

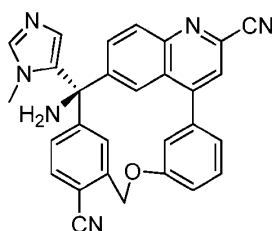
FARNESYLTRANSFERASE INHIBITORS FOR TREATMENT OF KRAS-DEPENDENT CANCERS

1. CROSS-REFERENCE

[001] This application claims the benefit of priority from U.S. Provisional Application Nos. 63/505,272, filed May 31, 2023, 63/580,680, filed September 5, 2023, 63/556,282, filed February 21, 2024, and 63/639,307, filed April 26, 2024, each of which is incorporated by reference in its entirety.

2. FIELD

[002] Provided herein are methods of using a farnesyltransferase inhibitor (FTI), such as Compound (I):



Compound (I)

or a pharmaceutically acceptable form thereof, optionally in combination with a KRAS inhibitor, to treat cancer. Pharmaceutical compositions, kits, and related products are also embodied within this disclosure.

3. BACKGROUND

[003] The Kristen rat sarcoma viral oncogene homolog (*KRAS*) gene belongs to the rat sarcoma (*RAS*) family of oncogenes that also includes Harvey rat sarcoma (*HRAS*) and neuroblastoma rat sarcoma (*NRAS*) viral oncogene homologs. When mutated, either by substitution, insertion, or deletion, or a combination, and/or amplified, these genes can initiate or promote cancer growth. Activating mutations in *KRAS* are among the most prevalent oncogenic driver mutations in human cancers, appearing in more than 80% of pancreatic cancers and more than 30% of colorectal cancers, cholangial cancers, and lung adenocarcinomas, and these mutations are associated with both tumorigenesis and aggressive tumor growth. Prevalent *KRAS* substitution mutations include G12C, G12D, G12V, G13D, and G12R.

[004] KRAS has been an intractable target for decades until the pioneering discovery of covalent inhibitors specific for the KRAS protein derived from the *KRAS* G12C, and successful clinical studies with sotorasib and adagrasib led to FDA breakthrough designations and approvals for both agents for the treatment of locally advanced or metastatic, *KRAS* G12C-mutant non-small cell lung cancer (NSCLC). Additional research efforts are aimed at the development of other mutant-specific (e.g., G12D, G12V, G12D), pan-KRAS inhibitors (that target two or more KRAS-mutant forms or at least one KRAS-mutant form and wild-type KRAS), and pan-RAS inhibitors (that target multiple RAS enzymes, e.g., KRAS, NRAS, and/or HRAS, optionally including mutant and/or wild-type forms of one or more RAS enzymes).

[005] *KRAS* mutations are prevalent in a range of cancer types, with G12C as the most common mutation in NSCLC (e.g., lung adenocarcinoma), and G12D and G12V as the most common mutation in gastrointestinal cancers, such as CRC and cancers of the esophagus, stomach, small bowel, and appendix. Various mutations were observed in cancers including pancreatic ductal adenocarcinoma (PDAC), appendix adenocarcinoma, small bowel adenocarcinoma, colorectal cancer, non-squamous NSCLC, extra-hepatic cholangial cancer, intra-hepatic cholangial cancer, germ cell cancer, cancer of unknown primary (CUP), esophageal adenocarcinoma, plasma cell neoplasm, GI-neuroendocrine tumor, endometrial cancer, myelodysplastic/myeloproliferative neoplasm, gastric adenocarcinoma, gall bladder cancer, ovarian cancer, peritoneal cancer, cervical cancer, urinary tract cancer, acute leukemia, and squamous NSCLC. Lee et al., Precision Oncol. 2022, 6, 91. For example, G12C mutations are observed at high rates in NSCLC (40% rate for non-squamous or lung adenocarcinoma; 36% rate for squamous), and to a lesser extent in colorectal cancer (CRC), PDAC, carcinomas of unknown primary (CUP), endometrial cancer, and ovarian cancer. G12D mutations are observed in CRC, non-squamous NSCLC, PDAC, CUP, endometrial cancer, ovarian cancer, intra-hepatic cholangial cancer, small bowel adenocarcinoma, and appendix adenocarcinoma. G12V mutations are observed in CRC, non-squamous NSCLC, PDAC, CUP, endometrial cancer, ovarian cancer, intra-hepatic cholangial cancer, small bowel adenocarcinoma, and appendix adenocarcinoma. G12R mutations are observed in PDAC and CUP cancers. G13D mutations are observed in CRC, non-squamous NSCLC, and endometrial cancer, among others. *KRAS* mutations account for the vast majority of RAS alterations in PDAC, CRC, and lung adenocarcinoma.

[006] Clinical responses to KRAS inhibitors for *KRAS*-mutant cancers such as CRC and NSCLC are variable, typically due to the development of resistance. For example, selective, irreversible KRAS G12C inhibitors show initial clinical response rates of 45% (adagrasib) and 37% (sotorasib) in patients with *KRAS* G12C-mutant NSCLC, but feedback reactivation of the MAPK and/or mTOR signaling pathways seems to limit therapeutic efficacy. In a Phase II study, all patients who achieved an objective response to sotorasib ultimately progressed on treatment. Skoulidis et al., N. Engl. J. Med. 2021;384:2371–81.

[007] Oncogenic KRAS alterations also include KRAS amplification or a combination of KRAS amplification and mutation. KRAS amplification is observed in about 8 to 9% of cancers, and amplification and mutation is observed in around 4% of cancers. Lee et al., 2002, supra. KRAS amplification is observed in a range of cancer types, including germ cell tumors, esophageal adenocarcinoma, gastric adenocarcinoma, gall bladder cancer, ovarian cancer, peritoneal cancer, gastric cancer, and squamous NSCLC.

Farnesyltransferase Inhibitors

[008] Farnesylation of mutant KRAS by farnesyltransferase was long considered as a drug target. Several types of FTIs were developed and tested clinically in various cancer types where RAS mutations are frequent, but all failed due to the alternative adaptation of RAS processing by the use of geranylgeranylation.

[009] Tipifarnib, an FTI, was tested broadly in clinical studies, but showed no significant antitumor activity or objective response rates in non-small-cell lung cancer, small-cell lung cancer, or breast cancer (Adje et al., J. Clin. Oncol. 2003, 21(9), 1760-1766; Heymach et al., Ann. Oncol. 2004, 15(8), 1187-1193; Yam et al., Invest New Drugs 2018, 36(2), 299-306). A second FTI, lonafarnib, showed no objective responses in colorectal cancer and did not improve progression-free or overall survival in ovarian cancer in combination with chemotherapy (Sharma et al., Ann. Oncol. 2002, 13(7), 1067-1071; Meier et al., Gynecol. Oncol. 2012, 126(2), 236-240). Indeed, FTI compounds showed limited clinical effect on *KRAS* mutation-bearing cancers due to alternative prenylation via the geranylgeranylation pathway (Ghimessy et al., Cancer Metastasis Rev. 2020, 39, 1159-1177). Tipifarnib treatment of colorectal carcinoma (CRC) and pancreatic adenocarcinoma (PDAC) tumors that are largely driven by *KRAS* mutations showed a modest increase in stable disease but did not improve overall survival

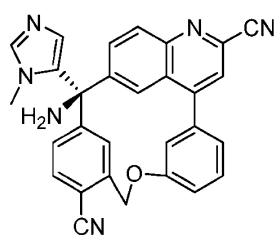
compared to supportive care (Rao et al., J. Clin. Oncol. 2004, 22, 3950-3957; Van Cutsem et al., J. Clin. Oncol. 2004, 22, 1430-1438). On the other hand, *HRAS*-mutant tumors are unable to use the alternative geranylgeranylation pathway. Thus, FTIs have been suggested in the treatment of *HRAS*-mutant tumors but not for *KRAS*-mutant tumors.

Combination of Tipifarnib and Adagrasib or Sotorasib

[0010] Despite the lack of evidence supporting use of FTIs in the treatment of *KRAS*-mutant cancers, the combination of tipifarnib with the KRAS G12C inhibitors adagrasib or sotorasib has been tested. Recently, the combination was shown to lead to significant increase in tumor regression in *KRAS* G12C NSCLC cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) models relative to either agent alone. Patel et al., Combination of tipifarnib with KRAS^{G12C} inhibitors to prevent adaptive resistance, Poster presented at American Association for Cancer Research (AACR) Annual Meeting, April 2023, Orlando, Abstract #1079; Delahaye et al., Using tipifarnib to prevent resistance to targeted therapies in oncogene-addicted tumors, Poster presented at 34th EORTC-NCI-AACR Symposium, October 2022, Barcelona. In addition, tipifarnib suppressed the feedback activation of mTOR signaling at the level of p-S6 (S235/236) that occurs after single-agent KRAS G12C inhibitor treatment. Thus, FTIs have the potential to overcome innate resistance mechanisms that come from single-agent KRAS inhibitor treatment and improve clinical outcomes in patients with *KRAS*-mutant cancers. There remains a need for improved treatments of *KRAS*-dependent cancers.

4. SUMMARY

[0011] Provided herein is a method of treating cancer in a subject comprising administering to the subject an FTI, such as Compound (I):



Compound (I)

or a pharmaceutically acceptable form thereof.

[0012] In another aspect is a method of treating cancer in a subject comprising administering to the subject (a) an FTI, such as Compound (I) or a pharmaceutically acceptable form thereof, and (b) a KRAS inhibitor.

[0013] In another aspect is a method of treating a *KRAS*-dependent cancer in a subject comprising administering to the subject an FTI, such as Compound (I) or a pharmaceutically acceptable form thereof.

[0014] In another aspect is a method of treating *KRAS*-dependent cancer in a subject comprising administering to the subject (a) an FTI, such as Compound (I) or a pharmaceutically acceptable form thereof, and (b) a KRAS inhibitor.

[0015] In another aspect is a method of delaying emergence of resistance to a KRAS inhibitor in a *KRAS*-dependent cancer in a subject, or overcoming resistance to a KRAS inhibitor in a *KRAS*-dependent cancer in a subject previously treated with a KRAS inhibitor, comprising administering to the subject (a) an FTI, such as Compound (I), or a pharmaceutically acceptable form thereof, optionally in combination with (b) a KRAS inhibitor; optionally wherein the KRAS inhibitor administered in combination with the FTI to the subject previously treated with a KRAS inhibitor is the same or a different KRAS inhibitor.

[0016] Without being limited by any theory, the use of the FTI and the KRAS inhibitor provides a more effective therapy compared to either single agent alone or compared to standard of care, such as chemotherapy, and impacts modes of resistance that develop in response to KRAS inhibitor therapy. The FTI, tipifarnib, has been shown to suppress the feedback reactivation of mTOR signaling that occurs after single-agent KRAS G12C inhibitor treatment. Patel 2023, *supra*; Delahaye 2022, *supra*. The combination may converge at the level of mTOR to block adaptive resistance to KRAS inhibitors.

[0017] In some embodiments, the combined use of the two agents is synergistic. Use of the combination of an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and a KRAS inhibitor according to the methods disclosed herein, can provide increased efficacy, increased durability of response, increased durability of resistance pathway inhibition, more rapid onset of antitumor response, prevention or delay of relapse or disease progression, and/or enhanced tumor cell death, or a combination thereof, in *KRAS*-dependent cancers, compared to either agent alone or to standard of care treatments, such as chemotherapy. In some embodiments, the combination has these improved effects while also mitigating therapeutic

resistance to a KRAS inhibitor, thereby reducing the impact of the development of resistance to those therapies.

[0018] The present disclosure also provides a pharmaceutical composition comprising an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient. In some aspects, the pharmaceutical composition also comprises a KRAS inhibitor. In some aspects, the pharmaceutical compositions are for use in the methods described herein.

[0019] The present disclosure also provides a pharmaceutical kit or packaging comprising (a) a pharmaceutical composition comprising an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient. In some aspects, the pharmaceutical kit or packaging also comprises a pharmaceutical composition comprising a KRAS inhibitor and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical kit or packaging comprises a pharmaceutical composition comprising an FTI such as Compound (I) or a pharmaceutically acceptable form thereof and a KRAS inhibitor.

5. BRIEF DESCRIPTION OF THE FIGURES

[0020] **FIGS. 1A-1M:** Plots of spheroid cell viability (%) vs. adagrasib concentration (nM) of adagrasib alone or in combination with various concentrations of tipifarnib in NCI-H2122 (**FIG. 1A**), NCI-1792 (**FIG. 1B**), NCI-H358 (**FIG. 1C**), and A549 (**FIG. 1D**) cell lines, and of adagrasib alone or in combination with various concentrations of Compound (I) in NCI-H2122 (**FIGS. 1E and 1I**), NCI-H1792 (**FIGS. 1F and 1K**), NCI-H358 (**FIG. 1G**), A549 (**FIGS. 1H and 1M**), NCI-H2030 (**FIG. 1J**), and NCI-H23 (**FIG. 1L**) cell lines.

