in combination with a KRAS G12C inhibitor. The treatment comprises administration of the (1) ERK 1/2 inhibitor and the (2) KRAS G12C inhibitor in amounts (e.g., dosages) that can result in the functionality as described herein.

[0299] In some embodiments, the EGFR inhibitor (e.g., an anti-EGFR antibody, e.g., cetuximab) administered to the subject is a dose equivalent to a dose for a mouse that is about 30 mg/kg or at least about 30 mg/kg. In some embodiments, the EGFR inhibitor (e.g., an anti-EGFR

antibody, e.g., cetuximab) is administered intravenously or subcutaneously. In some embodiments, the EGFR inhibitor (e.g., an anti-EGFR antibody, e.g., cetuximab) is administered at a frequency of twice a day, daily, or once every two days. In some embodiments, the EGFR inhibitor (e.g., an anti-EGFR antibody, e.g., cetuximab) is administered at a frequency of no more than twice a day, daily, or once every two days.

[0300] In some embodiments, treatment according to any of the methods or uses disclosed herein results in at least about a 2 fold, about a 2.5 fold, about a 3 fold, about a 3.5 fold, about a 4 fold, about a 4.5 fold, about a 5 fold, about a 5.5 fold, about a 6 fold, about a 6.5 fold, about a 7 fold, about a 7.5 fold, about a 8 fold, about a 8.5 fold, about a 9 fold, about a 9.5 fold, about a 10 fold, about a 10.5 fold, about a 11 fold, about a 12 fold, about a 15 fold, about a 18 fold, about a 20 fold, about a 21 fold, about a 22 fold, about a 23 fold, about a 24 fold, about a 25 fold, about a 26 fold, about a 27 fold, about a 28 fold, about a 29 fold, about a 30 fold, about a 31 fold, about a 32 fold, about a 33 fold, about a 34 fold, or about a 35 fold reduction in tumor size (e.g., tumor volume) compared to tumors that are not treated according to any of the methods or uses disclosed herein (e.g., single therapy or vehicle control).

[0301] In some embodiments, treatment according to any of the methods or uses disclosed herein results in at least about a 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 33.3%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% decrease in tumor growth inhibition compared to tumors that are not treated according to any of the methods or uses disclosed herein.

[0302] In some embodiments, treatment according to any of the methods or uses disclosed herein results in at least about a 2 fold, about a 2.5 fold, about a 3 fold, about a 3.5 fold, about a 4 fold, about a 4.5 fold, about a 5 fold, about a 5.5 fold, about a 6 fold, about a 6.5 fold, about a 7 fold, about a 7.5 fold, about a 8 fold, about a 8.5 fold, about a 9 fold, about a 9.5 fold, about a 10 fold, about a 12 fold, about a 14 fold, about a 16 fold, about a 18 fold, or about a 20 fold decrease in tumor weight compared to tumors that are not treated according to any of the methods or uses disclosed herein.

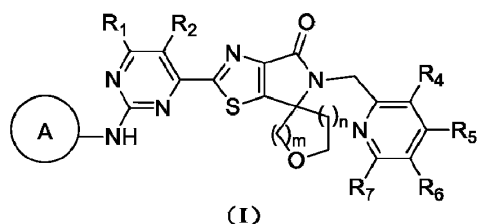
[0303] In some embodiments, treatment according to any of the methods or uses disclosed herein results in at least about a 2 fold, about a 2.5 fold, about a 3 fold, about a 3.5 fold, about a 4 fold, about a 4.5 fold, about a 5 fold, about a 5.5 fold, about a 6 fold, about a 6.5 fold, about a 7 fold, about a 7.5 fold, about a 8 fold, or about a 8.5 fold decrease in tumor weight compared to tumors that are not treated according to any of the methods or uses disclosed herein.

[0304] In some embodiments, treatment according to any of the methods or uses disclosed herein results in at least about a 2 fold, about a 2.5 fold, about a 3 fold, about a 3.5 fold, about a 4 fold, about a 4.5 fold, about a 5 fold, about a 5.5 fold, about a 6 fold, about a 6.5 fold, about a 7 fold, about a 7.5 fold, about a 8 fold, or about a 8.5 fold increase in survival in subjects (e.g., individuals) compared to the subjects (e.g., individuals) that are not treated according to any of the methods or uses disclosed herein (e.g., single therapy or vehicle control).

Kits for treating cancer

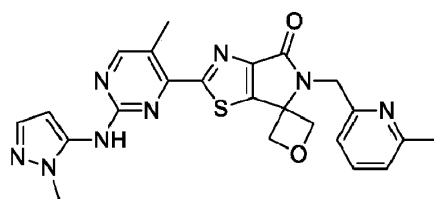
[0305] Provided is a kit comprising materials useful for the treatment of a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). In certain embodiments, the kit comprises a container containing an ERK 1/2 inhibitor as described herein, and a second container comprising a KRAS G12C inhibitor.

[0306] Provided is a kit comprising materials useful for the treatment of a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). In certain embodiments, the kit comprises a container containing an ERK 1/2 inhibitor as described herein, and a second container comprising a KRAS G12C inhibitor. In some embodiments, ERK 1/2 inhibitor comprises an agent comprising formula (I) or a pharmaceutically acceptable salt thereof,



wherein, R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ; R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution; n is 0 or 1; m is 1 or 2; Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R_d ; R_a and R_c are independently selected from D, F, Cl, Br and I; R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and said C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions; R is selected from F, Cl, Br and I.

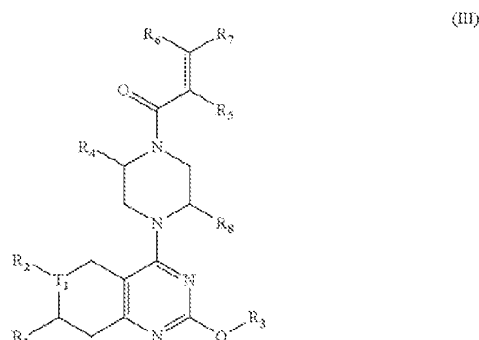
[0307] Provided is a kit comprising materials useful for the treatment of a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). In certain embodiments, the kit comprises a container containing an ERK 1/2 inhibitor as described herein, and a second container comprising a KRAS G12C inhibitor. In some embodiments, ERK 1/2 inhibitor comprises an agent comprising the following formula



or a pharmaceutically acceptable salt thereof.

[0308] Provided is a kit comprising materials useful for the treatment of a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal

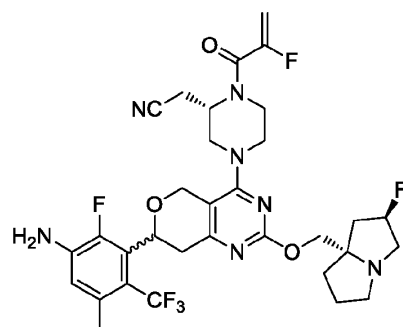
cancer, or rectal adenocarcinoma). In certain embodiments, the kit comprises a container containing an ERK 1/2 inhibitor as described herein, and a second container comprising a KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein T₁ is selected from O and N; R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a; when T₁ is O, R₂ is not present; when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b; R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c; R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d; R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F; R₈ is selected from H and CH₃; R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F; R_b is each independently selected from F, Cl, Br, I, OH and NH₂; R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R; R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN; R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino; provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H.

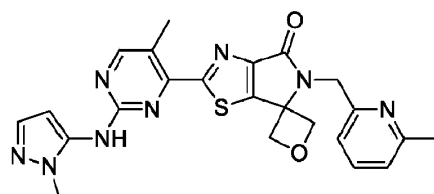
[0309] Provided is a kit comprising materials useful for the treatment of a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer,

peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). In certain embodiments, the kit comprises a container containing an ERK 1/2 inhibitor as described herein, and a second container comprising a KRAS G12C inhibitor; and wherein the KRAS G12C inhibitor comprises an agent comprising the following formula

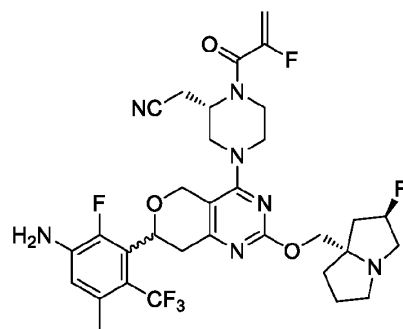


or a pharmaceutically acceptable salt thereof.

[0310] Provided is a kit comprising materials useful for the treatment of a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). In certain embodiments, the kit comprises a container containing an ERK 1/2 inhibitor as described herein, and a second container comprising a KRAS G12C inhibitor. In some embodiments, ERK 1/2 inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



; and wherein the KRAS G12C inhibitor comprises an agent comprising the following formula



or a pharmaceutically acceptable salt thereof.

[0311] In certain embodiments, the kit comprises a container and a label or package insert on or associated with the containers. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, test tubes, *etc.* The containers may be formed from a variety of materials such as glass or plastic. The first container holds a composition (e.g., a composition comprising an ERK 1/2 inhibitor as described herein) which is by itself or combined with another composition effective for treating (such as delaying the progression of) a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). The container may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one agent in the composition is an ERK 1/2 inhibitor as described herein. In some embodiments, the at least one agent in the composition is an ERK 1/2 inhibitor as described herein. In some embodiments, the label or package insert indicates that the composition is used in combination with a KRAS G12C inhibitor for treating a KRAS G12C mutant cancer (such as lung adenocarcinoma, non-small cell lung cancer, colon adenocarcinoma, colorectal adenocarcinoma, pancreatic cancer, cholangiocarcinoma, endometrial cancer, ovarian cancer, peritoneal cancer, bladder cancer, gastric cancer, thyroid cancer, melanoma, breast cancer, head and neck cancer, multiple myeloma, acute myeloid leukemia (AML), uterine cancer, gastro-esophageal cancer, or rectal adenocarcinoma). In some embodiments, the KRAS G12C inhibitor is Compound 17.

[0312] Moreover, the kit may comprise (a) a first container with a composition contained therein, wherein the composition comprises an ERK 1/2 inhibitor as described herein, and (b) a

second container with a composition contained therein, wherein the composition comprises KRAS G12C inhibitor (*e.g.*, a polypeptide, antibody, fusion polypeptide, antisense oligonucleotide or a small molecule drug that is capable of inhibiting the activity of the KRAS G12C mutant protein).

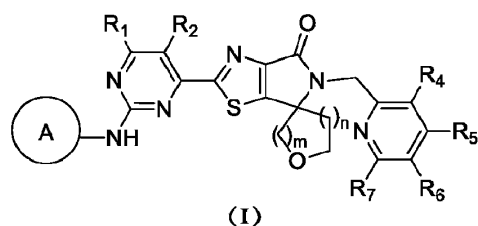
In some embodiments, the second container contains a small molecule KRAS G12C inhibitor.

Exemplary small molecule KRAS G12C inhibitors that can be packaged with the kits provided herein include, without limitation, *e.g.*, sotorasib, adagrasib, JAB-21822, GDC-6036, JDQ443, D-1553, GH35, GFH925, BPI-421286, and LY3537982, RMC-6291, RMC-8839, HBI-2438, JNJ-74699157, and Compound 17. In some embodiments, the KRAS G12C inhibitor is Compound 17. Additionally, the kit may further comprise an additional container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[0313] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

EXEMPLARY EMBODIMENTS

[0314] Embodiment 1. A method of treating cancer in an individual, comprising administering to the individual an effective amount of 1) an ERK1/2 inhibitor; and 2) a KRAS G12C inhibitor, wherein the ERK1/2 inhibitor comprises an agent comprising the formula (I) or a pharmaceutically acceptable salt thereof,



in,

R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ;

R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

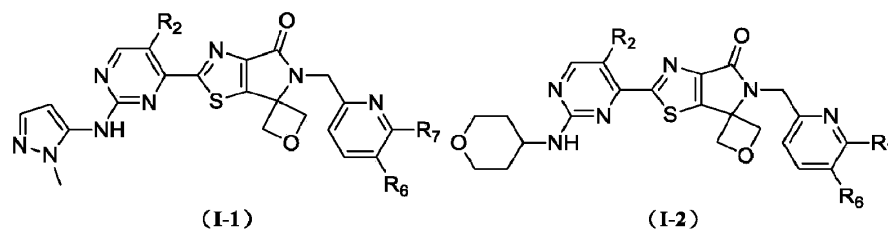
Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R;

R_a and R_c are independently selected from D, F, Cl, Br and I;

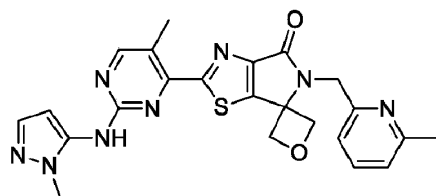
R_d is selected from F, Cl, Br, I, C₁₋₃ alkyl and C₁₋₃ alkoxy, and said C₁₋₃ alkyl and C₁₋₃ alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

[0315] Embodiment 2. The method of embodiment 1, wherein the ERK1/2 inhibitor is selected from:



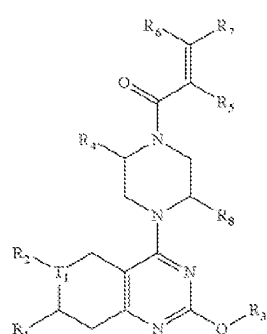
[0316] Embodiment 3. The method of embodiment 2, wherein the ERK1/2 inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



[0317] Embodiment 4. The method of any one of embodiments 1-3, wherein the KRAS G12C inhibitor is a small molecule.