[0021] **FIGS. 2A-2B:** Plots of spheroid cell viability (%) over time (days) of Dox-inducible shRHEB KRAS G12C NCI-H2122 cell line (**FIG. 2A**) with and without exposure to adagrasib, compared to control A549 cell line (**FIG. 2B**).

[0022] **FIGS. 3A-G:** Immunoblots of KRAS G12C NSCLC cell lines in 3D and 2D studies following exposure to FTIs and KRAS inhibitors, including NCI-H2122 cells, (a) Compound (I) and adagrasib alone and in combination (**FIGS. 3A and 3B**, 3D immunoblots), and (b) tipifarnib and sotorasib (**FIG. 3C**, 2D immunoblot), NCI-H2030 cells, tipifarnib and adagrasib (**FIG. 3D**, 2D immunoblot), and NCI-H1792 cells, tipifarnib and sotorasib (**FIG. 3E**, 2D immunoblot); and following exposure to adagrasib in a doxycycline-inducible shRNA NCI-H2122 system (**FIG. 3F**) and following exposure to adagrasib in a transfected siRNA NCI-H2122 system (**FIG. 3G**).

[0023] **FIGS. 4A-4C:** Plots of tumor volume (mm³) over time (days) for *in vivo* xenograft studies of FTI and KRAS inhibitor combinations in an NCI-H2122 CDX model with tipifarnib and adagrasib, **FIG. 4A**, tipifarnib and sotorasib, **FIG. 4B**, and Compound (I) and adagrasib, **FIG. 4C**.

[0024] **FIGS. 5A-5C:** Plots of tumor volume (mm³) over time (days) for *in vivo* xenograft studies of FTI and KRAS inhibitor combinations in an LU2512 PDX model with tipifarnib and adagrasib, **FIG. 5A**, tipifarnib and sotorasib, **FIG. 5B**, and Compound (I) and adagrasib, **FIG. 5C**.

[0025] **FIGS. 6A-6C:** Plots of tumor volume (mm³) over time (days) for *in vivo* xenograft studies of FTI and KRAS inhibitor combinations in an NCI-H2030 CDX model with tipifarnib and adagrasib, **FIG. 6A**, tipifarnib and sotorasib, **FIG. 6B**, and Compound (I) and adagrasib, **FIG. 6C**.

[0026] **FIGS. 7A-7B:** Plots of tumor volume (mm³) over time (days) (**FIG. 7A**) and change in tumor volume (%) over from day 0 to day 46 (**FIG. 7B**) for an *in vivo* xenograft study of the combination of Compound (I) and adagrasib in an NCI-H2030 CDX model.

[0027] **FIGS. 8A-8B:** Immunohistochemistry immunostaining images from NCI-H2122 endpoint tumor samples from combination groups treated with tipifarnib and adagrasib (**FIG. 8A**) and Compound (I) and adagrasib (**FIG. 8B**).

[0028] **FIGS. 9A-9D:** Results of a pharmacodynamic study of Compound (I) and adagrasib in NCI-H2122 CDX cell line through a Western blot of mTOR and MAPK pathway proteins (**FIG. 9A**), and IHC staining images (**FIGS. 9B and 9C**).

[0029] **FIGS. 10A-10B:** Plot of tumor volume (mm³) over time (days) for *in vivo* xenograft study of FTI and KRAS inhibitor combinations in a PA0787 PDX model with tipifarnib, Compound (I), MRTX1133, tipifarnib and MRTX1133, and Compound (I) and MRTX1133 (**FIG. 10A**), and in a SW1990 CDX model with Compound (I), MRTX1133, and Compound (I) and MRTX1133 (**FIG. 10B**).

[0030] **FIG. 11:** Immunoblot (2D signaling) of the AsPC-1 KRAS G12D PDAC cell line exposed to Compound (I) and MRTX1133.

[0031] **FIGS. 12A-12E:** Plots of tumor volume (mm³) over time (days) for *in vivo* xenograft studies of FTI and KRAS inhibitor combinations in a CR3262 PDX model with tipifarnib, Compound (I), MRTX1133, tipifarnib and MRTX1133, and Compound (I) and MRTX1133

(**FIG. 12A**), in a GP2D CDX model with Compound (I), MRTX1133, cetuximab, Compound (I) and MRTX1133, and cetuximab and MRTX1133 (**FIG. 12B**), in a CR1245 PDX model with Compound (I), MRTX1133, or the combination (**FIG. 12C**), and in a GP2D CDX model with Compound (I), RMC-6236, or the combination (**FIG. 12D**), or with Compound (I), MRTX1133, cetuximab, MRTX1133 and cetuximab, Compound (I) and MRTX1133, or Compound (I), MRTX1133, and cetuximab (**FIG. 12E**).

[0032] **FIG. 13:** Immunoblot analysis of GP2D colorectal cancer CDX tumors following treatment with Compound (I), MRTX1133, or the combination.

[0033] **FIGS. 14A-14B:** Plots of tumor volume (mm³) over time (days) for *in vivo* PDAC xenograft studies of Compound (I), adagrasib, and the combination in an MIA PaCa-2 KRAS G12C model (**FIG. 14A**) and in a PA1383 KRAS G12C model (**FIG. 14B**).

[0034] **FIGS. 15A-15D:** Plots of tumor volume (mm³) over time (days) for *in vivo* CRC xenograft studies in (a) a CR6256 KRAS G12C model with (i) tipifarnib, Compound (I), sotorasib, tipifarnib and sotorasib, and Compound (I) and sotorasib (**FIG. 15A**); (ii) in a CR6256 KRAS G12C model with tipifarnib, Compound (I), adagrasib, tipifarnib and adagrasib, and Compound (I) and adagrasib (**FIG. 15B**); (b) in a CR6243 KRAS G12C model with Compound (I), adagrasib, and the combination (**FIG. 15C**); and (c) in a SW837 KRAS G12C CRC model, Compound (I), adagrasib, and the combination (**FIG. 15D**).

[0035] **FIGS. 16A-16B:** Plots of tumor volume (mm³) over time (days) for *in vivo* NSCLC xenograft studies in an NCI-H358 KRAS G12C NSCLC model for two experiments: (a) tipifarnib, adagrasib (at two dose levels), and combinations thereof (**FIG. 16A**); and (b) tipifarnib, sotorasib (at two dose levels), and combinations thereof (**FIG. 16B**).

[0036] **FIGS. 17A-17F:** Plots of tumor volume (mm³) over time (days) for an *in vivo* NSCLC xenograft study in an NCI-H2122 NSCLC model with Compound (I), adagrasib, RMC-4550, BI-3406, everolimus, VT103, and combinations (all data: **FIG. 17A**; data extract: **FIG. 17B**); with Compound (I), adagrasib, RMC-4550, or combinations (**FIG. 17C**); Compound (I), adagrasib, BI-3406, and combinations (**FIG. 17D**); Compound (I), adagrasib, everolimus, and combinations (**FIG. 17E**); and Compound (I), adagrasib, VT103, and combinations (**FIG. 17F**).

[0037] **FIGS. 18A-18E:** Plots of tumor volume (mm³) over time (days) for *in vivo* NSCLC xenograft studies in an NCI-H2030 NSCLC model or an NCI-H2122 NSCLC model: (a) Compound (I), adagrasib, or one of two dosing regimens for Compound (I)/adagrasib (NCI-

H2030) (**FIG. 18A**); (b) Compound (I), adagrasib, or one of two dosing regimens for Compound (I)/adagrasib (NCI-H2122) (**FIG. 18B**); (c) Compound (I), sotorasib, sotorasib/adagrasib, sotorasib/adagrasib/Compound (I), and Compound (I)/adagrasib (NCI-H2122) (**FIG. 18C**); (d) adagrasib, adagrasib/RMC-6236, adagrasib/RMC-6236/Compound (I), and RMC-6236/Compound (I) (NCI-H2122) (**FIG. 18D**); RMC-6236, and one of two dosing regimens for RMC-6236/Compound (I) (NCI-H2122) (**FIG. 18E**).

[0038] **FIGS. 19A-19B:** Immunoblot analysis of (a) NCI-H2030 NSCLC CDX tumors following treatment with adagrasib for 28 or 56 days, Compound (I) addition at Day 28 to adagrasib for 56 days, or the upfront combination of Compound (I) and adagrasib for 28 or 56 days (**FIG. 19A**); and (b) NCI-H2122 NSCLC CDX tumors following treatment with sotorasib, sotorasib/adagrasib, sotorasib/adagrasib/Compound (I), adagrasib, Compound (I) addition at Day 14 to adagrasib, or adagrasib/Compound (I) upfront combination (**FIG. 19B**).

[0039] **FIG. 20:** Plot of tumor volume (mm³) over time (days) for *in vivo* NSCLC xenograft study in an NCI-H2122 NSCLC model with four dosing schedule regimens for Compound (I) and adagrasib.

[0040] **FIG. 21:** Plot of tumor volume (mm³) over time (days) for *in vivo* NSCLC xenograft study in an NCI-H2122 NSCLC model with Compound (I), divarasil (at two dose levels), and combinations thereof.

[0041] **FIGS. 22A-22B:** Plots of tumor volume (mm³) over time (days) for *in vivo* PDAC xenograft studies in (a) a Capan-1 KRAS G12V CDX model with Compound (I), BI-2493, and the combination (**FIG. 22A**); and (b) a PA-07-0041 KRAS G12V PDX model with Compound (I), BI-2493, and the combination (**FIG. 22B**).

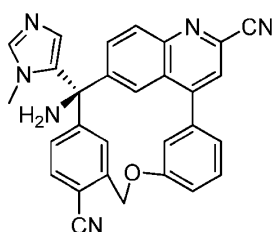
6. DETAILED DESCRIPTION

[0042] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0043] As used herein, and in the specification and the accompanying claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as single referents, unless the context clearly indicates otherwise.

[0044] As used herein, and unless otherwise specified, the terms “about” and “approximately,” when used in connection with doses, amounts, or weight percentages of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent within 30%, within 20%, within 15%, within 10%, or within 5%, of the specified dose, amount, or weight percent.

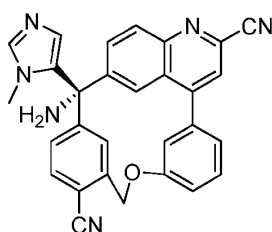
[0045] As used herein, Compound (I) has the structure shown below, which can be named “(S)-3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile.”



Compound (I)

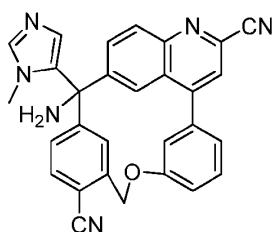
Compound (I) may be prepared as described in PCT Intl. Pat. Appl. No. PCT/US2022/80565, filed November 29, 2022 (published as PCT Intl. Pat. Appl. Publ. No. WO2023/102378).

[0046] As used herein, Compound (II) has the structure shown below, which can be named “(R)-3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile.”



Compound (II)

[0047] As used herein, Compound (III) has the structure shown below, which can be named “3-amino-3-(1-methyl-1*H*-imidazol-5-yl)-6-oxa-2(4,6)-quinolina-1,4(1,3)-dibenzenacyclohexaphane-2²,4⁴-dicarbonitrile.”



Compound (III)

[0048] As used herein, a “pharmaceutically acceptable form” of a compound disclosed herein includes, but is not limited to, Compound (I), (II), or (III), a tautomer, stereoisomer, mixture of stereoisomers, or racemic mixture thereof, or an isotopologue thereof, a pharmaceutically acceptable salt of any of the preceding forms, or a solvate of any of the preceding forms. In some embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, Compound (I), (II), or (III), or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0049] As used herein, the term “stereoisomer” or “stereoisomerically pure” means one stereoisomer of a compound that is substantially free of other stereoisomers of that compound. Stereoisomers include, for example, enantiomers, diastereomers, and atropisomers. For example, a stereoisomerically pure compound having one chiral center will be one enantiomer substantially free of the opposite enantiomer of the compound. For example, stereoisomerically pure Compound (I) is substantially free of Compound (II). Atropisomers are stereoisomers that arise because of hindered rotation about a single bond, where energy differences due to steric strain or other factors create a barrier to rotation sufficient to allow for identification and potentially isolation of individual conformers. A typical stereoisomerically pure compound comprises greater than about 80% by weight of one stereoisomer of the compound and less than about 20% by weight of other stereoisomers of the compound, greater than about 90% by weight of one stereoisomer of the compound and less than about 10% by weight of the other stereoisomers of the compound, greater than about 95% by weight of one stereoisomer of the compound and less than about 5% by weight of the other stereoisomers of the compound, or greater than about 97% by weight of one stereoisomer of the compound and less than about 3% by weight of the other stereoisomers of the compound. The compounds can have chiral centers and can occur as racemates, individual enantiomers or diastereomers, and mixtures thereof. All such stereoisomeric forms are included within the embodiments provided herein, including

mixtures thereof. The use of stereoisomerically pure forms of such compounds, as well as the use of mixtures of those forms, including unequal mixtures and racemic mixtures, are encompassed by the embodiments provided herein.

[0050] Stereoisomers may be asymmetrically synthesized or resolved using standard techniques such as chiral columns or chiral resolving agents. *See, e.g.,* Jacques, J., *et al.*, (Wiley-Interscience, New York, 1981); Wilen, S. H., *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, E. L., *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S. H., *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN, 1972); Todd, M., *Separation of Enantiomers : Synthetic Methods* (Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2014); Toda, F., *Enantiomer Separation: Fundamentals and Practical Methods* (Springer Science & Business Media, 2007); Subramanian, G. *Chiral Separation Techniques: A Practical Approach* (John Wiley & Sons, 2008); Ahuja, S., *Chiral Separation Methods for Pharmaceutical and Biotechnological Products* (John Wiley & Sons, 2011).

[0051] In certain embodiments, the pharmaceutically acceptable form is a tautomer, including tautomers of the imidazole moiety. As used herein, the term “tautomer” is a type of isomer that includes two or more interconvertible compounds resulting from at least one formal migration of a hydrogen atom and at least one change in valency. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH. Where tautomerization is possible (*e.g.*, in solution), a chemical equilibrium of tautomers can be reached. Tautomerizations (*i.e.*, the reaction providing a tautomeric pair) can be catalyzed by acid or base, or can occur without the action or presence of an external agent.

[0052] The term “isotopologue” refers to isotopically-enriched compounds that are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds described herein include isotopes of hydrogen or carbon, such as ^2H (deuterium) or ^{14}C , respectively. When the compounds are enriched with deuterium, the deuterium-to-hydrogen ratio on the deuterated atoms of the molecule substantially exceeds the naturally occurring deuterium-to-hydrogen ratio.

[0053] An embodiment described herein may include an isotopologue form of Compound (I), (II), or (III), or a pharmaceutically acceptable form thereof, wherein the isotopologue is

substituted on one or more atom members of said compound, or a pharmaceutically acceptable form thereof, with one or more deuterium atoms in place of one or more hydrogen atoms, optionally wherein the one or more hydrogen atoms are attached to a carbon atom.

[0054] As used herein, the term “pharmaceutically acceptable salt” refers to salts suitable for use in subjects without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, *Remington’s Pharmaceutical Sciences*, 18th eds., Mack Publishing, Easton PA (1990) or *Remington: The Science and Practice of Pharmacy*, 19th eds., Mack Publishing, Easton PA (1995). Pharmaceutically acceptable salts of the compounds provided herein include those derived from suitable inorganic and organic acids, such as suitable inorganic and organic addition acids. In certain embodiments, the pharmaceutically acceptable form of Compound (I), (II), or (III) is the free base of Compound (I), (II), or (III). In some embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt of Compound (I), (II), or (III).

[0055] In certain embodiments, the pharmaceutically acceptable form is a solvate (*e.g.*, a hydrate). As used herein, the term “solvate” refers to a complex between a compound and a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. The solvate can be of Compound (I), (II), or (III), or of a pharmaceutically acceptable salt thereof. In some embodiments, the solvate is a hydrate (solvate with water). Pharmaceutically acceptable solvates and hydrates are complexes that, for example, can include solvent/compound molar ratios of 0.1, 0.25, 0.50, 0.75, or 1, or 1 to about 100, or 1 to about 10, or one to about 2, about 3 or about 4.

[0056] Herein, if there is a discrepancy between a depicted structure and a name for that structure, the depicted structure is to be accorded more weight.

[0057] As used herein, the term “pharmaceutically acceptable excipient” means a carrier, diluent, or excipient approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. A pharmaceutical carrier refers to a diluent, adjuvant (*e.g.*, Freund’s adjuvant (complete and incomplete)), excipient, or vehicle with which a therapeutic agent is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean

oil, mineral oil, sesame oil, and the like. Water is a specific carrier for intravenously administered pharmaceutical compositions. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. For example, the term pharmaceutically acceptable carrier, diluent, or excipient includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions as disclosed herein is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions. Examples of excipients that can be used in oral dosage forms provided herein include, but are not limited to, binders, fillers, disintegrants, and lubricants.

[0058] As used herein, the term “therapeutically effective amount” or “effective amount” in connection with a compound means an amount capable of treating a cancer or symptoms thereof, or otherwise achieving the desired therapeutic or mechanistic effect, such as mitigating drug resistance.

[0059] As used herein, the terms “treat,” “treating,” and “treatment,” are used interchangeably herein, and means an alleviation or amelioration, in whole or in part, of a disease, or one or more of the symptoms associated with a disease, or slowing or halting of further progression or worsening of those symptoms, or alleviating or eradicating the cause(s) of the disease. In some embodiments, these terms refer to an approach for obtaining beneficial or desired results including, but not limited to, a therapeutic benefit or a prophylactic benefit. A therapeutic benefit resulting from the methods of treatment provided herein includes the eradication or amelioration of the underlying disease, being treated, the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disease such that an improvement is observed in the subject, notwithstanding that the subject can still be afflicted with the underlying disease. For example, when used in reference to a subject having cancer, “treating” refers to an action that reduces the severity of the cancer or slows the progression of the cancer, such as inhibiting the cancer growth, arresting development of the cancer, causing regression of the cancer, delaying or minimizing one or more symptoms associated with the presence of the cancer, or overcoming or delaying emergence of drug resistance. In some aspects, “treating” includes adjuvant therapy, which is therapy that is given

after primary treatments, such as surgery, to reduce the chance of the cancer returning. In some aspects, “treating” includes neoadjuvant therapy, which is therapy given initially to shrink a tumor before a main treatment, such as surgery. In some aspects, “treating” according to the methods described herein is first-line treatment, second-line treatment, later-line treatment (second or later line), adjuvant therapy, or neoadjuvant therapy, or is before or after, or concurrent with, one or more therapies in any of these classes.

[0060] As used herein, the terms “prevention” and “preventing” refer to an approach for obtaining beneficial or desired results including, but not limited to, prophylactic benefit. For prophylactic benefit, the compounds and pharmaceutical compositions disclosed herein can be administered to a subject at risk of developing cancer, to a subject reporting one or more of the physiological symptoms of cancer, even though a diagnosis of the cancer, may not have been made, or to a patient in remission from cancer. A prophylactic benefit resulting from the methods of treatment provided herein includes delaying or eliminating the appearance of a disease, delaying or eliminating the onset of symptoms of a disease, slowing, halting, or reversing the progression of a disease, or any combination thereof.

[0061] As used herein, the terms “mitigate” and “mitigating” with respect to resistance to a therapy includes slowing or delaying the time to emergence of drug resistance, preventing emergence of drug resistance, or reducing or overcoming drug resistance.

[0062] As used herein, the term “subject” to which administration is contemplated, can be an animal, including, but not limited to, a human (e.g., a male or female of any age group, such as an adult subject or an adolescent subject); a primate (e.g., cynomolgus monkey, rhesus monkey), and/or another mammal, including a commercially relevant mammal such as cattle, pig, horse, sheep, goat, cat, dog, rabbit, rodent, and/or bird. In some embodiments, the subject is a mammal. In some embodiments, the subject is a human. In some embodiments, the subject is an adolescent human. In some embodiments, the subject is an adult human.

[0063] As used herein, the term “first-line therapy” refers to the first therapy a subject receives for a cancer, e.g., the first therapy following a diagnosis of cancer. First-line therapies for treating cancer include, for example, surgery, chemotherapy, immunotherapy, or radiation, or a combination. Chemotherapy may include treatment with cisplatin or carboplatin, optionally in combination with paclitaxel, docetaxel, gemcitabine, etoposide, or premetrexed. Immunotherapy may include treatment with a PD-1/PD-L1 inhibitor (such as nivolumab, pembrolizumab,

cemiplimab, atezolizumab, or durvalumab) or a CTLA-4 inhibitor (such as ipilimumab or tremelimumab). First-line therapy is the first time a cancer is treated after recurrence or diagnosis of metastatic disease. In some cases, first-line therapy for CRC is the FOLFIRI regimen (leucovorin calcium (folinic acid), fluorouracil (5FU), and irinotecan hydrochloride) or FOLFOX regimen (leucovorin calcium (folinic acid), fluorouracil (5FU), and oxaliplatin). In some cases, first-line therapy for PDAC is the FOLFIRINOX regimen (leucovorin calcium (folinic acid), fluorouracil (5FU), irinotecan hydrochloride, and oxaliplatin), gemcitabine plus nab-paclitaxel, or the NALIRIFOX regimen (liposomal irinotecan (Nal-IRI or Onivyde®), fluorouracil (5FU), leucovorin, and oxaliplatin).

[0064] As used herein, the term “second-line therapy” refers to the second therapy that a subject receives for a cancer after a first therapy, e.g., if the subject is refractory to or relapses on such therapy. Second-line therapies for treating cancer are used, for example, when at least one prior treatment has failed to mitigate or reduce the severity of at least one symptom associated with the cancer. For example, a second-line therapy can include the use of chemotherapy, immunotherapy, or radiation, or a combination. In some cases, second-line therapy for CRC is the FOLFIRI regimen (leucovorin calcium (folinic acid), fluorouracil, and irinotecan hydrochloride) or FOLFOX regimen (leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin).

[0065] As used herein, the term “relapsed” refers to a disease that responded to treatment (e.g., achieved a complete response, partial response, or stable disease) but then showed disease progression. The treatment can include one or more lines of therapy. For example, “relapsed” cancer may refer to cancer that has been previously treated with and responded to a line of therapy, for example with remission, but subsequently recurred. Cancer may relapse following multiple lines of therapy, such as one, two, three, or four, or at least one, or at least two lines of therapy.

[0066] As used herein, the term “refractory” refers to a disease that has not responded, or has not responded completely, to a prior treatment. In some embodiments, a cancer is refractory where it exhibits a less than a complete response (CR) to the most recent therapy.

[0067] As used herein, the term “amplification” refers to tumors with an increase in the number of copies of a gene relative to a reference level. In some embodiments, the amplified gene is a wild-type gene. In some embodiments, the amplified gene is a mutant gene. In the

context of *KRAS*-dependent cancers, amplification is at least 3 copies, at least 4 copies, at least 5 copies, at least 6 copies, 3 to 450 copies, 3 to 200 copies, 3 to 50 copies, or 4 to 10 copies.

Preferably at least 4 copies, or 4 to 100 copies of the *KRAS* gene.

[0068] As used herein and unless otherwise indicated, the term “*KRAS*-dependent cancer” refers to a cancer with an oncogenic alteration in the *KRAS* gene, for example, in the sequence of the gene or its level of expression. Such alterations include, but are not limited to, oncogenic *KRAS* mutations, oncogenic amplification of the *KRAS* gene, or a combination thereof. In some embodiments, *KRAS*-dependent cancer is *KRAS*-mutant and/or *KRAS*-amplified, or a combination thereof. In some embodiments, *KRAS*-dependent cancer is *KRAS*-mutant cancer. In some embodiments, *KRAS*-dependent cancer is *KRAS*-wildtype and *KRAS*-amplified. *KRAS* mutations and amplification may be determined using methods known in the art. Oncogenic *KRAS* mutations include, for example, G12C, G12D, G12V, G12A, G12R, G12S, G13C, G13D, and Q61H. In some embodiments, the cancer to be treated is a *KRAS*-amplified cancer.

[0069] As used herein, the term “Duration of Response” or “DoR” is the time from achieving a response until relapse or disease progression. In some embodiments, DoR is the time from achieving a response $\geq$ partial response (PR) until relapse or disease progression. In some embodiments, DoR is the time from the first documentation of a response until the first documentation of progressive disease or death. In some embodiments, DoR is the time from the first documentation of a response $\geq$ partial response (PR) until to the first documentation of progressive disease or death.