[0318] Embodiment 5. The method of embodiment 4, wherein the KRAS G12C inhibitor is selected from the group consisting of: sotorasib, adagrasib, JAB-21822, GDC-6036, JDQ443, D-1553, GH35, GFH925, BPI-421286, and LY3537982, RMC-6291, RMC-8839, HBI-2438, and JNJ-74699157.

[0319] Embodiment 6. The method of embodiment 5, wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof.



(III)

wherein

T₁ is selected from O and N;

R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

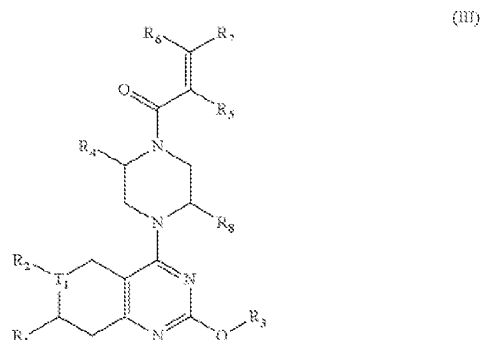
R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

R_d is each independently selected from F, Cl, Br, I, OH, NH₂ and CN;

R is each independently selected from H, F, Cl, Br, OH, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy and —C₁₋₃ alkyl-O—C(=O)—C₁₋₃ alkylamino;

provided that when R₁ is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH₂, CF₃, CH₂CH₃ and —C≡CH, and R₅, R₆ and R₇ are each independently H.

[0320] Embodiment 7. A method of treating cancer in an individual, comprising administering to the individual an effective amount of 1) an ERK1/2 inhibitor; and 2) KRAS G12C inhibitor, wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T₁ is selected from O and N;

R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

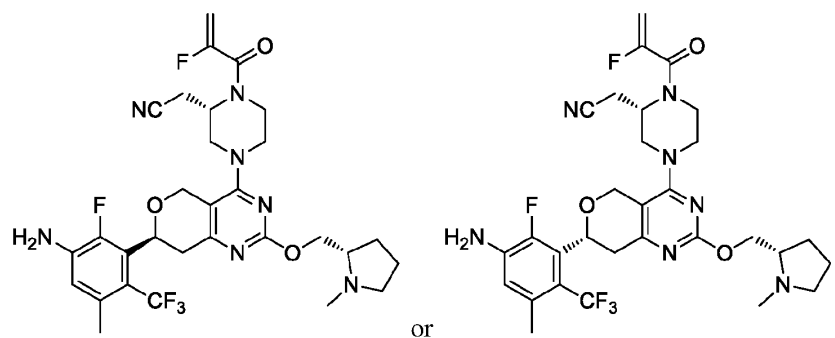
R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R ;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

R is each independently selected from H, F, Cl, Br, OH, CN, C_{1-3} alkyl, C_{1-3} alkoxy and $-C_{1-3} \text{ alkyl-O-C(=O)-}C_{1-3} \text{ alkylamino}$;

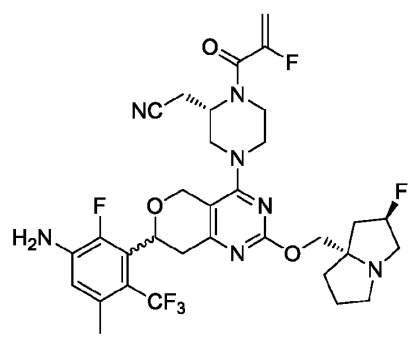
provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH_2 , CF_3 , CH_2CH_3 and $-C\equiv CH$, and R_5 , R_6 and R_7 are each independently H.

[0321] Embodiment 8. The method of embodiment 7, wherein the KRAS G12C inhibitor comprises an agent comprising the following formula



or a pharmaceutically acceptable salt thereof.

[0322] Embodiment 9. The method of embodiment 8, wherein the KRAS G12C inhibitor comprises an agent comprising the following formula



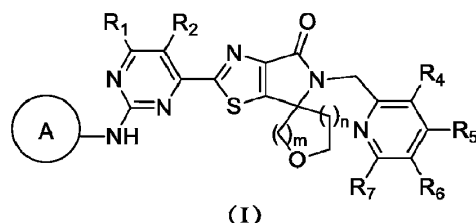
or a pharmaceutically acceptable salt thereof.

[0323] Embodiment 10. The method of any one of embodiments 7-9, wherein the ERK1/2 inhibitor is a small molecule.

[0324] Embodiment 11. The method of embodiment 10, wherein the ERK1/2 inhibitor is selected from the group consisting of: BVD-523 (ulixertinib), CC-90003, GDC-0994

(Ravoxertinib), KO-947, LTT462, LY3214996 (temuterkib), WX001, SCH772984, FR180204, and MK-8353.

[0325] Embodiment 12. The method of embodiment 10, wherein the ERK1/2 inhibitor comprises an agent comprising the formula (I) or a pharmaceutically acceptable salt thereof,



wherein,

R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ;

R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R ;

R_a and R_c are independently selected from D, F, Cl, Br and I;

R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and said C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

[0326] Embodiment 13. The method of any one of embodiments 1-12, wherein the KRAS G12C inhibitor is administered orally.

[0327] Embodiment 14. The method of any one of embodiments 1-13, wherein the ERK1/2 inhibitor is administered orally.

[0328] Embodiment 15. The method of any one of embodiments 1-14, wherein the cancer comprises one or more cancer cells that express a KRAS G12C mutant protein.

[0329] Embodiment 16. The method of any one of embodiments 1-15, wherein the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia,

uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma.

[0330] Embodiment 17. The method of any one of embodiments 1-16, wherein the cancer is a solid tumor, optionally wherein the solid tumor is an advanced, unresectable, and/or metastatic solid tumor.

[0331] Embodiment 18. The method of any one of embodiments 1-17, wherein the cancer is resistant to KRAS G12C inhibition, optionally wherein the cancer is resistant to a KRAS G12C inhibitor (e.g., MRTX849, e.g., AMG510).

[0332] Embodiment 19. The method of any one of embodiments 1-18, wherein the cancer was previously treated with a KRAS G12C inhibitor.

[0333] Embodiment 20. The method of embodiment 19, wherein the KRAS12C inhibitor is sotorasib.

[0334] Embodiment 21. The method of any one of embodiments 1-20, wherein the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously.

[0335] Embodiment 22. The method of any one of embodiments 1-21, wherein the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered concurrently.

[0336] Embodiment 23. The method of any one of embodiments 1-20, wherein the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered sequentially.

[0337] Embodiment 24. The method of embodiment 23, wherein the ERK1/2 inhibitor is administered prior to the KRAS G12C inhibitor.

[0338] Embodiment 25. The method of embodiment 23, wherein the KRAS G12C inhibitor is administered prior to the ERK1/2 inhibitor.

[0339] Embodiment 26. The method of any one of embodiments 1-25, wherein the ERK 1/2 inhibitor is administered in one or more doses.

[0340] Embodiment 27. The method of embodiment 26, wherein the dose is equivalent to a dose of about 10 mg/kg to about 100 mg/kg for a mouse.

[0341] Embodiment 28. The method of any one of embodiments 1-27, wherein the KRAS G12C inhibitor is administered in one or more doses.

[0342] Embodiment 29. The method of embodiment 28, wherein the dose is equivalent to a dose of about 10 mg/kg to about 50 mg/kg for a mouse.

[0343] Embodiment 30. The method of any one of embodiments 1-29, further comprising administering to the individual an effective amount of a third therapy.

[0344] Embodiment 31. The method of embodiment 30, wherein the third therapy comprises another anti-cancer agent.

[0345] Embodiment 32. The method of embodiment 31, wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents, optionally wherein the anti-cancer agent is an EGFR inhibitor, further optionally wherein the EGFR inhibitor is an anti-EGFR antibody (e.g., cetuximab).

[0346] Embodiment 33. The method of any one of embodiments 1-32, wherein the individual is a human.

[0347] Embodiment 34. The method of any one of embodiments 1-33, wherein the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that comprises an aberration in KRAS (e.g., KRAS G12C, e.g., KRAS G12D, e.g., KRAS Q61H), optionally wherein the aberration in KRAS comprises a) a KRAS G12C mutant protein, b) a KRAS G12D mutant protein and/or c) a KRAS Q61H mutant protein.

[0348] Embodiment 35. Use of an ERK1/2 inhibitor and a KRAS G12C inhibitor for the manufacture of a medicament for treating cancer.

[0349] Embodiment 36. The use of embodiment 35, wherein the cancer is selected from colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma.

[0350] Embodiment 37. The method of embodiment 16 or the use of embodiment 36, wherein the cancer is colorectal cancer (e.g., NSCLC).

[0351] Embodiment 38. The method of embodiment 16 or the use of embodiment 36, wherein the cancer is pancreatic cancer.

[0352] Embodiment 39. The method of embodiment 16 or the use of embodiment 36, wherein the cancer is lung cancer.

[0353] Embodiment 40. The method or use of any one of embodiments 1-39, wherein the treatment comprises a dose that is equivalent to a dose of 25 to 50 mg/kg of the ERK 1/2 inhibitor for a mouse.

[0354] Embodiment 41. The method or use of any one of embodiments 1-40, wherein the treatment comprises a dose that is equivalent to a dose of 10 to 100 mg/kg of the KRAS G12C inhibitor.

[0355] Embodiment 42. A kit for treating cancer in an individual, comprising: 1) an ERK1/2 inhibitor; and 2) a KRAS G12C inhibitor.

EXAMPLES

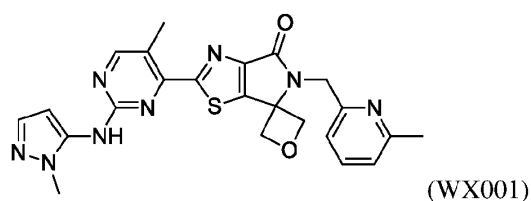
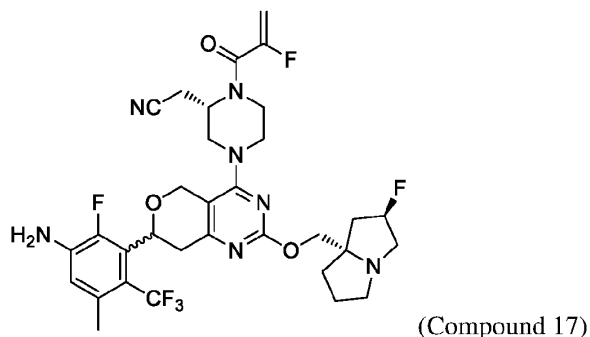
[0356] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the present invention, and are not intended to limit the scope of what the inventors regard as their invention nor are they intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (*e.g.* amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Evaluation of the anti-tumor efficacy of ERK1/2 inhibitor in combination with KRAS G12C inhibitor in NCI-H2122 human lung cancer xenograft mouse model.

[0357] The objective was to evaluate the *in vivo* anti-tumor efficacy of WX001 (*i.e.*, WX001; ERK1/2 inhibitor) in combination with Compound 17 (KRAS G12C inhibitor) in subcutaneous NCI-H2122 human lung cancer xenograft implanted in female BALB/c nude mice.

[0358] Unlike other ERK1/2 inhibitors, such as Erasca's ERAS-007m which requires a complex BID-QW dosing schedule, WX001 is administered on a simple and continuous QD

schedule without dosing holidays as described below, allowing a simple protocol that is convenient for patients.



[0359] While several potent ERK inhibitors, such as AZD0364, ERAS007, and MK-8353, have relatively long target protein-residence times (ranging from 190 to 550 minutes), the ERK protein residence time for WX001 is approximately 40 minutes. Inventors' have unique insights that WX001's intermediate protein residency time is more favorable because it is long enough to allow sufficient target blockade while short enough to permit pulsatile inhibition, which will help alleviate on-target toxicity in normal tissues. The clinical PK of WX001 is around 3-6 hours, further supporting an intermittent target inhibition profile when dosed once daily, twice a day or once every two days.