[0070] As used herein, the term “Event-Free Survival” or “EFS” means the time from treatment onset until any treatment failure, including disease progression, treatment discontinuation for any reason, or death.

[0071] As used herein, the term “Overall Response Rate” or “ORR” means the percentage of patients who achieve a response. In some embodiments, ORR means the sum of the percentage of patients who achieve complete and partial responses. In some embodiments, ORR means the percentage of patients whose best response $\geq$ partial response (PR).

[0072] As used herein, the term “Overall Survival” or “OS” means the time from treatment onset until death from any cause.

[0073] As used herein, the term “Progression Free Survival” or “PFS” means the time from treatment onset until tumor progression or death. In some embodiments, PFS means the time

from the first dose of compound to the first occurrence of disease progression or death from any cause. In some embodiments, PFS rates are computed using the Kaplan-Meier estimates.

[0074] As used herein, the term “Time to Progression” or “TTP” means the time from treatment onset until tumor progression; TTP does not include deaths.

[0075] As used herein, the term “Time to Response” or “TTR” means the time from the first dose of compound to the first documentation of a response. In some embodiments, TTR means the time from the first dose of compound to the first documentation of a response $\geq$ partial response (PR).

6.1 COMPOUNDS

[0076] In some embodiments, the methods provided herein include administering an FTI. In some embodiments, the FTI is tipifarnib, lonafarnib, FTI277, BMS214662, or Compound (I), or a pharmaceutically acceptable form thereof. In some embodiments, the methods include administering Compound (I), or an enantiomer (e.g., Compound (II)), mixture of enantiomers, or racemate thereof (e.g., Compound (III)), or a pharmaceutically acceptable form thereof, and optionally (b) a KRAS inhibitor to a subject. In some embodiments, the methods provided herein comprise administering Compound (I), or pharmaceutically acceptable salt thereof, or a solvate thereof. In some embodiments, the methods comprise administering a mixture of from 1000:1 to 51:49 of Compound (I) and Compound (II), or a pharmaceutically acceptable salt thereof, or a solvate thereof. In some embodiments, the methods comprise administering Compound (III) or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0077] The preparations of Compound (I), (II), or (III), as provided herein, are described in PCT Intl. Appln. No. PCT/US2022/80565 (published as PCT. Intl. Appl. Publ. No. WO2023/102378).

[0078] In some embodiments, the KRAS inhibitor is a KRAS inhibitor that selectively inhibits one or more mutant forms of KRAS, optionally inhibiting the mutant form(s) selectively over wild-type KRAS. In some embodiments, the KRAS inhibitor is a KRAS G12C inhibitor, a KRAS G12D inhibitor, a KRAS G12V inhibitor, a KRAS G13D inhibitor, a KRAS G12R inhibitor, a KRAS G12S inhibitor, or a pan-KRAS inhibitor (e.g., a pan-RAS inhibitor or “RAS(ON)” inhibitor, which targets mutant and/or wild-type protein in its active (or “on”) GTP-bound state). In some embodiments, the KRAS inhibitor selectively inhibits KRAS wild-type and KRAS-mutant protein in the inactive (or “off”) state. In some embodiments, a pan-KRAS

inhibitor selectively inhibits more than one mutant form of KRAS.

[0079] In some embodiments, the KRAS inhibitor is a KRAS G12C inhibitor. In some embodiments, the KRAS G12C inhibitor is adagrasib (KRAZATI[®], MRTX849, Amgen), sotorasib (LUMAKRAS[™], AMG-510, Amgen), divarasib (GDC-6036, Genentech/Roche), linperlisib (YL-15293), RM007, D-1553 (InvestisBio), JDQ443 (Novartis), LY3537982 (Eli Lilly), LY3499446, ERAS-601, ERAS-007, BI 1823911 (Boehringer Ingelheim), JAB-21822 (glecirasib), MK-1084, MK-1086, MK-1087, L-15293, D3S-001, RMC-6291 (Revolution), HBI-2438, FMC-376 (Frontier), BBO-8520 (BridgeBio), ZG19018 (Suzhou Zelgen), UCT-001024 (1200 Pharma), TEB-17231 (280Bio unit of Yingli Pharma), HYP-2A (Sichuan Huiyu), ABSK071 (Abbisko), IBI351 (GFH925; Innovent/Genfleet), ARS-853, ARS-1620, or JNJ-74699157 (ARS-3248). In some embodiments, the KRAS G12C inhibitor is adagrasib. In some embodiments, the KRAS G12C inhibitor is sotorasib. In some embodiments, the KRAS G12C inhibitor is adagrasib and the cancer is NSCLC. In some embodiments, the KRAS G12C inhibitor is adagrasib and the cancer is CRC. In some embodiments, the KRAS inhibitor is a KRAS G12C (OFF) inhibitor. In some embodiments, the KRAS inhibitor is a KRAS G12C (ON) inhibitor.

[0080] In some embodiments, the KRAS inhibitor is a KRAS G12D inhibitor. In some embodiments, the KRAS G12D inhibitor is MRTX1133 (Mirati), TH-Z827 (Mao et al., Cell Discov. 2022, 8, 5), TH-Z835, KD-8, BI-KRAS12D1-3 (Boehringer Ingelheim), BI-KRASG12D3 (Boehringer Ingelheim; Hofmann et al., Cancer Discovery 2022, 12, 924), RMC-9805 (Revolution), ASP3082, ASP4396, LY3962673, INCB161734, HRS-4642, or QTX3046 (Quanta). In some embodiments, the KRAS G12D inhibitor is MRTX1133. In some embodiments, the KRAS G12D inhibitor is MRTX1133 and the cancer is pancreatic cancer or PDAC. In some embodiments, the KRAS G12D inhibitor is MRTX1133 and the cancer is CRC. In some embodiments, Compound (I) induced an increase in depth and/or duration of inhibition of phosphorylation of ERK, p90, or mTOR (e.g., measured by S6K and S6 levels), or an increase in cell cycle arrest (measured by phosphorylation of Rb) or cell death (measured by cleaved caspase 3), when combined with a KRAS G12D inhibitor such as MRTX1133.

[0081] In some embodiments, the KRAS inhibitor is a KRAS G12V inhibitor.

[0082] In some embodiments, the KRAS inhibitor is a KRAS G13D inhibitor.

[0083] In some embodiments, the KRAS inhibitor is a KRAS G12R inhibitor.

[0084] In some embodiments, the KRAS G12R inhibitor is KRAS G12R inhibitor 1 (Shokat). In some embodiments, the KRAS inhibitor is a KRAS G12S inhibitor.

[0085] In some embodiments, the KRAS G12S inhibitor is G12Si-5 (Shokat).

[0086] In some embodiments, the KRAS inhibitor is a pan-KRAS inhibitor. In some embodiments, the pan-KRAS inhibitor inhibits at least two mutant forms of KRAS. In some embodiments, the pan-KRAS inhibitor inhibits at least one mutant form of KRAS and wild-type KRAS. In some embodiments, the pan-KRAS inhibitor is BI-2852, BI-pan-KRAS1-4 (BI1701963), RSC-1255, RMC-6236, RSC-1255, QTX3034 (Quanta), JAB-23425 (Beijing Jacobio), BI-2493, LY4066434, or VRTX-153 (VRise). In some embodiments, the pan-KRAS inhibitor is BI-2852. In some embodiments, the KRAS inhibitor is a pan-RAS inhibitor. In some embodiments, the pan-RAS inhibitor inhibits at least two mutant forms of KRAS. In some embodiments, the pan-RAS inhibitor inhibits at least two of KRAS, NRAS, and HRAS, optionally at least one mutant form of KRAS, NRAS, or HRAS. In some embodiments, the KRAS inhibitor is a pan-RAS inhibitor that is a RAS(ON) inhibitor (selective for the active or “on” state of the target protein(s)). In some embodiments, the pan-RAS inhibitor is selective for the active, GTO-bound or ON state of both mutant and wild-type variants of KRAS, NRAS, and HRAS. In some embodiments, the KRAS inhibitor is a pan-KRAS inhibitor that selectively inhibits wild-type and mutant forms of KRAS in the inactive (or “off”) state. In some embodiments, the pan-RAS inhibitor inhibits at least one mutant form of KRAS and the wild-type form of KRAS. In some embodiments, the KRAS inhibitor inhibits KRAS G12D, wild-type KRAS, wild-type NRAS, and wild-type HRAS, or any combination thereof. In some embodiments, the pan-RAS inhibitor is RMC-6236. In some embodiments, the pan-RAS inhibitor is RSC-1255.

[0087] In some embodiments, the KRAS inhibitor inhibits KRAS G12D and KRAS G12V. In some embodiments, the pan-RAS inhibitor is RMC-6236 and the cancer is lung cancer, non-small cell lung cancer, pancreatic cancer, PDAC, or CRC. In some embodiments, the cancer is KRAS G12D, G12V, G12R, G12A, or G12S mutated, or G12D, G12V, or G12R mutated. In some embodiments, the cancer is CRC and is G13X and/or Q61X KRAS mutated cancer.

[0088] In some embodiments, the KRAS inhibitor is BI-2852 and the cancer is KRAS-amplified gastric cancer or esophageal cancer.

[0089] In some embodiments, the KRAS inhibitor is BI-1701963. In some embodiments,

BI-1701963 inhibits both mutant and wild-type inactive KRAS forms.

6.2 PHARMACEUTICAL COMPOSITIONS, KITS, AND PACKAGING

[0090] In some embodiments, provided herein is a pharmaceutical composition comprising an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition comprises Compound (I) or a pharmaceutically acceptable salt thereof, or a solvate thereof.

[0091] In some embodiments, provided herein is a pharmaceutical composition comprising a KRAS inhibitor and a pharmaceutically acceptable excipient.

[0092] In some embodiments, provided herein is a pharmaceutical composition comprising an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and a KRAS inhibitor, and a pharmaceutically acceptable excipient.

[0093] Pharmaceutical compositions can be prepared using techniques and procedures well known in the art (see, *e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Twelfth Edition 2021). The pharmaceutical compositions provided herein may be administered at once or periodically at specified intervals of time, such as once daily (QD) or twice daily (BID).

[0094] In some embodiments, the pharmaceutical composition comprises about 0.1-1000 mg of the FTI such as Compound (I), or a pharmaceutically acceptable form thereof, such as a free base equivalent amount selected from about 0.1-2.5 mg, 0.5-5 mg, 0.5-10 mg, 0.5-25 mg, 0.5-50 mg, 0.5-75 mg, 0.5-100 mg, 0.5-200 mg, 0.5-250 mg, 0.5-300 mg, 0.5-600 mg, 0.5-900 mg, 1-5 mg, 1-10 mg, 1-25 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-300 mg, 1-600 mg, 1-900 mg, 20-100 mg, 20-200 mg, 20-250 mg, 20-300 mg, 40-75 mg, 50-75 mg, 50-100 mg, 50-150 mg, 50-200 mg, 50-250 mg, 50-300 mg, 75-100 mg, 100-200 mg, 125-200 mg, 150-300 mg, 200-250 mg, 200-400 mg, 300-600 mg, 250-500 mg, 400-600 mg, 500-750 mg, 600-900 mg, 700-100 mg, 650-1000 mg, and 800-1000 mg of the FTI such as Compound (I), or a pharmaceutically acceptable form thereof. In some embodiments, the pharmaceutical composition comprises a free base equivalent amount selected from about 0.1 mg, 0.2 mg, 0.25 mg, 0.3 mg, 0.4 mg, 0.5 mg, about 1 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg,

about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, and about 1000 mg of the FTI such as Compound (I), or pharmaceutically acceptable form thereof. In some embodiments, the pharmaceutical composition comprising the FTI such as Compound (I), or a pharmaceutically acceptable form thereof, is formulated in a tablet, such as a film-coated tablet. In some embodiments, the pharmaceutical composition comprising the FTI such as Compound (I), or a pharmaceutically acceptable form thereof, is formulated in a capsule.