[0360] Materials and methods:

[0361] NCI-H2122 tumor cells (ATCC, cat# CRL-5985) were maintained in RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% PS can cultures in an incubator set at 37°C with 5% CO₂. The tumor cells were routinely sub-cultured twice weekly. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[0362] Female BALB/c nude mice were inoculated subcutaneously at the right flank with NCI-H2122 tumor cells (5×10^6) in 0.2 mL of PBS with Matrigel (1:1) for tumor development. Treatments were started on day 6 after tumor inoculation when the average tumor volume reached 159 mm³. The animals were assigned into groups using an Excel-based randomization software

performing stratified randomization based upon their tumor volumes. Each group consisted of 6 tumor-bearing mice. The testing articles were prepared and were administrated to the mice according to the predetermined regimen as shown in the experimental design table (**Tables E1**).

Table E1: Experimental design and dosage for NCI-H2122 xenograft model

Group	N	Treatment	Dose (mg/kg)	Dose volume (mL/kg)	Dosing route	Schedule
1	6	Vehicle	-	10	PO	QD x 28 Days
2	6	MRTX849	100	10	PO	QD x 28 Days
3	6	AMG510	100	10	PO	QD x 28 Days
4	6	Compound 17	30	10	PO	QD x 28 Days
5	6	Compound 17	100	10	PO	QD x 28 Days
6	6	WX001	25	10	PO	BID x 28 Days
7	6	WX001	25	10	PO	QD x 28 Days
8	6	WX001	50	10	PO	QD x 28 Days
9	6	Compound 17+ WX001	30 +25	10	PO+PO	QD x 28 Days +BID x 28 Days
10	6	Compound 17+ WX001	30 +25	10	PO+PO	QD x 28 Days +QD x 28 Days
11	6	Compound 17+ WX001	30 +50	10	PO+PO	QD x 28 Days +QD x 28 Days

QD: daily, BID: two times a day.

[0363] Tumor volume was measured twice weekly in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: $V = 0.5 a \times b^2$ where *a* and *b* are the long and short diameters of the tumor, respectively. The T/C (%) value was calculated for each group using the formula: $T/C \% = T/C \times 100 \%$ (T: treatment group; C: control group, T and C are the mean tumor weight of the treated and control groups, respectively, on a given day).

[0364] Tumor Growth Inhibition (TGI) was calculated for each group using the formula: $TGI (\%) = [1 - (T_i - T_0) / (V_i - V_0)] \times 100$; T_i is the average tumor volume of a treatment group on a given day, T_0 is the average tumor volume of the treatment group on the first day of treatment, V_i is the average tumor volume of the vehicle control group on the same day with T_i , and V_0 is the average tumor volume of the vehicle group on the first day of treatment.

[0365] Statistical analysis of difference in the tumor volume and tumor weight among the groups were conducted on the data obtained at the 28th day after the start of treatment.

[0366] One-way ANOVA was performed to compare the tumor volume among groups, followed by Dunnet's multiple comparisons. All data were analyzed using Graphpad Prism software. A $p < 0.05$ was considered to be statistically significant.

[0367] Animal body weight was monitored regularly as an indirect measurement of toxicity. As historical data showed that mice bearing the NCI-H2122 xenograft in general can lose over 15% of body weight as tumor progression, thus all mice were supplied with nutrient gel and sunflower seeds.

[0368] Results:

[0369] NCI-H2122 is a non-small cell lung cancer (NSCLC) cell line harboring KRAS G12C mutation. Previous research (Cancer Discov. 2020 Jan;10(1):54-71) has shown that NCI-H2122 model represents a cancer phenotype that is partially sensitive to KRAS G12C inhibitors, such as MRTX849. In this study, the anti-tumor efficacy of WX001 in combination with Compound 17 was evaluated in NCI-H2122 cell line-derived xenograft model. Two clinical-stage KRAS G12C inhibitors, AMG510 and MRTX849 were included as monotherapy control arms. The efficacy of WX001 monotherapy at two different dose levels was also evaluated.

[0370] On average, treatment was well tolerated as indicated by the average percent body weight loss (**FIG. 1**). Notably, the body weight loss observed in the mice receiving combination therapy of Compound 17 and WX001 did not exceed that of the vehicle control (**FIG. 1**).

Table E3: Tumor volume over time

Days ²	Tumor volume (mm ³) ¹										
	Vehicle	MRTX849100 mg/kg QD	AMG510100 mg/kg QD	Compound 1730 mg/kg QD	Compound 17100 mg/kg QD	WX00125 mg/kg BID	WX00125 mg/kg QD	WX00150 mg/kg QD	Compound 17+WX00130 mg/kg+25mg/kg QD+BI D	Compound 17+WX00130 mg/kg+25mg/kg QD+QD	Compound 17+WX00130 mg/kg+50mg/kg QD+QD
0	159 ± 22	159 ± 20	159 ± 22	159 ± 19	159 ± 19	159 ± 22	159 ± 21	159 ± 22	159 ± 19	159 ± 20	159 ± 21
4	301 ± 65	148 ± 15	127 ± 31	162 ± 25	143 ± 15	204 ± 40	191 ± 24	221 ± 49	131 ± 23	142 ± 22	106 ± 9
7	454 ± 110	185 ± 21	205 ± 58	211 ± 39	170 ± 22	268 ± 67	271 ± 44	313 ± 94	139 ± 32	162 ± 37	111 ± 11
11	657 ± 115	251 ± 25	247 ± 78	265 ± 61	231 ± 30	301 ± 57	420 ± 82	415 ± 99	164 ± 34	231 ± 54	119 ± 11
14	865 ± 117	290 ± 40	283 ± 84	270 ± 66	286 ± 41	436 ± 107	629 ± 115	545 ± 145	194 ± 42	245 ± 50	141 ± 5
18	1,255 ± 173	375 ± 31	413 ± 111	386 ± 110	381 ± 57	538 ± 142	781 ± 179	666 ± 151	174 ± 26	273 ± 55	109 ± 8
21	1,528 ± 265	384 ± 36	457 ± 129	431 ± 150	412 ± 80	643 ± 201	894 ± 184	668 ± 117	188 ± 34	289 ± 59	119 ± 16
25	1,772 ± 284	501 ± 38	526 ± 132	489 ± 147	485 ± 87	738 ± 244	970 ± 170	689 ± 96	195 ± 30	302 ± 63	154 ± 10
28	2,359 ± 375	556 ± 40	615 ± 123	527 ± 148	548 ± 88	778 ± 193	1,182 ± 129	777 ± 131	262 ± 37	420 ± 91	184 ± 16

Note:

1. Data was shown as mean ± SEM;
2. Days refer to the day post treatment initiation.

Table E4: Tumor growth inhibition analysis for each treatment in the NCI-H2122 xenograft model calculated based on tumor volume measurements on Day 28

Group number	Treatment	N	TV (mm ³) ¹ on PG-D28	T/C ² (%)	TGI ³ (%)	p value ⁴
1	Vehicle	6	2,359±375	--	--	--
2	MRTX849, 100 mg/kg, QD	6	556±40	23.56	81.97	<0.0001
3	AMG510, 100 mg/kg, QD	6	615±123	26.09	79.25	<0.0001
4	Compound 17, 30 mg/kg, QD	6	527±148	22.36	83.25	<0.0001
5	Compound 17, 100 mg/kg, QD	6	548±88	23.23	82.31	<0.0001
6	WX001, 25 mg/kg, BID	6	778±193	33.00	71.84	<0.0001
7	WX001, 25 mg/kg, QD	6	1,182±129	50.13	53.47	<0.0001
8	WX001, 50 mg/kg, QD	6	777±131	32.94	71.91	<0.0001
9	Compound 17+WX001, 30 mg/kg+25 mg/kg, QD+BID	6	262±37	11.11	95.31	<0.0001
10	Compound 17+WX001, 30 mg/kg+25 mg/kg, QD+QD	6	420±91	17.81	88.14	<0.0001
11	Compound 17+WX001, 30 mg/kg+50 mg/kg, QD+ QD	6	184±16	7.79	98.88	<0.0001

Note:

1. Mean ± SEM;
2. T/C is calculated using the formula: $T/C \% = T/C \times 100 \%$ (T: treatment group; C: control group, T and C are the mean tumor weight of the treated and control groups, respectively, on a given day);
3. $TGI (\%) = [1 - (T_{28} - T_0) / (V_{28} - V_0)] \times 100\%$;
4. p value was calculated based on tumor volume (TV)

Table E5: Statistical analysis of the difference between Compound 17 monotherapy and combination therapy of Compound 17 with WX001

P value		Group number			
		4	9	10	11
		Compound 17 30 mg/kg QD	Compound 17+WX001 30 mg/kg+25mg/kg QD+BID	Compound 17+WX001 30mg/kg+25mg/kg QD+QD	Compound 17+WX001 30 mg/kg+50mg/kg QD+QD
Group number	4	/	0.1179	0.7307	0.0339
	9	0.1179	/	0.4688	0.8684
	10	0.7307	0.4688	/	0.1794
	11	0.0339	0.8684	0.1794	/
	11				

Note:

Calculated based on tumor volume measurements on Day 28.

Table E6: The average weight of isolated tumors from each group on day 28

Treatment	N	Tumor weight (g) ¹	T/C ² (%)	p value ³
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Vehicle	6	2.051 ± 0.382	--	--
MRTX849, 100 mg/kg, QD	6	0.487 ± 0.046	23.76	< 0.0001
AMG510, 100 mg/kg, QD	6	0.588 ± 0.132	28.64	< 0.0001
Compound 17, 30 mg/kg, QD	6	0.421 ± 0.094	20.52	< 0.0001
Compound 17, 100 mg/kg, QD	6	0.417 ± 0.056	20.32	< 0.0001
WX001, 25 mg/kg, BID	6	0.759 ± 0.157	37.01	< 0.0001
WX001, 25 mg/kg, QD	6	1.114 ± 0.222	54.31	0.0007
WX001, 50 mg/kg, QD	6	0.742 ± 0.087	36.18	< 0.0001
Compound 17+WX001, 30 mg/kg+25 mg/kg, QD+BID	6	0.191 ± 0.021	9.30	< 0.0001
Compound 17+WX001, 30 mg/kg+25 mg/kg, QD+QD	6	0.312 ± 0.057	15.21	< 0.0001
Compound 17+WX001, 30 mg/kg+50 mg/kg, QD+ QD	6	0.175 ± 0.012	8.53	< 0.0001

Note:

1. Mean ± SEM;
2. T/C % = T/C × 100 % (T: treatment group; C: control group, T and C are the mean tumor weight of the treated and control groups, respectively, on a given day);
3. *p* value was calculated based on tumor weight.

[0371] In this study, the therapeutic efficacy of Compound 17 and WX001 as single agents or as a combination therapy was evaluated in subcutaneous NCI-H2122 human lung cancer xenograft model. The results of tumor volume in different groups at different time points after tumor inoculation are shown in the Tables **E3 and E4, FIGs. 2 and 3**. The results of the tumor weight are shown in **Tables E5 and FIG. 4**.

[0372] The mean tumor volume of the vehicle control group reached 2,359 mm³ on day 28 after administration. Treatments with reference compounds MRTX849 at 100 mg/kg (QD) and AMG510 at 100 mg/kg (QD) produced significant antitumor activity with mean tumor volume of 556 mm³ (T/C = 23.56%, TGI = 81.97%, *p* < 0.001) and 615 mm³ (T/C = 26.09%, TGI = 79.25%, *p* < 0.001), respectively. While tumor regression was often observed in other KRAS G12C models at this dose level (100 mg/kg) for both AMG510 and MRTX849, only significant tumor growth inhibition, no such effect on tumor regression, was observed in the NCI-H2122 model. These data are in line with

published results (Cancer Discov. 2020 Jan; 10(1):54-71) and suggest NCI-H2122 is partially resistant to KRAS G12C inhibitors.

[0373] Consistently, treatment with Compound 17, a potent and selective KRAS G12C inhibitor currently in clinical trial (NCT05410145) only resulted in tumor growth inhibition, too. No tumor regression was observed at either 30 mg/kg (QD) or 100 mg/kg (QD). Treatments with Compound 17 at 30 mg/kg (QD) and 100 mg/kg (QD) produced anti-tumor activity when compared with vehicle control group, with mean tumor volumes of 527 mm³ (T/C = 22.36%, TGI = 83.25%, $p < 0.001$), 548 mm³ (T/C = 23.23%, TGI = 82.31%, $p < 0.001$), respectively. There is no difference between the group treated with Compound 17 at 30 mg/kg and the group treated with Compound 17 at 100 mg/kg, indicating tumor inhibition cannot be further enhanced with increase dose for Compound 17 as monotherapy in this partially resistant model.

[0374] Treatments with WX001, ERK1/2 inhibitor, as monotherapy at 25 mg/kg (BID), 25 mg/kg (QD) and 50 mg/kg (QD) produced significant anti-tumor activity when compared with vehicle control group, with mean tumor volumes of 778 mm³ (T/C = 33.00%, TGI = 71.84%, $p < 0.001$), 1182 mm³ (T/C = 50.13%, TGI = 53.47%, $p < 0.001$) and 777 mm³ (T/C = 32.94%, TGI = 71.91%, $p < 0.001$), respectively. These data indicate WX001 has a moderate anti-tumor activity in NCI-H2122 xenograft model.

[0375] When Compound 17 at 30 mg/kg QD was combined with WX001 at 25 mg/kg (BID), 25 mg/kg (QD) or 50 mg/kg (QD), the anti-tumor activity was more potent than each single agent at its corresponding dosage, with the average tumor volumes of 262 mm³ (T/C = 11.11%, TGI = 95.31%), 420 mm³ (T/C = 17.81%, TGI = 88.14%) and 184 mm³ (T/C = 7.79%, TGI = 98.88%), respectively. When compared with Compound 17 30 mg/kg monotherapy group, the combination of Compound 17 30 mg/kg QD with WX001 at 50 mg/kg QD led to significantly enhanced anti-tumor efficacy with a p value of 0.0339. These results demonstrated a combined use of WX001 and KRAS G12C inhibitor such as Compound 17, leading to almost complete tumor growth inhibition in this KRAS G12C mutant tumor model that is partially resistant to a KRAS G12C inhibitor.

[0376] Animal body weight was monitored regularly as an indirect measure of toxicity. As historical data showed that NCI-H2122 bearing mice might lose over 15% of body weight as tumor progression, all mice were supplied with nutrient gel and sunflower seeds. Two, one and two mice in Vehicle group showed body weight loss > 15% on PG-D14, PG-D21 and PG-D28 respectively. One mouse in Group 5 (Compound 17, 100 mg/kg, QD), one mouse in Group 6 (WX001, 25

mg/kg, BID) and one mouse in Group 9 (Compound 17+WX001, 30 mg/kg+25 mg/kg, QD+BID) showed body weight loss>15% on PG-D11. Three mice in Group 6 (WX001, 25 mg/kg, BID), three mice in Group 7 (WX001, 25 mg/kg, QD), one mouse in Group 8 (WX001, 50 mg/kg, QD) and two mice in Group 9 (Compound 17+WX001, 30 mg/kg +25 mg/kg, QD+BID) showed body weight loss>15% on PG-D18. The overall body weight change in all treatment groups was similar to vehicle control group, suggesting the treatments were well tolerated in this study.

Example 2: Evaluation of the anti-tumor efficacy of ERK1/2 inhibitor in combination with KRAS G12C inhibitor in SW-837 human colorectal cancer xenograft mouse model.

[0377] The objective of this study was to evaluate preclinically the *in vivo* therapeutic efficacy of WX001 in combination with Compound 17, a KRAS G12C inhibitor currently in clinical development, in the treatment of human colorectal cancer xenograft model SW-837, a cell line-derived xenograft model harboring KRAS G12C mutation. The anti-tumor efficacy of Compound 17 or WX001 each as a single agent in this model is also evaluated in comparison to combination treatment.

[0378] Materials and methods:

[0379] The groups were designed as described in Table E7, and the drug formulation and dosage was administered as described in Table E7. Dosing volume was adjusted for body weight (dosing volume = 5 μ L/g).

Table E7: Study Design for SW-837 xenograft model

Group	No. of mice	Treatment	Dose Level (mg/kg)	Dosing Solution (mg/mL)	Dosing Volume (μ L/g)	ROA	Dosing Frequency & Duration
1	8	Vehicle control	-	-	10	p.o.	QD
2	8	Compound 17	10	1	10	p.o.	QD
3	8	WX001	25	2.5	10	p.o.	QD
4	8	WX001	50	5	10	p.o.	QD
5	8	Compound 17	10	1	10	p.o.	QD
		WX001	25	2.5	10	p.o.	QD
6	8	Compound 17	10	1	10	p.o.	QD
		WX001	50	5	10	p.o.	QD

[0380] The SW-837 tumor cells were maintained *in vitro* with L-15(100% air) medium supplemented with 10% fetal bovine serum at 37°C in an atmosphere of 5% CO₂ in the air. The cells in exponential growth phase were harvested and quantitated by cell counter before tumor inoculation. Each mouse was inoculated subcutaneously in the right lower flank region with SW-

837 tumor cells (5×10^6 cells/mouse) in 0.1 ml of PBS mixed with Matrigel (1:1) for tumor development.

[0381] The randomization started when the mean tumor size reaches approximately 144 mm^3 . A total of 48 mice were enrolled in the study. All animals were randomly allocated to 6 study groups, 8 mice in each group. Randomization was performed based on “Matched distribution” method (StudyDirector™ software, version 3.1.399.19). Dosing was implemented right after randomization on Day 0. The treatment was initiated on the same day of randomization (Day 0) as per the study design (Table E7).

[0382] The treatment started when the mean tumor volume reached around 144 mm^3 . The experiment was performed for a total of 41 days (Day 0 to Day 40) after randomization, including the efficacy study from Day 0 to Day 39. On Day 40, plasma sampling was performed after one final dose on the day. Tumor Growth Inhibition (TGI) calculation was based on Day 39, the end of the efficacy study.

[0383] Body weight was measured twice per week. Tumor volumes were also measured twice per week after randomization in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: “ $V = (L \times W \times W)/2$ ”, where V was tumor volume, L was tumor length (the longest tumor dimension) and W was tumor width (the longest tumor dimension perpendicular to L). Dosing as well as tumor and body weight measurements were conducted in a Laminar Flow Cabinet. The body weights and tumor volumes were measured by using StudyDirector™ software (version 3.1.399.19). The body weights of all animals were monitored throughout the study and animals were euthanized if they lose over 20% of their body weight relative to the weight on the first day of treatment. The individual mouse was euthanized if its tumor volume exceeded 3000 mm^3 .

[0384] The date of randomization was denoted as day 0. The study was terminated on the day determined by the sponsor or treated until the tumor size of individual mouse exceeding 3000 mm^3 . The study was terminated on the specified day post the randomization when the tumor volume of individual mouse met the humane endpoint and as requested by the sponsor. The treatment was performed for 41 days starting from grouping (from Day 0 to Day 40), and the mice were sacrificed on Day 41.

[0385] To compare tumor volumes of different groups at a pre-specified day, Bartlett's test was first used to check the assumption of homogeneity of variance across all groups. When the p-value of Bartlett's test was ≥ 0.05 , a one-way ANOVA was run to test overall equality of means across all groups. If the p-value of the one-way ANOVA was < 0.05 , further post hoc testing was performed by running Tukey's HSD (honest significant difference) tests for all pairwise

comparisons, and Dunnett's tests for comparing each treatment group with the vehicle group. When the p-value of Bartlett's test was <0.05 , a Kruskal-Wallis test was executed to test overall equality of medians among all groups. If the p-value the Kruskal-Wallis test was <0.05 , further post hoc testing was performed by running Conover's non-parametric test for all pairwise comparisons or for comparing each treatment group with the vehicle group, both with single-step p-value adjustment.

[0386] In addition, a pairwise comparison was performed without multiple comparison correction and nominal/uncorrected p-values were reported directly from Welch's t-test or Mann-Whitney U test. Specifically, Bartlett's test was used to check the assumption of homogeneity of variance for a pair of groups. When the p-value of Bartlett's test was ≥ 0.05 , Welch's t-test or the Mann-Whitney U test was executed to obtain nominal p-values.

[0387] All statistical analyses were done in R-a language and environment for statistical computing and graphics (version 3.3.1). All tests have two-sided unless otherwise specified, and p-values of <0.05 were regarded as statistically significant.

[0388] Results:

[0389] In this study, the in vivo efficacy of test compounds Compound 17 (KRAS G12C inhibitor) and WX001 (ERK1/2 inhibitor), as a single agent or as combination therapies, was evaluated in the treatment of the subcutaneous human colorectal cancer xenograft model SW-837 harboring KRAS G12C mutation.

[0390] During the dosing course, only a few of animals showed minimal to moderate amounts of treatment-related body weight loss in the compound treatment groups (**FIG. 5**). No dosing holiday was given to the mice from treatment groups due to the body weight loss being over 15%. No animals were found dead during the entire dosing course. No mice were euthanized prior to study termination due to the tumor volume exceeding 3000 mm³. The test drugs were generally tolerated by tumor-bearing mice in this study.

[0391] Bartlett's test was performed to test homogeneity of variance and normality, non-parametric test is run to compare groups. $P < 0.05$ was considered to be statistically significant. Compound 17 dosed at 10 mg/kg as a single agent produced statistically significant anti-tumor efficacy in the subcutaneous xenograft model SW-837, with TGI values of 100.92% ($p < 0.001$ vs. vehicle control). Treatment with WX001 at 25 mg/kg and 50 mg/kg as a single agent produced anti-tumor efficacy with a TGI values of 29.43% and 53.64% respectively (both $p < 0.05$ vs. vehicle control) (**Table E9, FIG. 6A**).

Table E9: Antitumor Activity of Test Compound in SW-837 Model

Group	Treatment	Tumor Volume on Day 39 (mm ³) (mean ± SEM)	ΔT/C (%) on Day 39	ΔTGI (%) on Day 39	Mean tumor volume change from baseline (%)	p Value (v.s Vehicle control)	p Value (v.s Compound 17 monotherapy group)
1	Vehicle control	2580.32±160.57	-	-	1690.34	-	-
2	Compound 17, 10 mg/kg, QD	121.68±8.84	-0.92	100.92	-15.02	<0.001	-
3	WX001, 25 mg/kg, QD	1863.38±98.65	70.57	29.43	1198.19	0.0022	<0.001
4	WX001, 50 mg/kg, QD	1273.36±132.97	46.36	53.64	792.63	<0.001	<0.001
5	Compound 17, 10 mg/kg; WX001, 25 mg/kg, QD	32.41±2.07	-4.58	104.58	-77.45	<0.001	<0.001
6	Compound 17, 10 mg/kg; WX001, 50 mg/kg, QD	19.40±3.96	-5.11	105.11	-86.64	<0.001	<0.001

[0392] WX001 at 25 mg/kg or 50 mg/kg in combination with Compound 17 at 10 mg/kg demonstrated significantly more potent anti-tumor efficacy compared with Compound 17 at 10 mg/kg alone (both $p < 0.001$ vs. Compound 17 monotherapy group), with TGI values of 104.58% and 105.11%, respectively (**Table E9, FIG. 6A**). In analysis of the mean tumor volume change from baseline, WX001 at 25 mg/kg or 50 mg/kg in combination with Compound 17 at 10 mg/kg demonstrated significantly deeper anti-tumor response with -77.45% and -86.64% tumor regression from baseline, respectively, while Compound 17 at 10 mg/kg alone resulted in -15.02% tumor regression from baseline.

[0393] Overall, these data indicate that ERK1/2 inhibitor WX001 can significantly augment the antitumor effect of KRAS G12C inhibitor Compound 17 in SW837 colorectal cancer xenograft model with KRAS G12C mutation.

[0394] Animals showed minimal treatment-related body weight loss during the entire experiment period. See FIG. 5. The test articles Compound 17 and WX001 were well tolerated by tumor-bearing mice as single agents or in combination in this study.

[0395] Moreover, adding WX001 to Compound 17 and cetuximab doublet achieved curative anti-tumor effects in SW837 colorectal cancer model. Specifically, mice were treated with sub-optimal dose of Compound 17 (3mg/kg), combination of WX001 (25mg/kg BID) with Compound 17 (3mg/kg), combination of Cetuximab with Compound 17 (3mg/kg), or triplet combination. In this experiment, doublet combination of WX001 (25mg/kg BID) +Compound 17 (3mg/kg) resulted in significantly prolonged antitumor effect, indicating a synergy between Compound 17 and WX001. In addition, Cetuximab + Compound 17, or triplet combination of Cetuximab+Compound 17+WX001 all improved event-free survival. Strikingly, triplet combination of Cetuximab+Compound 17 (30mg/kg)+WX001 (25mg/kg BID) achieved 100% complete tumor remission with no tumor re-growth even thirty days after treatment had stopped, suggesting that the triple combination achieved a durable anti-tumor efficacy. See FIGs. 6C-6D.