[0095] In some embodiments, the pharmaceutical composition comprises 10-1000 mg of the KRAS inhibitor (in free base/acid equivalent amount), such as an amount selected from 10-300 mg, 10-200 mg, 10-150 mg, 10-100 mg, 10-50 mg, 25-400 mg, 25-300 mg, 25-200 mg, 25-150 mg, 25-100 mg, 25-50 mg, 50-400 mg, 50-300 mg, 50-200 mg, 50-150 mg, 50-100 mg, 100-400 mg, 100-300 mg, 100-200 mg, 150-250 mg, 175-225 mg, 200-400 mg, and 200-300 mg. In some embodiments, the pharmaceutical composition comprises about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 260 mg, about 270 mg, about 275 mg, about 280 mg, about 290 mg, about 300 mg, about 320 mg, about 325 mg, about 350 mg, about 375 mg, or about 400 mg. In some embodiments, the KRAS inhibitor is adagrasib and the pharmaceutical composition comprises 200 mg of adagrasib, optionally as a tablet, optionally comprising colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, and microcrystalline cellulose. In some embodiments, the KRAS inhibitor is sotorasib, and the pharmaceutical composition comprises 120 mg or 320 mg of sotorasib, optionally as a tablet, optionally comprising microcrystalline

cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate.

[0096] In some embodiments, the pharmaceutical compositions are provided for administration to a subject in dosage forms such as tablets, capsules, microcapsules, pills, powders, granules, troches, suppositories, injections, syrups, patches, creams, lotions, ointments, gels, sprays, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable forms thereof. In some embodiments, the pharmaceutical compositions provided herein are in the form of a tablet. In some embodiments, the pharmaceutical compositions provided herein are in the form of a capsule.

[0097] It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens may be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the pharmaceutical compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed pharmaceutical compositions.

[0098] The pharmaceutical compositions are intended to be administered by a suitable route, including but not limited to orally, parenterally, rectally, topically, locally, intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The pharmaceutical compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. In some embodiments, the pharmaceutical compositions provided herein are administered orally. For oral administration, capsules and tablets can be formulated.

[0099] In some embodiments, provided herein is a pharmaceutical kit comprising (a) an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and optionally (b) a KRAS inhibitor. In some embodiments, provided herein is a pharmaceutical kit comprising (a) a pharmaceutical composition comprising an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient, and optionally (b) a

pharmaceutical composition comprising a KRAS inhibitor, and a pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical kit further comprises instructions that detail a dosing regimen for administering the FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and optionally for administering the KRAS inhibitor for one or more cycles. In some embodiments, the pharmaceutical kit comprises a color-coded system that details a dosing regimen for each agent for one or more cycles. In some embodiments, the pharmaceutical kit is a pharmaceutical packaging.

[00100] In some embodiments, the pharmaceutical kit or the pharmaceutical packaging comprises instructions for administering the contents of the kit to a subject. For example, in some embodiments, the instructions may be color-coded with one color indicating the dosing regimen for administering the FTI such as Compound (I), or a pharmaceutically acceptable form thereof, during a treatment cycle, such as a 28-day treating cycle, such as administering once or twice per day on days 1-7, on days 1-7 and 15-21, on days 1-14, on days 1-21, or on each day of a 28-day treatment cycle, while indicating with a different color the dosing regimen for administering the KRAS inhibitor during a treatment cycle, such as a 28-day treating cycle, for example, administering the KRAS inhibitor once or twice daily on each day of a 28-day treatment cycle.

6.3 METHODS, DOSING REGIMENS AND SCHEDULES

6.3.1 THERAPEUTIC USES AND METHODS

[00101] In some embodiments, provided herein is a method of treating cancer in a subject comprising administering to the subject an FTI such as Compound (I) or a pharmaceutically acceptable form thereof. In some embodiments, provided herein is a method of treating cancer in a subject comprising administering to the subject (a) an FTI such as Compound (I) or a pharmaceutically acceptable form thereof, and (b) a KRAS inhibitor. In some embodiments, the cancer is a *KRAS*-dependent cancer. In some embodiments, the methods comprise administering to the subject a therapeutically effective amount of the FTI such as Compound (I) or a pharmaceutically acceptable form thereof. In some embodiments, the methods comprise administering to the subject a therapeutically effective amount of the KRAS inhibitor. In some embodiments, the administering comprises administering to the subject a pharmaceutical composition comprising the FTI such as Compound (I) or a pharmaceutically acceptable form thereof, or a KRAS inhibitor, or a combination thereof, and a pharmaceutically acceptable

excipient.

[00102] In another aspect is a method of delaying emergence of resistance to a KRAS inhibitor in a *KRAS*-dependent cancer in a subject, or overcoming resistance to a KRAS inhibitor in a *KRAS*-dependent cancer in a subject previously treated with a KRAS inhibitor, comprising administering to the subject (a) an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, optionally in combination with (b) a KRAS inhibitor. In some embodiments, the subject was previously treated with the same or a different KRAS inhibitor, and may be relapsed or refractory to such treatment. In some embodiments, the subject was not previously treated with a KRAS inhibitor.

[00103] In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is an advanced solid tumor. In some embodiments, the cancer is an adenocarcinoma. In some embodiments, the cancer is lung cancer, pancreatic cancer, gynecologic cancer, gastrointestinal cancer, breast cancer, neoplasm (metastatic neoplasm, germ cell cancer, plasma cell neoplasm, or myelodysplastic/myeloproliferative neoplasm), carcinoma of unknown primary (CUP), or leukemia. In some embodiments, the cancer is leukemia or acute leukemia. In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC), non-squamous NSCLC, squamous NSCLC, or lung adenocarcinoma. In some embodiments, the gastrointestinal cancer is colorectal cancer (CRC), colon cancer, pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), biliary tract cancer, appendiceal cancer, small bowel cancer, stomach cancer, cholangiocarcinoma, ampullary cancer, gallbladder cancer, gastric cancer, gastric adenocarcinoma, esophageal cancer, esophageal adenocarcinoma, urinary tract cancer, GI-neuroendocrine tumor, or gastroesophageal junction adenocarcinoma. In some embodiments, the gynecological cancer is ovarian cancer, endometrial cancer, peritoneal cancer, or cervical cancer. In some embodiments, the cancer is non-small lung cancer, colorectal cancer, or pancreatic ductal adenocarcinoma.

[00104] In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12C mutation and is NSCLC, lung adenocarcinoma, non-squamous NSCLC, squamous NSCLC, CRC, pancreatic cancer, PDAC, CUP, endometrial cancer, ovarian cancer, cervical cancer, gastric cancer, gastric adenocarcinoma, cholangiocarcinoma, esophageal cancer, stomach cancer, small bowel cancer, appendiceal cancer, biliary tract cancer (BTC), ampullary cancer, gallbladder cancer, breast cancer, or metastatic neoplasm. In some embodiments, the *KRAS*-

dependent cancer comprises a *KRAS* G12C mutation and is NSCLC, CRC, or PDAC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12C mutation and is NSCLC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12C mutation and is CRC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12C mutation and is PDAC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12C mutation and is an advanced solid tumor.

[00105] In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12D mutation and is pancreatic cancer, PDAC, CRC, NSCLC, non-squamous NSCLC, CUP, endometrial cancer, ovarian cancer, small bowel adenocarcinoma, appendiceal adenocarcinoma, gastric cancer, gastric adenocarcinoma, or cholangiocarcinoma. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12D mutation and is pancreatic cancer, PDAC, CRC, NSCLC, gastric cancer, gastric adenocarcinoma, or cholangiocarcinoma. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12D mutation and is pancreatic cancer, PDAC, CRC, or NSCLC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12D mutation and is PDAC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12D mutation and is CRC. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12D mutation and is NSCLC.

[00106] In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12V mutation and is CRC, NSCLC, non-squamous NSCLC, PDAC, CUP, endometrial cancer, ovarian cancer, cholangiocarcinoma, small bowel adenocarcinoma, appendiceal adenocarcinoma, gastrointestinal cancer, esophageal cancer, and stomach cancer. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12V mutation and is CRC, NSCLC, or PDAC.

[00107] In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12R mutation and is pancreatic cancer, PDAC, or CUP. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12R mutation and is cholangiocarcinoma. In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G12R mutation and is pancreatic cancer or PDAC.

[00108] In some embodiments, the *KRAS*-dependent cancer comprises a *KRAS* G13D mutation and is CRC, non-squamous NSCLC, or endometrial cancer.

[00109] In some embodiments, the *KRAS*-dependent cancer comprises more than one *KRAS* mutation and is NSCLC, CRC, pancreatic cancer, PDAC, or cholangiocarcinoma.

[00110] *KRAS* mutations account for the vast majority of RAS alterations in PDAC, CRC,

NSCLC, and lung adenocarcinoma. In some embodiments, the *KRAS*-dependent cancer is PDAC, CRC, NSCLC, or lung adenocarcinoma. In some embodiments, the *KRAS*-dependent cancer is PDAC. In some embodiments, the *KRAS*-dependent cancer is CRC. In some embodiments, the *KRAS*-dependent cancer is NSCLC. In some embodiments, the *KRAS*-dependent cancer is lung adenocarcinoma.

[00111] In some embodiments, the *KRAS*-dependent cancer is *KRAS*-amplified. In some embodiments, the *KRAS*-dependent cancer is germ cell tumors, esophageal adenocarcinoma, gastric adenocarcinoma, gall bladder cancer, ovarian cancer, peritoneal cancer, gastric cancer, or squamous NSCLC.

[00112] In some embodiments, the cancer may be diagnosed by one skilled in the art, for example, by analysis of plasma or a tissue biopsy, such as a tumor tissue biopsy, from the subject. In some embodiments, the cancer is in remission. In some embodiments, the cancer is early stage, advanced, locally advanced, relapsed, metastatic, refractory, recurrent, or a combination thereof. In some embodiments, the cancer is locally advanced or metastatic. In some embodiments, the cancer is early stage. In some embodiments, the cancer is metastatic or locally advanced. In some embodiments, the cancer is relapsed. In some embodiments, the cancer is refractory. In some embodiments, the cancer is metastatic.

[00113] In some embodiments, the cancer has been previously treated with first-line therapy, for example, surgery, systemic therapy (e.g., chemotherapy, immunotherapy), or radiation, or a combination. In some embodiments, the cancer has been previously treated with a systemic therapy (e.g., chemotherapy or immunotherapy or other systemic therapy). Chemotherapy may include treatment with cisplatin or carboplatin, optionally in combination with paclitaxel, docetaxel, gemcitabine, etoposide, or pemetrexed. Immunotherapy may include treatment with a PD-1/PD-L1 inhibitor (such as nivolumab, pembrolizumab, cemiplimab, atezolizumab, or durvalumab) or a CTLA-4 inhibitor (such as ipilimumab or tremelimumab). In some embodiments, the cancer has been previously treated with second-line therapy, such as chemotherapy, immunotherapy, or radiation, or a combination. In some embodiments, the cancer has been previously treated with immunotherapy or an inhibitor of the EGFR signaling pathway, such as an anti-EGFR monoclonal antibody, such as cetuximab. In some embodiments, the cancer is resistant to, refractory to, or relapsed after treatment with immunotherapy or an inhibitor of the EGFR signaling pathway, such as an anti-EGFR

monoclonal antibody, such as cetuximab. In some embodiments, the cancer has been previously treated with a KRAS inhibitor. In some embodiments, the prior systemic therapy is a KRAS inhibitor, which may be the same as or different from the KRAS inhibitor to be administered with the FTI. In some embodiments, the subject relapsed following treatment with the prior KRAS inhibitor. In some embodiments, the subject was refractory to the prior KRAS inhibitor. In some embodiments, the prior KRAS inhibitor was adagrasib, and the KRAS inhibitor for administration with the FTI is adagrasib. In some embodiments, the prior KRAS inhibitor was sotorasib. In some embodiments, the cancer has been previously treated with localized or loco-regional disease therapies, such as surgery, radiation, chemoradiation, or induction chemotherapy, or combinations thereof. In some embodiments, the subject has received at least one prior treatment for the cancer, optionally wherein the at least one prior treatment has failed to treat the cancer, has failed to delay, halt, or prevent progression of the cancer, or has failed to mitigate or reduce the severity of at least one symptom associated with the cancer. In some embodiments, the at least one prior treatment is a first-line therapy or is second-line therapy.