Example 3: Evaluation of the anti-tumor efficacy of ERK1/2 inhibitor in combination with KRAS G12C inhibitor in CR9537 HuPrime® colorectal cancer xenograft mouse model.

[0396] The objective of this study is to evaluate the *in vivo* therapeutic efficacy of test articles Compound 17, WX001 and a reference compound MRTX849 (adagrasib) as a monotherapy and/or in combination with cetuximab in HuPrime® colorectal cancer patient-derived xenograft model CR9537.

[0397] Patient-derived xenografts (PDX) models are established from patient tumor tissues. PDX models retain the original histopathological features and genetic background of the patient tumor and can be passaged in immune deficient mouse. For these reasons, PDX models are widely used in discovery and translation research, serving as a valuable tool in evaluating preclinical efficacy of new treatments and providing translational insights toward therapeutic susceptibility.

[0398] Materials and methods:

[0399] The CR9537 PDX model (Crown Biosciences) is established from biopsy samples of a patient with KRAS G12C mutant colorectal cancer. The patient was enrolled in a clinical trial of

MRTX849 after the disease progressed on front-line and second-line chemotherapy. The patient eventually became resistant to MRTX849 treatment. Genetic analysis of tumor tissue biopsy from this patient identified acquired KRAS Q61H mutation, indicating the resistant mechanism is due to secondary KRAS mutation. Thus represents a patient population with limited treatment options and high unmet medical needs. To discover novel treatment strategies for this patient population, patient-derived xenograft (PDX) model was established by mincing tumor biopsy tissues into small tumor fragments with 2-3 mm in diameter and subcutaneously implanting into BALB/c nude immunodeficient mice. Tumors that successfully grow *in vivo* were further passed into the next passage of mice and cryopreserved. KRAS G12C and KRAS Q61H mutation were confirmed in NGS profiling for this model.

[0400] The study design, including groups of mice, number of mice per group and treatment, was summarized in the following table. Tumor growth was monitored over time after treatment.

Table E10: Experimental design and dosage for CR9537 patient-derived xenograft (PDX) model

Group	No. of mice	Treatment	Dose level (mg/kg)	Dosing Solution (mg/mL)	Dosing Volume (μL/g)	ROA	Dosing Frequency & Duration
1	6	Vehicle control	-	-	10	p.o.	QD×61days
2	6	MRTX849	50	5	10	p.o.	QD×64days
3	6	Compound 17	50	5	10	p.o.	QD×64days
4	6	WX001	50	5	10	p.o.	QD×64days
5	6	MRTX849	50	5	10	p.o.	QD×64days
		WX001	50	5	10	p.o.	QD×64days
6	6	Compound 17	50	5	10	p.o.	QD×64days
		WX001	50	5	10	p.o.	QD×64days
7	6	Cetuximab	30	3	10	i.p.	BIW×19 doses
8	6	Cetuximab	30	3	10	i.p.	BIW×19doses
		Compound 17	50	5	10	p.o.	QD×64days
9	6	Cetuximab	30	3	10	i.p.	BIW×19doses
		Compound 17	50	5	10	p.o.	QD×64days
		WX001	50	5	10	p.o.	QD×64days
10	6	Cetuximab	30	3	10	i.p.	BIW×19doses
		MRTX849	50	5	10	p.o.	QD×64days
11	6	Cetuximab	30	3	10	i.p.	BIW×19doses
		MRTX849	50	5	10	p.o.	QD×64days
		WX001	50	5	10	p.o.	QD×64days

[0401] A total of 66 mice were enrolled in the study. All animals were randomly allocated to 11 study groups, 6 mice in each group. Randomization was performed based on “Matched distribution” method (StudyDirector™ software, version 3.1.399.19). The day of randomization was denoted as Day 0. Treatment (**Table E10**) initiated on the same day of randomization (Day 0). The treatment started when the mean tumor volume reached around 145 mm³. Tumor Growth Inhibition (TGI) calculation was based on the day when the first mouse in vehicle group had to be euthanized due to tumor volume exceeding 3000 mm³, a predefined humane endpoint. The treatment was performed for 64 days starting from grouping (from Day 0 to Day 63), and the remaining mice were sacrificed on Day 63.

[0402] Tumor volumes were measured twice per week after randomization in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: “ $V = (L \times W \times W)/2$ ”, where V was tumor volume, L was tumor length (the longest tumor dimension) and W was tumor width (the longest tumor dimension perpendicular to L). Dosing as well as tumor and body weight measurements were conducted in a Laminar Flow Cabinet. The body weights and tumor volumes were measured by using StudyDirector™ software (version 3.1.399.19).

[0403] To compare tumor volumes of different groups at a pre-specified day, Bartlett's test was first used to check the assumption of homogeneity of variance across all groups. When the p-value of Bartlett's test was ≥ 0.05 , the one-way ANOVA was performed to test overall equality of means across all groups. If the p-value of the one-way ANOVA was < 0.05 , post hoc testing was performed by running Tukey's HSD (honest significant difference) tests for all pairwise comparisons, and Dunnett's tests for comparing each treatment group with the vehicle group. When the p-value of Bartlett's test was < 0.05 , a Kruskal-Wallis test was performed to test overall equality of medians among all groups. If the p-value the Kruskal-Wallis test was < 0.05 , post hoc testing by Conover's non-parametric test was performed for all pairwise comparisons or for comparing each treatment group with the vehicle group, both with single-step p-value adjustment.

[0404] For TGI calculations, Day 32 was considered as endpoint, as on Day 32 tumor measurement, one of the tumors in vehicle control group and cetuximab treatment group, respectively, had exceeded volume of 3000 mm³, a predefined humane endpoint. Tumor volume

growth curves from Day 0 to Day 63 were plotted using Prism GraphPad software and shown in **FIG. 7**.

[0405] In addition, pairwise comparisons without multiple comparison correction was performed and the nominal/uncorrected p-values were reported directly from Welch's t-test or Mann-Whitney U test. Specifically, Bartlett's test was first used to check the assumption of homogeneity of variance for a pair of groups. When the p-value of Bartlett's test was ≥ 0.05 , Welch's t-test or the Mann-Whitney U test was performed to obtain nominal p-values.

[0406] All statistical analyses had been done in R-a language and environment for statistical computing and graphics (version 3.3.1). All tests have two-sided unless otherwise specified, and p-values of <0.05 were regarded as statistically significant.

[0407] Results:

[0408] This study evaluated the *in vivo* efficacy of test articles Compound 17 (a KRAS G12C inhibitor from D3 Bio), WX001 (an ERK1/2 inhibitor from D3 Bio) and a reference compound MRTX849 (a KRAS G12C inhibitor that is currently in clinical investigation for the treatment of KRAS G12C-mutant colorectal cancer) as a monotherapy and/or in combination with cetuximab in the CR9537 colorectal cancer PDX model.

[0409] Reference compound MRTX849 dosed at 50 mg/kg and test article Compound 17 dosed at 50 mg/kg, as a single agent, produced statistically significant anti-tumor efficacy in the subcutaneous xenograft model CR9537, with TGI values of 56.94% and 67.29% ($P < 0.05$ vs. vehicle control), respectively (**Table E12, FIG. 7**). Treatment with WX001 at 50 mg/kg and cetuximab dosed at 30 mg/kg, as a single agent, did not produce significant anti-tumor efficacy with TGI values of 51.28% and 17.11% ($P > 0.05$ vs. vehicle control), respectively.

Table E12: Anti-tumor Activity of Test Compound in CR9537 Model

Group	Treatment	Tumor Volume on Day 32 (mm ³) (mean $\pm$ SEM)	T/C (%) on Day 32	TGI (%) on Day 32	p Value
1	Vehicle control	2141.46 $\pm$ 266.70	-	-	-
2	MRTX849 50 mg/kg	922.03 $\pm$ 119.98	43.06	56.94	0.0311
3	Compound 17 50 mg/kg	700.41 $\pm$ 57.24	32.71	67.29	0.0011
4	WX001 50mg/kg	1043.31 $\pm$ 132.25	48.72	51.28	0.101
5	MRTX849 50 mg/kg; WX001 50 mg/kg	287.91 $\pm$ 55.85	13.44	86.56	<0.001
6	Compound 17 50 mg/kg; WX001 50 mg/kg	552.81 $\pm$ 149.07	25.81	74.19	<0.001

7	Cetuximab 30 mg/kg	1775.02±282.70	82.89	17.11	1.000
8	Cetuximab 30 mg/kg; Compound 17 50 mg/kg	582.09±127.19	27.18	72.82	<0.001
9	Cetuximab 30 mg/kg; Compound 17 50 mg/kg; WX001 50 mg/kg	470.53±86.72	21.97	78.03	<0.001
10	Cetuximab 30 mg/kg; MRTX849 50 mg/kg	636.87±95.73	29.74	70.26	<0.001
11	Cetuximab 30 mg/kg; MRTX849 50 mg/kg; WX001 50 mg/kg	324.32±74.92	15.14	84.86	<0.001

[0410] For the combinational treatment groups, WX001 in combination with a) MRTX849 and b) Compound 17 respectively produced statistically significant anti-tumor efficacy in the subcutaneous xenograft model CR9537, with TGI values of 86.56% and 74.19% (P<0.001 vs. vehicle control) (**Table E12, FIG. 7**), demonstrating a consistent better effect than a) cetuximab and MRTX849 with TGI values of 70.26% and b) cetuximab in combination with Compound 17 with TGI values of 72.82% . Specifically, the combination of MRTX849 and Compound 17 achieved a TGI that is 23% higher than the combination of MRTX849 and cetuximab.

[0411] These results demonstrated that in patient population with acquired secondary KRAS mutations, e.g., KRAS Q61H, the combination of an ERK 1/2 inhibitor (e.g., WX001) with an KRAS G12C inhibitor (either MRTX849 or Compound 17) is more effective than cetuximab in combination with KRAS G12C inhibitor. These data provided previously unknown evidence to support clinical investigation of the combination of WX001 and a KRAS G12C inhibitor in treating patients who has previously been treated with KRAS G12C inhibitor and developed resistance to KRAS G12C inhibitor due to acquired secondary KRAS mutations. Such advantageous effects are also expected with other acquired secondary KRAS mutations.

[0412] Animals showed minimal to moderate amounts of body weight loss during the treatment period (**FIG. 8**). Test articles Compound 17 and WX001 were well tolerated by tumor-bearing mice in this study.

Example 4: Evaluation of the anti-tumor efficacy of ERK1/2 inhibitor in combination with KRAS G12C inhibitors in AMG510 resistant Mia PaCa-2 human pancreatic cancer xenograft mouse model.

[0413] The objective of this study is to evaluate the in vivo anti-tumor efficacy of MRTX849, Compound 17 and WX001 in the subcutaneous AMG510-R-xMia PaCa-2 clone #2 xenograft model in female BALB/c nude mice. AMG510-R-xMIA PaCa-2 clone #2 was a single clone cell line picked from AMG510-R-xMiaPaCa-2 (CP2) cell population. This cell line was derived from a AMG510-R-MIA PaCa-2 (CP2) resistant tumor, which was induced by continuous treatment of AMG-510 in MIA PaCa-2 human pancreatic cancer xenograft model. KRAS gene amplification was identified by RNAseq and WES analysis in AMG510-R-xMIA PaCa-2 clone #2.

[0414] Materials and methods:

[0415] The AMG510-R-xMia PaCa-2 (CP2) clone #2 tumor cells were maintained in DMEM/F12 medium supplemented with 10% fetal bovine serum, 1% Antibiotic-Antimycotic, 1 μ M AMG510, at 37 °C in an atmosphere of 5% CO₂ in air. The tumor cells were routinely subcultured twice weekly by trypsin-EDTA treatment. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[0416] Each mouse was inoculated subcutaneously at the right flank with AMG510-R-xMia PaCa-2 (CP2) clone #2 tumor cells (1×10^6) in 0.2 mL of PBS with Matrigel® for tumor development. Treatments were started when the average tumor size reached approximately 128 mm³. The animals were assigned into 8 groups using an Excel-based randomization software performing stratified randomization based upon their tumor volumes. Each group consisted of 8 tumor-bearing mice. The testing articles were administrated to the mice according to the predetermined regimen as shown in **Table E13**. Dosing volume was adjusted dosing volume based on body weight (10 μ L/g).

Table E13: Experimental design and dosage for AMG510-R-xMIA PaCa-2 xenograft model

Group	N ^a	Treatment	Dose (mg/kg)	Dosing Volume (μ L/g) ^b	Dosing Route	Dosing Schedule
1	8	Vehicle	-	10	PO	QD
2	8	MRTX849	30	10	PO	QD
3	8	AMG510	30	10	PO	QD
4	8	Compound 17	30	10	PO	QD
5	8	WX001	25	10	PO	QD

6	8	WX001	50	10	PO	QD
7	8	Compound 17+ WX001	30+25	10	PO	QD
8	8	Compound 17+ WX001	30+50	10	PO	QD

[0417] The major endpoint was to see if the tumor growth could be delayed or mice could be cured. Tumor size was measured twice weekly in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: $V = 0.5 a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. The tumor sizes are then used for the calculations of both T/C and TGI values. The tumor size was then used for calculations of T/C values. $T/C (\%) = T_{RTV} / C_{RTV} \times 100 \%$; T_{RTV} is mean relative tumor volume of treatment group, and C_{RTV} is mean relative tumor volume of control group. RTV is calculated as $RTV = V_n / V_0$, V_0 is the tumor volume on the day of treatment start, and V_n is the tumor volume on certain day. For the T/C (%) calculation, T_{RTV} and C_{RTV} on the same day should be used.

[0418] TGI was calculated for each group using the formula: $TGI (\%) = [1 - (T_i - T_0) / (V_i - V_0)] \times 100$; T_i is the average tumor volume of a treatment group on a given day, T_0 is the average tumor volume of the treatment group on the first day of treatment, V_i is the average tumor volume of the vehicle control group on the same day with T_i , and V_0 is the average tumor volume of the vehicle group on the first day of treatment.

[0419] The other endpoint studied was animal survival. Animals that show deteriorating and moribund condition (animals have body weight loss > 20%) and animals that could not consume adequate food or water were euthanized. Except euthanasia and death, survival time was assessed by time to tumor volume reaching 1000 mm³. Median survival time (MST) was calculated for each group.

[0420] Statistical analysis of difference in the tumor volume among the groups was conducted on the data on the 17th day after treatment (the day when the first mouse in vehicle group was sacrificed due to tumor burden). One-way ANOVA was performed to compare the tumor volume and the tumor weight among groups. The Kaplan-Meier curves were constructed for each group and the log-rank test is used to compare survival curves between groups. The event was defined as the tumor volume reaching 1000 mm³. All data were analyzed using prism 8.0. $p < 0.05$ was considered to be statistically significant.

[0421] Results:

[0422] Animal body weight was monitored regularly as an indirect measure of toxicity. Body weight was largely stable over the period of observation. On average, severe body weight loss (>15%) was not observed between treatment groups (**FIG. 10, FIG. 11**).

[0423] Results:

[0424] In this study, the therapeutic efficacy of MRTX849, Compound 17 and WX001 in the treatment of subcutaneous AMG510-R-xMia PaCa-2 clone #2 xenograft model were evaluated (**Table E15, Table E16, FIG. 11**). Tumor growth inhibition was calculated based on tumor volume measurements at day 17 (the day when the first mouse in vehicle group was sacrificed due to tumor burden) (**Table E16**). At day 17 after treatment start, the mean tumor size of the vehicle reached 2,456 mm³. The mean tumor volume of MRTX849 (30 mg/kg), AMG510 (30 mg/kg), WX001 (25 mg/kg) and WX001 (50 mg/kg) was 1,397 mm³, 1,776 mm³, 1,937 mm³ and 1,731 mm³, respectively (T/C = 56.82%, 72.23%, 78.74% and 70.41%; TGI = 45.51%, 29.21%, 22.32% and 31.12%, p values=0.0213, 0.3110, 0.6367, 0.2409) (**Table E15, Table E16, FIG. 11**).

[0425] Treatment with Compound 17 (30 mg/kg), Compound 17+WX001 (30+25 mg/kg) and Compound 17+WX001 (30+50 mg/kg) produced a significant antitumor activity with mean tumor sizes of 264 mm³, 164 mm³ and 71 mm³, respectively (T/C = 10.74%, 6.65% and 2.90%; TGI = 94.18%, 98.50% and 102.45%, all p values less than 0.0001) (**Table E15, Table E16, FIG. 11**).

Table E15: Mean tumor volume over time

Days ^b	Tumor volume (mm ³) ^a							
	Vehicle	MRTX849	AMG510	Compound 17	WX001	WX001	Compound 17+WX001	Compound 17+WX001
		30mg/kg	30mg/kg	30mg/kg	25mg/kg	50mg/kg	30+25mg/kg	30+50mg/kg
0	128±9	128±9	129±9	128±8	129±7	129±8	129±8	128±9
3	272±21	268±39	226±30	147±12	347±51	300±51	128±16	94±13
7	617±71	590±112	599±131	151±17	829±107	707±115	69±12	59±11
10	1,122±116	736±137	866±181	170±19	1,072±132	917±172	77±12	53±10
14	1,823±141	1,175±197	1,355±277	197±32	1,553±255	1,314±239	133±29	55±11
17	2,456±200	1,397±241	1,776±358	264±40	1,937±344	1,731±345	164±43	71±18
21	2,723±222	1,860±363	1,733±340	359±63	2,036±456	1,594±229	216±53	104±33
24	3,115±80	2,024±429	1,844±338	417±78	1,940±477	1,978±286	289±83	129±48

28	-- ^c	1,936±5 14	1,984±3 50	595±127	1,991±6 84	2,587±3 76	393±126	172±53
31	--	1,848±6 06	1,982±1 28	855±237	1,481±6 46	2,297±6 17	474±150	184±58
35	--	1,594±1 54	2,562±2 74	1,146±349	1,932±1 074	2,238±8 20	545±184	203±67
38	--	1,833±2 62	2,715±4 06	1,124±295	838	1,690	651±241	241±80
42	--	2,276±5 09	3,063	1,510±378	787	2,181	784±301	268±82
45	--	2,736±5 65	--	1,475±366	879	2,393	826±305	298±87
49	--	2,753	--	1,572±389	997	2,726	900±330	352±98
52	--	3,090	--	1,728±421	1,241	3,022	964±353	388±100
56	--	--	--	2,240±577	2,009	--	730±259	419±107
59	--	--	--	1,912±794	2,612	--	808±290	453±119
63	--	--	--	625±625	3,366	--	921±321	497±136
66	--	--	--	639±639	--	--	1,111±40 5	561±145
70	--	--	--	656±656	--	--	867±293	626±155
73	--	--	--	697±697	--	--	960±323	667±160
77	--	--	--	798±798	--	--	1,140±37 1	776±177
80	--	--	--	883±883	--	--	1,290±40 6	829±184
84	--	--	--	1,055±105 5	--	--	1,412±44 9	867±183
87	--	--	--	1,179±117 9	--	--	1,531±48 7	918±199
91	--	--	--	1,301±130 1	--	--	1,351±51 0	984±208
94	--	--	--	1,568±156 8	--	--	1,038±43 3	1,051±22 3
98	--	--	--	0	--	--	1,105±47 8	1,066±22 1
101	--	--	--	0	--	--	1,204±53 9	1,077±22 7
105	--	--	--	0	--	--	1,286±59 2	769±156

a. Mean ± SEM

b. Days after treatment.

c. Mice with tumor volumes greater than 3000mm³ were euthanized.

Table E16: Tumor growth inhibition for test compounds in the AMG510-R-xMia PaCa-2 clone #2 xenograft model

Treatment	tumor volume (mm ³) ^a (at day17)	T/C ^b (%)	TGI ^c (%)	p value ^d (%)
Vehicle	2,456±200	--	--	--
MRTX849 (30mg/kg)	1,397±241	56.82	45.51	0.0213

AMG510 (30mg/kg)	1,776±358	72.23	29.21	0.3110
Compound 17 (30mg/kg)	264±40	10.74	94.18	<0.0001
WX001 (25mg/kg)	1,937±344	78.74	22.32	0.6367
WX001 (50mg/kg)	1,731±345	70.41	31.15	0.2409
Compound 17+WX001 (30+25mg/kg)	164±43	6.65	98.50	<0.0001
Compound 17+WX001 (30+50mg/kg)	71±18	2.90	102.45	<0.0001

a. Mean ± SEM.

b. $T/C = T_{RTV} / C_{RTV} \times 100 \%$;

c. $TGI (\%) = [1 - (T_{17} - T_0) / (V_{17} - V_0)] \times 100$

d. p (One-way ANOVA): p value when comparing each group with Vehicle.

[0426] A statistically significant difference in survival time was observed in Compound 17 (30 mg/kg), Compound 17+WX001 (30+25 mg/kg), and Compound 17+WX001 (30+50 mg/kg) treated groups when compared with Vehicle group (all p values = 0.0001) (**FIG. 12**). No significant difference in survival time was observed between vehicle group and other treatment groups. When compared between treatment groups, Compound 17 (30 mg/kg) treated group significantly prolonged the median survival time than MRTX849 (30 mg/kg) treated group and AMG510 (30 mg/kg) treated group ($P=0.001$ and $P<0.0001$, respectively). Furthermore, Compound 17+WX001 (30+50 mg/kg) treated group significantly prolonged the median survival time than Compound 17 (30 mg/kg) monotherapy group ($P=0.006$).

[0427] Animal body weight was monitored regularly as an indirect measure of toxicity. Mouse #706789 and mouse #706803 in Group 4 (Compound 17, 30 mg/kg) showed body weight loss over 15% on day 52 and recovered within 3 days. Mouse #706744 in Group 8 (Compound 17+WX001, 30+50 mg/kg) showed body weight loss over 15% on day 45 and recovered within 3 days; Mouse #706736 in Group 8 (Compound 17+WX001, 30+50 mg/kg) showed body weight loss over 15% on day 105 and was sacrificed on day 105 (the end time point of the study). No severe body weight loss (>15%) was observed in other groups.

Table E17: Kaplan-Meier survival analysis for test compounds in the AMG510-R-xMia PaCa-2 clone #2 xenograft model calculated based on survival data up to day 105

Treatment	Median survival, days	P value for Log-rank test ^a
Vehicle	12.0	-
MRTX849 (30mg/kg)	14.0	0.0782
AMG510 (30mg/kg)	14.0	0.2190
Compound 17 (30mg/kg)	36.5	0.0001
WX001 (25mg/kg)	10.5	0.5539
WX001 (50mg/kg)	14.0	0.2804

Compound 17+WX001 (30+25mg/kg)	68.0	0.0001
Compound 17+WX001 (30+50mg/kg)	99.5	0.0001

a. All data were analyzed using GraphPad Prism 8.0. Comparisons between groups were carried out with Log-rank test (compared with control group).

Table E18: Statistical Analysis of Difference among Treatment Groups

Treatment	P value						
	1	2	3	4	5	6	7
Vehicle	-	-	-	-	-	-	-
MRTX849 (30mg/kg)	0.0782	-	-	-	-	-	-
AMG510 (30mg/kg)	0.2190	0.2848	-	-	-	-	-
Compound 17 (30mg/kg)	0.0001	0.0001	<0.0001	-	-	-	-
WX001 (25mg/kg)	0.5539	0.7749	0.8126	0.0175	-	-	-
WX001 (50mg/kg)	0.2804	0.3482	0.8975	0.0001	0.8083	-	-
Compound 17+WX001 (30+25mg/kg)	0.0001	0.0001	<0.0001	0.1715	0.0006	0.0001	-
Compound 17+WX001 (30+50mg/kg)	0.0001	<0.0001	<0.0001	0.0060	<0.0001	<0.0001	0.1775

a. Pairwise compared between each group using Log-Rank test.

Example 5.

[0428] WX001 properties and inhibitory effects were assessed.

[0429] Overall properties of WX001 are shown in FIG. 13. WX001 has demonstrated favorable selectivity in Kinome profiling and follow-up IC₅₀ assays. *See* FIGs. 14A-14C.

[0430] As shown in FIGs. 15A-15B, WX001 effectively inhibited downstream signaling pathway and cancer cell proliferation with improved potency when compared with two other clinical stage ERK1/2 inhibitors.

[0431] As shown in FIGs. 16A-16B, WX001 demonstrated potent anti-tumor effects in cancers harboring KRAS mutations (G13C, G13D).

Example 6. Evaluation of anti-tumor efficacy of ERK1/2 inhibitor in combination with KRAS G12C inhibitor in NCI-H358 NSCLC xenograft mouse model.