[00114] In some embodiments, the combination therapy methods disclosed herein provide a synergistic or therapeutic benefit to the subject, for example, such as by improving efficacy, suppressing tumor growth, or inducing tumor regression, better than either compound therapy alone. In some embodiments, the methods provided herein improve efficacy, suppress tumor growth, or induce tumor regression, better than the sum of the results for each single compound therapy. In some embodiments, the methods provided herein delay, halt, or prevent progression of cancer or tumor growth. In some embodiments, the methods provided herein reduce tumor size or growth rate, delay the appearance of primary or secondary tumors, slow the development of primary or secondary tumors, decrease the occurrence of primary or secondary tumors, or arrest tumor growth. In some embodiments, the methods provided herein relieve tumor-related symptoms. In some embodiments, the methods provided herein slow or decrease the severity of secondary effects associated with the cancer. In some embodiments, the methods provided herein increase Time to Progression (TTP), Progression Free Survival (PFS), Event-free survival (EFS), Overall Survival (OS), overall response rate (ORR), duration of response (DoR), disease control rate (DCR; complete response (CR) plus partial response (PR) plus stable disease (SD)), rate of CR, or rate of SD, or decrease time to response (TTR), better than no therapy or either compound therapy alone. In some embodiments, the methods provided herein increase TTP,

PFS, EFS, OS, ORR, DoR, DCR, rate of CR, or rate of SD, or decrease TTR, better than first-line therapy, second-line therapy, chemotherapy, localized or loco-regional disease therapies, supportive care, or no treatment.

[00115] In some embodiments, the methods provided herein mitigate KRAS inhibitor resistance. In some embodiments, the mitigating comprises preventing development or emergence of resistance, slowing progression of resistance, increasing the time to emergence of resistance, or overcoming resistance. In some embodiments, the methods provided herein reduce the risk of relapse, e.g., delay relapse to KRAS inhibitor therapy. In some embodiments, the cancer has been treated previously with a KRAS inhibitor and is either refractory to and or relapsed to such therapy; in such cases, the methods mitigate resistance to the KRAS inhibitor and include treatment with the FTI and either the same or a different KRAS inhibitor than the prior therapy. In some embodiments, the cancer has been treated previously with two different KRAS inhibitors and is refractory or relapsed following such treatments.

[00116] In some embodiments, the therapeutically effective amount of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, and/or the KRAS inhibitor, can depend on absorption, tissue distribution, metabolism, and excretion rates of the active compound, the dosage schedule, the amount administered, and the particular formulation, as well as other factors known to those of skill in the art. The therapeutically effective amount may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans.

6.3.2 DOSES AND REGIMENS

[00117] In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered before, after, or simultaneously with the KRAS inhibitor, optionally during one or more treatment cycles, such as one or more 28-day cycles. In some embodiments, the administration of the two agents is concurrent or sequential, and independently continuous, intermittent, or in cycles.

[00118] In some embodiments, the methods provided herein comprise administering to the subject an FTI such as Compound (I), or a pharmaceutically acceptable form thereof (or a pharmaceutical composition comprising the same. In some embodiments, the combination methods provided herein comprise administering to the subject (a) an FTI such as Compound (I), or a pharmaceutically acceptable form thereof, and (b) a KRAS inhibitor. In some embodiments,

the methods provided herein comprise administering to the subject a daily dose of one or both agents. The daily dose of each agent may be administered using one dosage form or multiple dosage forms, e.g., one, two, or three tablets or capsules. The multiple dosage forms may contain the same or different amounts of active ingredients but the sum of the amounts is the desired daily dose for that active ingredient.

[00119] In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject according to the methods provided herein at a daily dose of about 0.1-2400 mg per day (free base equivalent). In some embodiments, the daily dose of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is selected from about 0.1-2.5 mg, 0.5-5 mg, 0.5-10 mg, 0.5-25 mg, 0.5-50 mg, 0.5-75 mg, 0.5-100 mg, 0.5-300 mg, 0.5-600 mg, 0.5-1200 mg, 1-5 mg, 1-10 mg, 1-25 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-300 mg, 1-600 mg, 1-1200 mg, 1-2400 mg, 20-100 mg, 40-75 mg, 50-75 mg, 50-100 mg, 50-150 mg, 75-100 mg, 100-200 mg, 125-200 mg, 150-300 mg, 200-250 mg, 200-400 mg, 300-600 mg, 250-500 mg, 400-600 mg, 500-750 mg, 600-900 mg, 700-100 mg, 650-1000 mg, 800-1200 mg, 900-1500 mg, 1000-1600 mg, 1000-2000 mg, 1200-1600 mg, 1500-2000 mg, 1500-2400 mg, 1800-2400 mg and 2000-2400 mg per day (free base equivalent). In some embodiments, the daily dose of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is about 0.5 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, and about 2400 mg

per day (free base equivalent). In some embodiments, the daily dose is administered across 1, 2, 3, or 4 doses per day, for example, is administered once or twice per day, such as once per day. For example, for twice daily dosing, the daily dose is split into two equal or unequal doses that are administered to the subject during a day, such as once in the morning and once in the evening.

[00120] In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject according to the methods provided herein at a daily dose of about 0.01-50 mg/kg body weight per day (free base equivalent). In some embodiments, the dose of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is selected from about 0.01-1 mg/kg, 0.01-2.5 mg/kg, 0.01-5 mg/kg, 0.1-5 mg/kg, 0.1-10 mg/kg, 0.1-20 mg/kg, 1-30 mg/kg, 1-40 mg/kg, 5-50 mg/kg, 10-50 mg/kg, 15-50 mg/kg, 20-50 mg/kg, 25-50 mg/kg, 30-50 mg/kg, 40-50 mg/kg, 20-40 mg/kg, and 20-25 mg/kg body weight per day (free base equivalent). In some embodiments, the daily dose is split into two doses that are administered to the subject according to the methods provided herein. In some embodiments, the daily dose is administered across 1, 2, 3, or 4 times per day, for example, is administered once or twice per day, such as once per day. For example, for twice daily dosing, the daily dose is split into two equal or unequal doses that are administered to the subject during a day, such as once in the morning and once in the evening.

[00121] In some embodiments, the dose of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject monthly, weekly, or daily, according to the methods provided herein. In some embodiments, the daily dose of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject for one or more cycles, for example, once or twice per day for one or more cycles, such as once per day for one or more cycles. In some embodiments, the daily dose of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject across 1, 2, 3 or 4 times per day continuously for unlimited days or until remission achieved in said subject, or until relapse occurs. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject QD for one or more cycles, such as QD for two or more cycles, QD for three or more cycles, or QD for four or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject BID for one or more cycles, such as BID for two or

more cycles, BID for three or more cycles, or BID for four or more cycles. In some embodiments, the cycle (sometimes referred to herein as a treating cycle or maintenance cycle) is 1 day, 7 days, 14 days, 21 days, or 28 days. In some embodiments, the treating cycle is a 28-day cycle. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject QD for one or more 28-day cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject BID for one or more 28-day cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable salt thereof, is administered to the subject once or twice per day every other week during a 28-day cycle, with alternating weeks of rest.

[00122] In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject 1, 2, 3 or 4 times per day on days 1-7, days 1-7 and 15-21, days 1-14, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one or more cycles, according to the methods provided herein. For example, in some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-7, days 1-7 and 15-21, days 1-14, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one or more cycles. For example, in some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7, days 1-7 and 15-21, days 1-14, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject on QD on days 1-7 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-7 and 15-21 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-7 and 15-21 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-14 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-14 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as

Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on days 1-21 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on days 1-21 of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD on each day (*i.e.*, days 1-28) of a 28-day cycle, for one or more cycles. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject BID on each day (*i.e.*, days 1-28) of a 28-day cycle, for one or more cycles.

[00123] In some embodiments, the KRAS inhibitor is administered to the subject at a daily dose of 10-2000 mg per day. In some embodiments, the daily dose of the KRAS inhibitor administered to the subject is selected from about 10-300 mg, about 50-400 mg, about 200-400 mg, about 500-1500 mg, about 800-1200 mg, or about 1100-1500 mg per day. In some embodiments, the daily dose of the KRAS inhibitor is administered to the subject across 1, 2, 3 or 4 times per day, for example, is administered once or twice per day, such as once per day. In some embodiments, the KRAS inhibitor is adagrasib and is administered at a daily dose of about 1200 mg, optionally wherein about 600 mg is administered twice daily. In some embodiments, the KRAS inhibitor is adagrasib and is administered at a daily dose of about 800 mg, optionally wherein about 400 mg is administered twice daily. In some embodiments, the KRAS inhibitor is sotorasib, and is administered at a daily dose of about 960 mg, optionally administered once daily. In some embodiments, the adagrasib is administered in 200 mg tablets, *e.g.*, three 200 mg tablets administered twice daily. In some embodiments, the sotorasib is administered in 120 mg or 320 mg tablets, for example three 320 mg tablets or 8 120 mg tablets.

[00124] In some embodiments, the daily dose of the KRAS inhibitor is administered to the subject daily for one or more cycles according to the methods provided herein. In some embodiments, the daily dose of the KRAS inhibitor is split into two doses that are administered to the subject according to the methods provided herein. In some embodiments, the daily dose of the KRAS inhibitor is administered across 1, 2, 3 or 4 times per day for one or more cycles, for example, is administered once or twice per day for one or more cycles, such as once per day for one or more cycles. In some embodiments, the KRAS inhibitor is administered to the subject 1, 2, 3 or 4 times per day continuously for unlimited days or until remission achieved in said subject. In some embodiments, the KRAS inhibitor is administered to the subject once per day

(QD) for one or more cycles, such as QD for two or more cycles, QD for three or more cycles, or QD for four or more cycles. In some embodiments, the KRAS inhibitor is administered to the subject twice per day (BID) for one or more cycles, such as BID for two or more cycles, BID for three or more cycles, or BID for four or more cycles. In some embodiments, the cycle (*e.g.*, a treating cycle or maintenance cycle) is 1 day, 7 days, 14 days, 21 days, or 28 days. In some embodiments, the treating cycle is a 28-day cycle. In some embodiments, the KRAS inhibitor is administered to the subject once per day for one or more 28-day cycles. In some embodiments, the KRAS inhibitor is administered to the subject twice per day for one or more 28-day cycles.

[00125] In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, and the KRAS inhibitor are administered to the subject concurrently or sequentially. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject before the administration of the KRAS inhibitor. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject after the administration of the KRAS inhibitor. In some embodiments, the FTI such as Compound (I), or pharmaceutically acceptable form thereof, is administered to the subject QD or BID on days 1-7, days 1-7 and 15-21, days 1-14, days 1-21, or each day, of a 28-day treatment cycle, and the KRAS inhibitor is administered QD or BID each day of the 28-day treatment cycle.

[00126] In some embodiments, the cancer was treated with a prior KRAS inhibitor and is refractory to or relapsed following such treatment, and the subject ceased therapy with such agent for at least two weeks, at least three weeks, at least four weeks, at least one month, at least two months, at least three months, or at least six months, prior to initiating treatment according to a method described herein. In some embodiments, the prior KRAS inhibitor is sotorasib. In some embodiments, the prior KRAS inhibitor is adagrasib.

[00127] In some embodiments, the combination of the FTI such as Compound (I), or pharmaceutically acceptable form thereof, and the KRAS inhibitor is administered further in combination with an additional anticancer agent. In some embodiments, the additional anticancer agent is selected from an immunotherapy agent, an anti-EGFR monoclonal antibody, an inhibitor of the EGFR signaling pathway, cetuximab, panitumumab, chemotherapy, a platinum-based anticancer agent (*e.g.*, cisplatin or carboplatin), leucovorin, fluorouracil, a topoisomerase inhibitor (*e.g.*, irinotecan or topotecan), a taxane (*e.g.*, paclitaxel, docetaxel, or

nab-paclitaxel), gemcitabine, etoposide, pemetrexed, vinorelbine, a VEGF inhibitor (e.g., bevacizumab or ramucirumab), an EGFR inhibitor (e.g., osimertinib, afatinib, erlotinib, dacomitinib, gefitinib, panitumumab, cetuximab, or amivantamab), an ALK inhibitor (e.g., alectinib, brigatinib, lorlatinib, ceritinib, or crizotinib), a ROS1 inhibitor, a BRAF inhibitor (e.g., dabrafenib, trametinib, or vemurafenib), a SHP2 inhibitor (e.g., TNO155, JAB-3312), a SOS1 inhibitor, and radiation, and combinations thereof.

7. EXAMPLES

Methods:

3D Spheroid Growth Assays

[00128] Cells were seeded in 96-well ultralow attachment plates at a density of 2,000 cells/well. Cells were centrifuged at 1000 rpm for 2 min to form spheroids. The following day, spheroids were treated with adagrasib and tipifarnib or Compound (I). Baseline growth was measured using 3D Cell Titer Glo (CTG) reagent (Promega). Spheroids were incubated with drugs for 7 days and a final CTG reading was taken to assess spheroid growth.

Dox-Inducible Lentiviral System

[00129] Cells were transduced with shScramble (shControl), shRHEB#1, and shRHEB#2 lentiviruses (Transomic) and selected with 2 µg/mL puromycin for 5 days. Stable cell lines were pretreated with 1 µg/mL doxycycline for 72 h. Cells were seeded in 96-well ultralow attachment plates at a density of 2,000 cells/well. Cells were centrifuged at 1000 rpm for 2 min to form spheroids. The following day, spheroids were treated with adagrasib. Spheroids were treated with doxycycline every 3 days. 3D CTG readings were taken on Days 0, 3, 5, 7, and 10 to assess spheroid growth.

Transfection of siRNA

[00130] NCI-H2122 cells (500,000) were seeded on 60 mm dishes and transfected with Dharmacon ON-TARGETplus siRNA SMARTPool against RHEB (Horizon Discovery) using Lipofectamine RNAiMAX (ThermoFisher). Cells were incubated for 72 hours prior to collection for immunoblotting to allow for depletion of *RHEB* expression.

Immunoblotting

[00131] For immunoblotting of cell lines grown in 2D, 2 million cells were plated onto 10 cm dishes. For 3D immunoblotting, 10,000 cells were plated onto 96-well ultralow attachment plates and cells were centrifuged at 1000 rpm for 2 min to form spheroids. 24 spheroids were pooled together for one sample. Cell lysates were prepared on ice by washing cells once with PBS, resuspending in 1X cell lysis buffer (Cell Signaling Technology #9803) or RIPA buffer supplemented with Halt protease inhibitor cocktail (Thermo Scientific #78430) and briefly sonicating or vortexing. Tumor lysates were prepared by adding tumor fragments to hard tissue homogenizing tubes (2 mL reinforced polypropylene tubes) containing RIPA buffer and five 2.8 mm ceramic beads (Fisher Scientific). Tumors were then homogenized for 30s at 4.5 m/s using a bead mill. Lysates were cleared by centrifugation (maximum speed, 10 min) and protein concentration was determined by BCA assay (Pierce). 20-60 µg of lysate was loaded on to 4-12% Bis-Tris gels (NuPAGE, Invitrogen) for electrophoresis and immunoblotting.

Xenograft Models

[00132] The following human patient-derived xenograft (PDX) models were used for these studies: non-small cell lung cancer KRAS G12C model LU2512, pancreatic cancer KRAS G12C model PA1383, colorectal cancer KRAS G12C model CR6256, colorectal cancer KRAS G12C model CR6243, colorectal cancer KRAS G12D model CR3262, colorectal cancer KRAS G12D model CR1245, pancreatic cancer KRAS G12D model PA0787 (Crown Bioscience, Beijing), and pancreatic cancer KRAS G12V model PA-07-0041 (WuXi, Shanghai) in female BALB/c nude mice.

[00133] The following cell-derived xenograft (CDX) models were used for these studies: NCI-H2122 (BALB/c nude), NCI-H2030 (NOD/SCID), and NCI-H358 (NOD/SCID) KRAS G12C human non-small cell lung cancer, and MIA PaCa-2 (BALB/c nude) KRAS G12C human pancreatic cancer, SW1990 (NOD/SCID) KRAS G12D human pancreatic cancer, and SW837 (NOD/SCID) KRAS G12C human colorectal cancer (Crown Bioscience, Beijing); and NCI-H2030 (BALB/c nude) KRAS G12C human non-small cell lung cancer, GP2D (BALB/c nude) KRAS G12D human colorectal cancer, and Capan-1 KRAS G12V human pancreatic cancer (WuXi, Shanghai).

[00134] For PDX models: Tumor fragments from stock mice were harvested and used for inoculation into mice. Each mouse was inoculated subcutaneously in the right upper flank with

primary human tumor xenograft model tumor fragment (2-3 mm in diameter) for tumor development. Randomization started when the mean tumor size reached approximately 300-400 mm³. The treatment period was performed for 4-8 weeks.

[00135] For NCI-H2122, NCI-H2030, and NCI-H358 CDX models: Tumor cells were maintained *in vitro* with RPMI-1640 supplemented with 10% fetal bovine serum at 37 °C in an atmosphere of 5% CO₂ in 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 upper flank region with 1×10⁷ in 0.1 mL of PBS (NCI-H2122), 1-2×10⁷ in 0.2-0.25 mL of PBS (NCI-H2030), or 5×10⁶ in 0.1 mL of PBS (NCI-H358) tumor cells per mouse mixed with Matrigel (1:1) for tumor development. Randomization started when the mean tumor size reached approximately 300-400 mm³ (NCI-2122 and NCI-H358) or 300-500 mm³ (NCI-H2030).

[00136] For GP2D, MIA PaCa-2, SW1990, and SW837 CDX models: Tumor cells were maintained *in vitro* with DMEM (GP2D and MIA PaCa-2) or L-15 (SW1990 and SW837) supplemented with 10% fetal bovine serum at 37 °C in an atmosphere of 5% CO₂ in air (GP2D, MIA PaCa-2, and SW837) or 100% air (SW1990). The cells in exponential growth phase were harvested and quantitated by cell counter before tumor inoculation. Unless otherwise specified, each mouse was inoculated subcutaneously in the right upper flank region with 5×10⁶ in 0.1 mL of PBS (MIA PaCa-2 and SW837) tumor cells per mouse mixed with Matrigel (1:1) for tumor development. Randomization started when the mean tumor size reached approximately 400-500 mm³ (MIA PaCa-2) or 300-400 mm³ (SW837, SW1990, and GP2D).

[00137] Randomization was performed based on “Matched distribution” method (StudyDirector™ software, version 3.1.399.19). The date of randomization was denoted as Day 0. The treatment was initiated on the same day of randomization (Day 0) as per the study design. After tumor inoculation, the animals were checked daily for morbidity and mortality. During routine monitoring, the animals were checked for any effects of tumor growth and treatments on behavior such as mobility, food and water consumption, body weight gain/loss (body weights would be measured three times/daily per week after randomization), eye/hair matting and any other abnormalities. Mortality and observed clinical signs were recorded for individual animals in detail. Tumor volumes were measured three times per week after randomization in two dimensions using a caliper, and the volume was expressed in mm³ using the formula: V = (L x W

$\times W)/2$, where V is tumor volume, L is tumor length (the longest tumor dimension), and W is 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 Study Director TM software (version 3.1.399.19). Tumor samples were collected for all groups 2 hours post the last dose. Each tumor was split into 2 pieces; half was snap frozen for protein and the other half fixed for histological studies.

In Vivo Drug Treatments

[00138] NCI-H2122, LU2512, and CR6256 xenografts were treated orally with: control vehicle, QD; tipifarnib, 60 mg/kg (aqueous suspension), BID; Compound (I), 15 mg/kg (aqueous suspension), BID; adagrasib, 100 mg/kg (suspension in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; sotorasib, 100 mg/kg (suspension in 2% HPMC and 1% Tween 80), QD; tipifarnib, 60 mg/kg, BID, plus adagrasib, 100 mg/kg, QD; tipifarnib, 60 mg/kg, BID, plus sotorasib, 100 mg/kg, QD; or Compound (I), 15 mg/kg, BID, plus adagrasib, 100 mg/kg, QD.

[00139] NCI-H2030, PA1383, and CR6243 xenografts were treated orally with: control vehicle, BID; Compound (I), 10 mg/kg (aqueous suspension), BID; adagrasib, 100 mg/kg (suspension in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; or Compound (I), 10 mg/kg, BID plus adagrasib, 100 mg/kg, QD.

[00140] MIA PaCa-2 and SW837 xenografts were treated orally with: control vehicle, BID; Compound (I), 20 mg/kg (aqueous suspension), BID; adagrasib, 100 mg/kg (suspension in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; or Compound (I), 20 mg/kg, BID plus adagrasib, 100 mg/kg, QD.

[00141] NCI-H358 xenografts were treated orally with: control vehicle (10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; tipifarnib, 60 mg/kg (aqueous suspension), BID; adagrasib, 100 mg/kg (suspension in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; adagrasib, 20 mg/kg (suspension in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; sotorasib, 30 mg/kg (suspension in 2% HPMC and 1% Tween 80), QD; sotorasib, 10 mg/kg (suspension in 2% HPMC and 1% Tween 80), QD; tipifarnib, 60 mg/kg, BID plus adagrasib, 100 mg/kg, QD; tipifarnib, 60 mg/kg, BID plus adagrasib, 20 mg/kg, QD; tipifarnib, 60 mg/kg, BID plus sotorasib, 30 mg/kg, QD; or tipifarnib, 60 mg/kg, BID plus sotorasib, 10 mg/kg, QD.

[00142] NCI-H2030 xenografts (WuXi) were treated orally with: control vehicle, BID; tipifarnib, 60 mg/kg (aqueous suspension), BID; Compound (I), 15 mg/kg (aqueous suspension), BID; adagrasib, 30 mg/kg (suspension in 5% DMSO + 40% PEG-400), QD; adagrasib, 100 mg/kg (suspension in 5% DMSO + 40% PEG-400), QD; sotorasib, 100 mg/kg (suspension in 5% DMSO + 40% PEG-400), QD; tipifarnib, 60 mg/kg, BID plus adagrasib, 30 mg/kg, QD; tipifarnib, 60 mg/kg, BID, plus adagrasib, 100 mg/kg, QD; tipifarnib, 60 mg/kg, BID, plus sotorasib, 100 mg/kg, QD; Compound (I), 15 mg/kg, BID plus adagrasib, 30 mg/kg, QD; or Compound (I), 15 mg/kg, BID, plus adagrasib, 100 mg/kg, QD.

[00143] PA0787 and CR3262 xenografts were treated with: control vehicle, PO, BID; tipifarnib, 80 mg/kg (aqueous suspension), PO, BID; Compound (I), 20 mg/kg (aqueous suspension), PO, BID; MRTX1133, 30 mg/kg (aqueous suspension), IP, BID; tipifarnib, 80 mg/kg, PO, BID, plus MRTX1133, 30 mg/kg, IP, BID; or Compound (I), 20 mg/kg, PO, BID, plus MRTX1133, 30 mg/kg, IP, BID.

[00144] CR1245 xenografts were treated on study days 0-14 with: control vehicle, PO, BID; Compound (I), 10 mg/kg (aqueous suspension), PO, BID; MRTX1133, 10 mg/kg (suspension in 10% Captisol, 50 mM citrate buffer, pH 5.0), IP, BID; or Compound (I), 10 mg/kg, PO, BID plus MRTX-1133, 10 mg/kg, IP, BID. On study days 14-28, CR1245 xenografts were treated with: control vehicle, PO, BID; Compound (I), 20 mg/kg (aqueous suspension), PO, BID; MRTX1133, 30 mg/kg (suspension in 10% Captisol, 50 mM citrate buffer, pH 5.0), IP, BID; or Compound (I), 20 mg/kg, PO, BID plus MRTX-1133, 30 mg/kg, IP, BID.

[00145] SW1990 xenografts were treated with: control vehicle, PO, BID; Compound (I), 20 mg/kg (aqueous suspension), PO, BID; MRTX1133, 10 mg/kg (suspension in 10% Captisol, 50 mM citrate buffer, pH 5.0), IP, BID; or Compound (I), 20 mg/kg, PO, BID plus MRTX-1133, 10 mg/kg, IP, BID.

[00146] In a first GP2D model experiment, GP2D xenografts (WuXi) were treated with: control vehicle, PO, BID; Compound (I), 20 mg/kg (aqueous suspension), PO, BID; MRTX1133, 20 mg/kg (suspension in 10% Captisol, 50 mM citrate buffer, pH 5.0), IP, BID; cetuximab, 0.25 mg/dose (saline) IP, Q3D; Compound (I), 20 mg/kg, PO, BID plus MRTX1133, 20 mg/kg, IP, BID; or cetuximab, 0.25 mg/dose (saline) IP, every 3 days (Q3D) plus MRTX1133, 20 mg/kg, IP, BID.

[00147] In a second GP2D model experiment, female, 6- to 8-week-old BALB/c nude mice

(GemPharmatech) were inoculated subcutaneously at the right flank with 10×10^6 cells for tumor development. The animals were randomized into 11 treatment groups of 8 animals each when the average tumor size reached approximately 300 mm^3 . GP2D tumors were treated with: control vehicle (10% HP- β -CD and 0.1% Tween 80), PO, BID; Compound (I), 10 mg/kg (aqueous suspension), PO, BID; MRTX1133, 10 mg/kg (suspension in 10% Captisol, 50 mM citrate buffer, pH 5.0), IP, BID; RMC-6236, 10 mg/kg or 25 mg/kg (suspension in 10% Captisol, 50 mM citrate buffer, pH 5.0), PO, QD; cetuximab, 0.25 mg/dose (saline) IP, Q3D; Compound (I), 10 mg/kg, plus MRTX1133, 10 mg/kg; Compound (I), 10 mg/kg, plus RMC-6236, 10 mg/kg; Compound (I), 10 mg/kg, plus RMC-6236, 25 mg/kg; cetuximab, 0.25 mg/dose, plus MRTX1133, 10 mg/kg; or Compound (I), 10 mg/kg, plus cetuximab, 0.25 mg/dose, plus MRTX1133, 10 mg/kg.