[0432] In KRAS G12C inhibitor-sensitive NCI-H358 NSCLC model, adding WX001 to Compound 17, a clinical stage KRAS G12C inhibitor, resulted in fast and deep anti-tumor response, and reduced the time required to achieve complete tumor remission when compared with Compound 17 monotherapy. Combination of Compound 17 and WX001 achieved 100% complete tumor remission on day 87 whereas at the same time point (day 87) zero out of seven mice achieved complete response with WX001 monotherapy. For Compound 17 monotherapy, it took 119 days for

all mice to achieve complete response. These data indicate a synergy between Compound 17 and WX001. See FIGs. 17A and 17B.

Example 7. Evaluation of the anti-tumor efficacy of Compound 17 and WX001 combination therapy in NCI-H1373 human lung cancer xenograft mouse model.

[0433] The objective was to evaluate the *in vivo* anti-tumor efficacy of MRTX849 (KRAS G12C inhibitor), Compound 17 (KRAS G12C inhibitor), WX001 (ERK 1/2 inhibitor) in subcutaneous NCI-H1373 human lung cancer xenograft implanted in female BALB/c nude mice after they became resistant to KRAS G12C inhibitor.

[0434] Materials and methods:

[0435] NCI-H1373 human lung cancer cells were maintained *in vitro* in RPMI-1640 cell culture media supplemented with 10% fetal bovine serum and 1% anti-mycotic/anti-biotic at 37°C in an atmosphere of 5% CO₂ in air. The tumor cells will be routinely sub-cultured twice weekly by trypsin-EDTA treatment. Cells growing in an exponential growth phase are harvested and counted for tumor inoculation.

[0436] Each BALB/c nude mouse was inoculated subcutaneously at the right flank with NCI-H1373 tumor cells (5×10^6) in 0.2 mL of PBS with Matrigel (1:1) for tumor development. Treatments were started on day 5 after tumor inoculation when the average tumor volume reached an average volume of 198 mm³. The animals were randomly assigned into groups based upon their tumor volumes. Each group consisted of 6 tumor-bearing mice. The testing articles were administrated to the mice according to the predetermined regimen as shown in the experimental design table (Tables E18).

Table E18: Description of experimental design for *in vivo* NCI-H1373 xenograft models

Group	N ^a	Treatment	Dose (mg/kg)	Dose Volume (μL/g) ^b	Dosing Route	Schedule ^c	Study Phase ^d
1	6	Vehicle	--	10	PO	QDx73 days (PG-DO-PG-D72)	Monotherapy
2	6	Compound 17	30	10	PO	QDx168 days	Monotherapy
3	6	MRTX849	30	10	PO	QDx132 days (PG-D0-PG-D131)	Monotherapy

		Compound 17	100	10	PO	QDx15 days (PG-D132-PG-D146)	Monotherapy-R
		Compound 17 + WX001	30 + 50	10 + 10	PO	(QD + QD)x21 days (PG-D147-PG-D167)	Combination-R

QD: daily

- N: number of animals per group;
- Dosing volume: adjust dosing volume based on body weight 10 $\mu\text{L/g}$; If body weight loss >15%, treatment will be suspended until body weight loss < 10%;
- The experiment's duration was 168 days.
- The entire study period consisted of 3 phases. Monotherapy phase: treatment with single agent of Compound 17 and MRTX849 until tumor relapse. Monotherapy-R: treatment switched to 100 mg/kg Compound 17 after relapse from monotherapy phase. Combination-R: treatment switched to Compound 17 and WX001 after relapse from monotherapy-R phase. Tumor relapse was defined as mean TV that rebounded from regressions to 500 mm^3 .

[0437] Tumor volume was measured twice weekly in two dimensions using a caliper, and the volume was expressed in mm^3 using the formula: $V = 0.5 a \times b^2$ where a and b are the long and short diameters of the tumor, respectively. The T/C (%) value is calculated for each group using the formula: $T/C \% = T/C \times 100 \%$ (T: treatment group; C: control group, T and C are the mean tumor weight of the treated and control groups, respectively, on a given day). Tumor Growth Inhibition (TGI) is calculated for each group using the formula: $TGI (\%) = [1 - (T_i - T_0) / (V_i - V_0)] \times 100$; T_i is the average tumor volume of a treatment group on a given day, T_0 is the average tumor volume of the treatment group on the first day of treatment, V_i is the average tumor volume of the vehicle control group on the same day with T_i , and V_0 is the average tumor volume of the vehicle group on the first day of treatment.

[0438] All tumors were weighed at the end of the experiment (i.e. PG-D167). No tumor samples were preserved.

[0439] Statistical analysis of difference in the tumor volume and tumor weight among the groups were conducted on the data obtained at the 34th day after the start of treatment. One-way ANOVA was performed to compare the tumor volume among groups, followed by Games-Howell test. All data were analyzed using SPSS 29.0. A p value < 0.05 was considered to be statistically significant.

[0440] Results:

[0441] In this study, the therapeutic efficacy of KRAS G12C inhibitors including MRTX849 and Compound 17 in NCI-H1373 human lung cancer xenograft model (a KRAS G12C inhibitor sensitive model) was investigated (monotherapy phase). In addition, the potential of Compound 17 as a single agent or in combination with WX001 to overcome MRTX849 acquired resistance was evaluated (monotherapy-R and combination-R phase, respectively).

[0442] Body weight change during the monotherapy phase of the experiment is shown in FIG. 18. Because tumor volume exceeded 3,000 mm³, mice in vehicle group were sacrificed during the monotherapy phase. Because of bad health condition, one mouse in group 3 was sacrificed during the monotherapy phase.

[0443] During monotherapy phase, Compound 17 at 30 mg/kg demonstrated a more durable response than MRTX849 at the same dose, indicating upfront treatment with a more potent KRAS G12C inhibitor to achieve complete target inhibition is important and insufficient target inhibition may lead to fast tumor progression (*See FIG. 20*). The analysis of tumor growth inhibition for each group is summarized in Table E19.

Table E19: Tumor growth inhibition analysis for each treatment in the NCI-H1373 xenograft model calculated based on tumor volume measurements on Day 34 (the day when vehicle group needs to be sacrificed due to tumor burden)

Treatment	Tumor Size (mm ³) ^a at day 34	T/C ^b (%)	TGI ^c (%)	p value ^d
Vehicle	2,469 ± 270	-	-	-
Compound 17, 30 mg/kg	15 ± 1	0.61	108.08	<0.001
MRTX849, 30 mg/kg	19 ± 1	0.77	107.91	<0.001

a. Mean ± SEM;

- b. Tumor Growth Inhibition is calculated by dividing the group average tumor volume for the treated group by the group average tumor volume for the vehicle control group (T/C);
- c. $TGI (\%) = [1 - (T_{34} - T_0) / (V_{34} - V_0)] \times 100\%$;
- d. p value for comparison of treatment group with vehicle group is calculated based on tumor size.

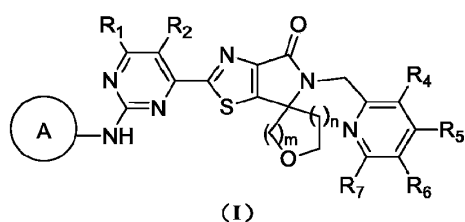
[0444] Once acquired resistance was observed, the treatment of Group 3 (MRTX849 monotherapy) was switched to 100 mg/kg Compound 17 to investigate whether Compound 17, a more potent KRAS G12C inhibitor, could overcome the resistance to MRTX849. Once tumor relapsed from 100 mg/kg Compound 17 (Day 147), mice were treated with Compound 17 in combination with WX001 to investigate whether the addition of ERK1/2 kinase inhibitor WX001 could yield a deeper anti-tumor effect than Compound 17 monotherapy.

[0445] Body weight change during the monotherapy-R and combination-R phase of the experiment is shown in FIG. 19. During the monotherapy-R phase, all mice in Group 3 were well tolerated to up to 100 mg/kg Compound 17 single agent treatment. During the combination-R phase, all mice in Group 3 were well tolerated to Compound 17 + WX001, 30 mg/kg + 50 mg/kg.

[0446] During monotherapy-R and combination-R phase, once tumor progressed, re-challenging with higher dose Compound 17 is effective but did not achieve complete tumor remission, while the addition of ERK1/2 inhibitor WX001 contributes to rapid tumor regression (*See FIG. 21*).

CLAIMS

1. A method of treating cancer in an individual, comprising administering to the individual an effective amount of 1) an ERK1/2 inhibitor; and 2) a KRAS G12C inhibitor, wherein the ERK1/2 inhibitor comprises an agent comprising the formula (I) or a pharmaceutically acceptable salt thereof,



wherein,

R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ;

R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

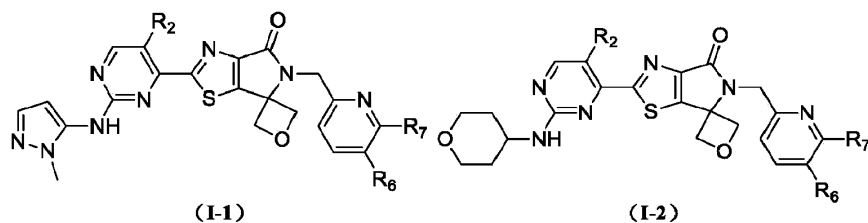
Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R;

R_a and R_c are independently selected from D, F, Cl, Br and I;

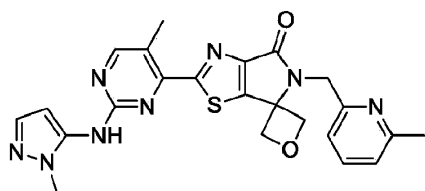
R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and said C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

2. The method of claim 1, wherein the ERK1/2 inhibitor is selected from:



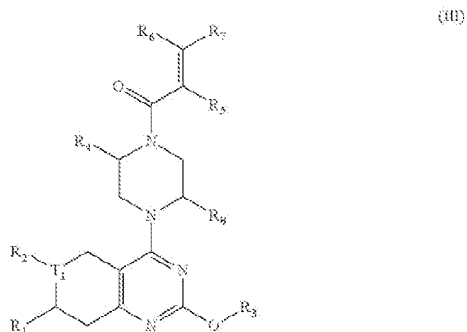
3. The method of claim 2, wherein the ERK1/2 inhibitor comprises an agent comprising the following formula or a pharmaceutically acceptable salt thereof,



4. The method of any one of claims 1-3, wherein the KRAS G12C inhibitor is a small molecule.

5. The method of claim 4, wherein the KRAS G12C inhibitor is selected from the group consisting of: sotorasib, adagrasib, JAB-21822, GDC-6036, JDQ443, D-1553, GH35, GFH925, BPI-421286, and LY3537982, RMC-6291, RMC-8839, HBI-2438, and JNJ-74699157.

6. The method of claim 4 wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T_1 is selected from O and N;

R_1 is selected from C_{6-10} aryl and 5- to 10-membered heteroaryl, wherein the C_{6-10} aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a ;

when T_1 is O, R_2 is not present;

when T_1 is N, R_2 is selected from H, C_{1-3} alkyl, $-C(=O)-C_{1-3}$ alkyl and $-S(=O)_2-C_{1-3}$ alkyl, wherein the C_{1-3} alkyl, $-C(=O)-C_{1-3}$ alkyl and $-S(=O)_2-C_{1-3}$ alkyl are optionally substituted with 1, 2 or 3 R_b ;

R_3 is C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_c ;

R_4 is selected from H and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 R_d ;

R_5 , R_6 and R_7 are each independently selected from H, F, Cl, Br, I, and C_{1-3} alkyl, wherein the C_{1-3} alkyl is optionally substituted with 1, 2 or 3 F;

R_8 is selected from H and CH_3 ;

R_a is each independently selected from F, Cl, Br, I, OH, NH_2 , CN, C_{1-3} alkyl, C_{1-3} alkoxy, C_{2-3} alkynyl and C_{2-3} alkenyl, wherein the C_{1-3} alkyl, C_{1-3} alkoxy, C_{2-3} alkynyl and C_{2-3} alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH_2 ;

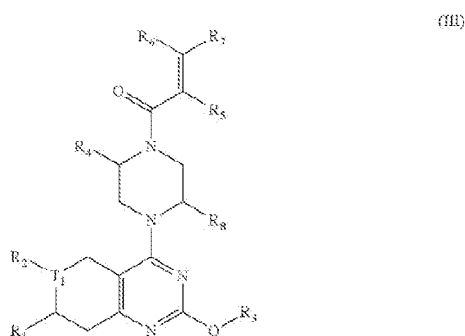
R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

R is each independently selected from H, F, Cl, Br, OH, CN, C_{1-3} alkyl, C_{1-3} alkoxy and $-C_{1-3}$ alkyl-O-C(=O)- C_{1-3} alkylamino;

provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH_2 , CF_3 , CH_2CH_3 and $-C\equiv CH$, and R_5 , R_6 and R_7 are each independently H.

7. A method of treating cancer in an individual, comprising administering to the individual an effective amount of 1) an ERK1/2 inhibitor; and 2) KRAS G12C inhibitor, wherein the KRAS G12C inhibitor comprises an agent comprising formula (III) or a pharmaceutically acceptable salt thereof,



wherein

T₁ is selected from O and N;

R₁ is selected from C₆₋₁₀ aryl and 5- to 10-membered heteroaryl, wherein the C₆₋₁₀ aryl and 5- to 10-membered heteroaryl are optionally substituted with 1, 2, 3, 4 or 5 R_a;

when T₁ is O, R₂ is not present;

when T₁ is N, R₂ is selected from H, C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl, wherein the C₁₋₃ alkyl, —C(=O)—C₁₋₃ alkyl and —S(=O)₂—C₁₋₃ alkyl are optionally substituted with 1, 2 or 3 R_b;

R₃ is C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_c;

R₄ is selected from H and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 R_d;

R₅, R₆ and R₇ are each independently selected from H, F, Cl, Br, I, and C₁₋₃ alkyl, wherein the C₁₋₃ alkyl is optionally substituted with 1, 2 or 3 F;

R₈ is selected from H and CH₃;

R_a is each independently selected from F, Cl, Br, I, OH, NH₂, CN, C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl, wherein the C₁₋₃ alkyl, C₁₋₃ alkoxy, C₂₋₃ alkynyl and C₂₋₃ alkenyl are optionally substituted with 1, 2 or 3 F;

R_b is each independently selected from F, Cl, Br, I, OH and NH₂;

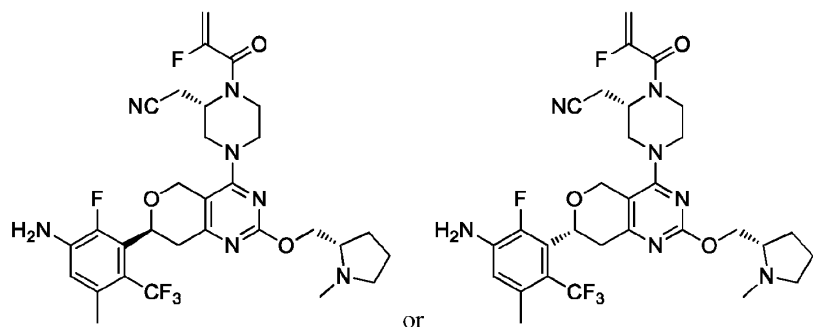
R_c is each independently selected from 4- to 8-membered heterocycloalkyl, wherein the 4- to 8-membered heterocycloalkyl is optionally substituted with 1, 2 or 3 R ;

R_d is each independently selected from F, Cl, Br, I, OH, NH_2 and CN;

R is each independently selected from H, F, Cl, Br, OH, CN, C_{1-3} alkyl, C_{1-3} alkoxy and $-C_{1-3}$ alkyl-O-C(=O)- C_{1-3} alkylamino;

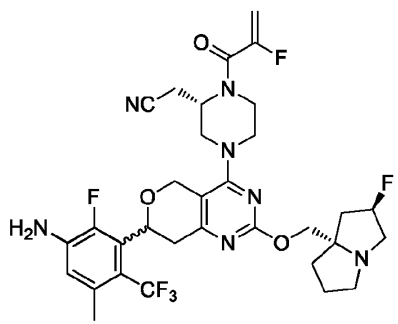
provided that when R_1 is naphthyl, the naphthyl is optionally substituted with F, Cl, Br, OH, NH_2 , CF_3 , CH_2CH_3 and $-C\equiv CH$, and R_5 , R_6 and R_7 are each independently H.

8. The method of claim 7, wherein the KRAS G12C inhibitor comprises an agent comprising the following formula



or a pharmaceutically acceptable salt thereof.

9. The method of claim 8, wherein the KRAS G12C inhibitor comprises an agent comprising the following formula

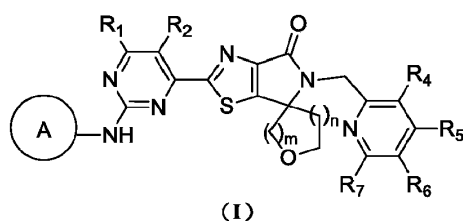


or a pharmaceutically acceptable salt thereof.

10. The method of any one of claims 7-9, wherein the ERK1/2 inhibitor is a small molecule.

11. The method of claim 10, wherein the ERK1/2 inhibitor is selected from the group consisting of: BVD-523 (ulixertinib), CC-90003, GDC-0994 (Ravoxertinib), KO-947, LTT462, LY3214996 (temuterkib), WX001, SCH772984, FR180204, and MK-8353.

12. The method of claim 10, wherein the ERK1/2 inhibitor comprises an agent comprising the formula (I) or a pharmaceutically acceptable salt thereof,



wherein,

R_1 and R_2 are independently selected from H and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally substituted by 1, 2 or 3 R_a ;

R_4 , R_5 , R_6 and R_7 are independently selected from H, F, Cl, Br, I and C_{1-3} alkyl, and the C_{1-3} alkyl is optionally replaced by 1, 2 or 3 R_c substitution;

n is 0 or 1;

m is 1 or 2;

Ring A is selected from pyrazolyl and tetrahydropyranyl optionally substituted with 1, 2 or 3 R;

R_a and R_c are independently selected from D, F, Cl, Br and I;

R_d is selected from F, Cl, Br, I, C_{1-3} alkyl and C_{1-3} alkoxy, and said C_{1-3} alkyl and C_{1-3} alkoxy are optionally replaced by 1, 2 or 3 R substitutions;

R is selected from F, Cl, Br and I.

13. The method of any one of claims 1-12, wherein the KRAS G12C inhibitor is administered orally.

14. The method of any one of claims 1-13, wherein the ERK1/2 inhibitor is administered orally.

15. The method of any one of claims 1-14, wherein the cancer comprises one or more cancer cells that express a KRAS G12C mutant protein.

16. The method of any one of claims 1-15, wherein the cancer is colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma, optionally wherein the cancer is selected from the group consisting of colon cancer, lung cancer and pancreatic cancer.

17. The method of any one of claims 1-16, wherein the cancer is a solid tumor, optionally wherein the solid tumor is an advanced, unresectable, and/or metastatic solid tumor.

18. The method of any one of claims 1-17, wherein the cancer was previously treated with a prior KRAS G12C inhibitor, optionally wherein the cancer was previously treated with two different prior KRAS G12C inhibitors.

19. The method of any one of claims 1-18, wherein the cancer is resistant to or has acquired resistance to a prior KRAS G12C inhibition, optionally wherein the cancer is resistant to or has acquired resistance to a prior KRAS G12C inhibitor (e.g., MRTX849, e.g., AMG510).

20. The method of claim 19, wherein the cancer is resistant to or has acquired resistance to two different prior KRAS G12C inhibitors.

21. The method of claim 19 or claim 20, wherein the individual has acquired a secondary mutation in KRAS, optionally wherein the individual has acquired a secondary KRAS mutation on codon 13, 18, 59, 61, 68, 95, 96, 117, or 146 after the prior KRAS inhibitor treatment, further

optionally the individual has acquired a G13C/D, A18D, Q61H/L, A59T, R68S/M, H95D/Q/R, Y96C/D, K117N, and/or A146T secondary mutation after the prior KRAS inhibitor treatment, further optionally wherein the secondary mutation comprises Q61H.

22. The method of any one of claims 19-21, wherein the cancer has an increased copy number of a mutant KRAS as compared to the cancer before the treatment of the prior KRAS G12C inhibition.
23. The method of any one of claims 19-22, wherein the individual develops a resistance to KRAS inhibitor that is independent from a MAPK pathway.
24. The method of any one of claims 1-17, wherein the cancer was not previously treated with a prior KRAS G12C inhibitor.
25. The method of any one of claims 18-24, wherein the prior KRAS G12C inhibitor is or comprises sotorasib or adagrasib.
26. The method of any one of claims 1-25, wherein the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered simultaneously or concurrently.
27. The method of any one of claims 1-25, wherein the ERK1/2 inhibitor and the KRAS G12C inhibitor are administered sequentially, optionally wherein a) the ERK1/2 inhibitor is administered prior to the KRAS G12C inhibitor or b) the KRAS G12C inhibitor is administered prior to the ERK1/2 inhibitor.
28. The method of any one of claims 1-27, wherein the KRAS G12C inhibitor is administered orally, intravenously, or subcutaneously.
29. The method of any one of claims 1-28, wherein the ERK1/2 inhibitor is administered orally, intravenously, or subcutaneously.

30. The method of any one of claims 1-29, wherein the ERK 1/2 inhibitor is administered in one or more doses, optionally wherein the ERK 1/2 inhibitor is administered twice a day, daily, or once every two days for at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days.

31. The method of claim 30, wherein the dose is equivalent to a dose of about 10 mg/kg to about 100 mg/kg for a mouse, optionally wherein the dose is equivalent to a dose of about 10 mg/kg to about 50 mg/kg for a mouse.

32. The method of any one of claims 1-31, wherein the KRAS G12C inhibitor is administered in one or more doses, optionally wherein the KRAS G12C inhibitor is administered twice a day, daily or once every two days for at least 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 150, 200, 250, 300, 350, or 365 days.

33. The method of claim 32, wherein the dose is equivalent to a dose of about 10 mg/kg to about 100 mg/kg for a mouse, optionally wherein the dose is equivalent to a dose of about 10 mg/kg to about 50 mg/kg for a mouse.

34. The method of any one of claims 1-33, further comprising administering to the individual an effective amount of a third therapy.

35. The method of claim 34, wherein the third therapy comprises another anti-cancer agent.

36. The method of claim 35, wherein the anti-cancer agent is selected from the group consisting of an immune checkpoint inhibitor, a cytotoxic agent, a cytostatic agent, an anti-angiogenic agent, a debulking agent, a chemotherapeutic agent, an antibody-drug conjugate, radiotherapy and radiotherapeutic agents, a targeted anti-cancer agent, BRMs, a therapeutic antibody, a cancer vaccine, cytokines, hormone therapies, radiation therapy, and anti-metastatic agents, optionally wherein the anti-cancer agent is an EGFR inhibitor, further optionally wherein the EGFR inhibitor is an anti-EGFR antibody, further optionally wherein the anti-EGFR antibody is cetuximab.

37. The method of any one of claims 1-36, wherein the individual is a human.
38. The method of any one of claims 1-37, wherein the method comprises selecting the individual for treatment based on the presence of one or more cancer cells that comprises an aberration in KRAS (e.g., KRAS G12C, e.g., KRAS G12D, e.g., KRAS Q61H), optionally wherein the aberration in KRAS comprises a) a KRAS G12C mutant protein, b) a KRAS G12D mutant protein and/or c) a KRAS Q61H mutant protein.
39. Use of an ERK1/2 inhibitor and a KRAS G12C inhibitor for the manufacture of a medicament for treating cancer.
40. The use of claim 39, wherein the cancer is selected from colon cancer, lung cancer, breast cancer, ovarian cancer, melanoma, bladder cancer, renal cell carcinoma, liver cancer, prostate cancer, stomach cancer, pancreatic cancer, lymphoma, leukemia, uterine cancer, cervical cancer, testicular cancer, esophageal cancer, gastrointestinal cancer, gastric cancer, colorectal cancer, kidney cancer, clear cell renal carcinoma, head and neck cancer, germ cell cancer, bone cancer, thyroid cancer, skin cancer, neoplasm of the central nervous system, mesothelioma, chronic lymphocytic leukemia, diffuse large B cell lymphoma, follicular lymphoma, Hodgkin lymphoma, myeloma, and sarcoma.
41. The method of claim 16 or the use of claim 40, wherein the cancer is colorectal cancer (e.g., NSCLC).
42. The method of claim 16 or the use of claim 40, wherein the cancer is pancreatic cancer.
43. The method of claim 16 or the use of claim 40, wherein the cancer is lung cancer.
44. The method or use of any one of claims 1-43, wherein the treatment comprises a dose that is equivalent to a dose of 25 to 50 mg/kg of the ERK 1/2 inhibitor for a mouse.

45. The method or use of any one of claims 1-44, wherein the treatment comprises a dose that is equivalent to a dose of 10 to 100 mg/kg of the KRAS G12C inhibitor.
46. A kit for treating cancer in an individual, comprising: 1) an ERK1/2 inhibitor; and 2) a KRAS G12C inhibitor.