[00148] Head-to-head comparisons of various combinations with adagrasib: NCI-H2122 *KRAS*^{G12C} NSCLC xenografts were treated orally with: control vehicle (10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; Compound (I), 10 or 20 mg/kg (aqueous suspension), BID; adagrasib, 100 mg/kg (in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; Compound (I), 10 or 20 mg/kg, BID, plus adagrasib, 100 mg/kg, QD; RMC-4550 (SHP2 inhibitor), 30 mg/kg (in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; Compound (I), 10 or 20 mg/kg, BID, plus RMC-4550, 30 mg/kg, QD; BI-3406 (SOS1 inhibitor), 50 mg/kg (in 0.5% HEC), BID; Compound (I), 10 or 20 mg/kg, BID, plus BI-3406, 50 mg/kg, BID; everolimus, 10 mg/kg (in 30% propylene glycol: 5% Tween 80: 65% ddH₂O), QD; Compound (I), 10 or 20 mg/kg, BID, plus everolimus, 10 mg/kg, QD; VT103 (TEAD1 inhibitor), 10 mg/kg (in 0.5% Natrosol(HEC)), QD; or Compound (I), 10 or 20 mg/kg, BID, plus VT103, 10 mg/kg, QD.

[00149] *In vivo* pretreatment studies: NCI-H2030 and NCI-H2122 *KRAS*^{G12C} NSCLC xenografts were treated orally with: control vehicle (10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; Compound (I), 10 mg/kg (aqueous suspension), BID; adagrasib, 60 or 100 mg/kg (in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; sotorasib, 100 mg/kg (in 2% HPMC and 1% Tween 80), QD; adagrasib, 60 or 100 mg/kg, QD plus Compound (I), 10 mg/kg, BID, added upfront or at a later timepoint during treatment; RMC-6236, 25 mg/kg (in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; or RMC-6236, 25 mg/kg, QD plus Compound (I), 10 mg/kg, BID added upfront or at a later timepoint

during treatment.

[00150] Dose scheduling study: NCI-H2122 *KRAS*^{G12C} NSCLC xenografts were treated orally with: control vehicle (10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD; adagrasib, 100 mg/kg (in 10% research grade Captisol in 50 mM citrate buffer, pH 5.0), QD every other week; adagrasib, 100 mg/kg, QD, plus Compound (I), 10 mg/kg (aqueous suspension), BID, both continuously; adagrasib, 100 mg/kg (continuous dosing), QD, plus Compound (I), 10 mg/kg, BID, every other week; adagrasib, 100 mg/kg, QD, plus Compound (I), 10 mg/kg, BID, both every other week (synchronous discontinuous dosing); or adagrasib, 100 mg/kg, QD, plus Compound (I), 10 mg/kg, BID, both every other week (nonsynchronous discontinuous dosing).

[00151] NCI-H2122 *KRAS*^{G12C} NSCLC xenografts were also treated orally with: control vehicle (0.5% methylcellulose), QD; Compound (I), 10 mg/kg (aqueous suspension), BID; divarasil, 25 or 100 mg/kg (in 0.5% methylcellulose), QD; or Compound (I), 10 mg/kg, BID, plus divarasil, 25 or 100 mg/kg, QD.

[00152] Capan-1 and PA-07-0041 xenografts were treated orally with: control vehicle (0.5% Natrosol/5% HP- β -CD), BID; Compound (I), 10 mg/kg (aqueous suspension), BID; BI-2493, 30 mg/kg (in 0.5% Natrosol/5% HP- β -CD), BID; or Compound (I), 10 mg/kg, BID, plus BI-2493, 30 mg/kg, BID.

Immunohistochemistry (IHC)

[00153] All immunostainings were performed at Histowiz, Inc., Brooklyn, New York, using the Leica Bond RX automated stainer (Leica Microsystems). The slides were dewaxed using xylene and alcohol based dewaxing solutions. Epitope retrieval was performed by heat-induced epitope retrieval (HIER) of the formalin-fixed, paraffin-embedded (FFPE) tissue using citrate-based pH 6 solution for 20 mins at 95 °C. The tissues were first incubated with peroxide block buffer (Leica Microsystems), followed by incubation with the primary antibodies Ki67 (ab15580), CC3 (CST9661), p-S6 (CST4858), and p-4EBP1 (CST2855) at 1:800, 1:300, 1:200, and 1:800 dilutions respectively for 30 mins, followed by DAB rabbit secondary reagents: polymer, DAB refine and hematoxylin (Leica Microsystems). The slides were dried, cover slipped and visualized using a Leica Aperio AT2 slide scanner (Leica Microsystems).

Results:

[00154] The combination of tipifarnib with adagrasib caused a decrease in spheroid viability in a dose-dependent manner in NCI-H2122 (**FIG. 1A**), NCI-1792 (**FIG. 1B**), and NCI-H358 (**FIG. 1C**) KRAS G12C NSCLC cell lines compared to A549 KRAS G12S (control) NSCLC cell line (**FIG. 1D**). The combination of Compound (I) with adagrasib caused a decrease in spheroid viability in a dose-dependent manner in a range of KRAS G12C NSCLC cell lines (Experiment 1: NCI-H2122, **FIG. 1E**; NCI-1792, **FIG. 1F**; NCI-H358, **FIG. 1G**; control A549, **FIG. 1H**; Experiment 2: NCI-H2122, **FIG. 1I**; NCI-2030, **FIG. 1J**; NCI-H1792, **FIG. 1K**; NCI-H23, **FIG. 1L**; control A549, **FIG. 1M**).

[00155] To assess potential mechanism of action of the effects of combination treatment of FTIs with KRAS G12C inhibitors, a doxycycline-inducible shRHEB system was used to knockdown RHEB expression in the NCI-H2122 KRAS G12C NSCLC cell line. Dox-inducible RHEB knockdown alone did not cause significant changes in spheroid growth, while adagrasib single agent treatment slowed down growth. In contrast, spheroid growth decreased in both RHEB-knockdown stable cell lines treated with adagrasib, suggesting that RHEB might be an important player in the inhibitory effects of FTIs when combined with a KRAS G12C inhibitor (**FIG. 2A**). As a control, spheroid growth in the A549 dox-inducible RHEB knockdown stable cell line did not have any significant effects with or without adagrasib treatment (**FIG. 2B**).

[00156] Important proteins involved in the mTOR and MAPK signaling pathways were assessed by 3D and 2D immunoblotting to further determine the mechanism of action of combination of FTIs with KRAS G12C inhibitors. In the NCI-H2122 KRAS G12C NSCLC cell line, both 3D and 2D signaling showed enhanced inhibition of HER3, p-S6 (S235/236), p-p90 RSK (S380), p-p70 S6K (T389), and p-Rb (S807/811) by 48 h of combination treatment with either Compound (I) and adagrasib (**FIGS. 3A, 3B**) or tipifarnib and sotorasib (**FIG. 3C**). Additionally, there was an enhanced increase in the apoptotic marker cleaved caspase 3 in both combination treatments compared to single agent treatments. In the NCI-H2030 KRAS G12C NSCLC cell line, combination treatment with tipifarnib and adagrasib caused an enhanced decrease in p-Rb (S807/811) and enhanced increase in cleaved PARP in comparison to single agent adagrasib (**FIG. 3D**). In the NCI-H1792 KRAS G12C NSCLC cell line, combination treatment with tipifarnib and sotorasib caused an enhanced decrease in p-S6 (S235/236), p-4EBP1 (S65), and p-Rb (S807/811) and an enhanced increase in cleaved PARP compared to

single agent sotorasib (**FIG. 3E**). These results suggest that combination of an FTI with a KRAS G12C inhibitor can potentially inhibit various nodes within the mTOR pathway that would otherwise undergo feedback reactivation by single agent KRAS G12C inhibitor treatment.

[00157] The signaling effects of adagrasib treatment in a shRHEB stable cell line with genetic depletion of RHEB (essentially serving as a mimic for FTI treatment) were compared to the effects observed with the combination of Compound (I) and adagrasib in the NCI-H2122 KRAS G12C NSCLC cell line (shown in **FIG. 3B**). First, RHEB expression was depleted in two samples of cells using a doxycycline-inducible shRNA system (**FIG. 3F**). In both dox-inducible shRHEB cell lines cultured as 3D tumor spheroids, by 48 h treatment with adagrasib, there was a decrease in HER3 levels, p-p70 S6K, p-S6, p-4EBP1, and p-Rb compared to the shScramble control cell line (**FIG. 3F**). NCI-H2122 cells cultured in 2D were also transfected with siRNAs against RHEB and exposed to adagrasib. Levels of p-70 S6K, S6 ribosomal protein, and 4EBP1 phosphorylation were decreased in the siRHEB-transfected cells following adagrasib exposure compared to cells transfected with a non-targeting control siRNA pool (**FIG. 3G**). These results suggest that inhibition of RHEB contributes to the decrease in mTOR signaling observed with combination of FTI and adagrasib.

[00158] For the combination treatment groups in KRAS G12C NSCLC models NCI-H2122 (CDX), LU2512 (PDX), and NCI-H2030 (CDX), tipifarnib in combination with adagrasib and sotorasib as well as Compound (I) in combination with adagrasib, were all able to produce significant anti-tumor efficacy with tumor growth inhibition (TGI) values of 88.62%, 85.01%, and 88.00% in the NCI-H2122 model (**Table 1**), 87.87%, 86.37%, and 87.92% in the LU2512 model (**Table 2**), and 117.21%, 116.61%, and 117.79% in the NCI-H2030 model (**Table 3**) ($P < 0.05$ vs. vehicle control), respectively.

Table 1. Anti-tumor Activity of Test Compounds in NCI-H2122 NSCLC Model

Group	Treatment	Tumor Volume on Day 27 (mm ³) (mean $\pm$ SEM)	T/C (%) on Day 27	TGI (%) on Day 27	<i>p</i> Value
1	Vehicle control	1559.54 $\pm$ 225.48	-	-	-
2	Tipifarnib, 60 mg/kg	1000.38 $\pm$ 77.44	64.15	35.85	0.238
3	Compound (I), 15 mg/kg	1062.47 $\pm$ 125.00	68.13	31.87	0.438
4	Adagrasib, 100mg/kg	600.26 $\pm$ 42.03	38.49	61.51	0.0002
5	Sotorasib, 100mg/kg	643.34 $\pm$ 58.23	41.25	58.75	0.0003
6	Tipifarnib, 60 mg/kg; Adagrasib, 100mg/kg	177.55 $\pm$ 32.31	11.38	88.62	<0.001
7	Tipifarnib, 60 mg/kg;	233.84 $\pm$ 7.03	14.99	85.01	<0.001

Group	Treatment	Tumor Volume on Day 27 (mm ³) (mean ± SEM)	T/C (%) on Day 27	TGI (%) on Day 27	p Value
	Sotorasib, 100mg/kg				
8	Compound (I), 15 mg/kg; Adagrasib, 100mg/kg	187.07±85.97	12.00	88.00	<0.001

Note: Bartlett's test was performed to test homogeneity of variance and normality, non-parametric test is run to compare groups. $P < 0.05$ vs. vehicle control is statistically significant. $TGI\% = (1 - Ti/Ci) \times 100$; $T/C\% = Ti/Ci \times 100$; Ti and Ci are the mean tumor volumes of the treatment and control groups, respectively, on a given day.

Table 2. Anti-tumor Activity of Test Compounds in LU2512 NSCLC Model

Group	Treatment	Tumor Volume on Day 25 (mm ³) (mean ± SEM)	T/C (%) on Day 25	TGI (%) on Day 25	p Value
1	Vehicle control	2449.42±303.02	-	-	-
2	Tipifarnib, 60 mg/kg	996.06±107.77	40.67	59.33	0.125
3	Compound (I), 15 mg/kg	1464.16±247.99	59.78	40.22	0.689
4	Adagrasib, 100mg/kg	1270.51±369.65	51.87	48.13	0.116
5	Sotorasib, 100mg/kg	758.41±306.19	30.96	69.04	0.0057
6	Tipifarnib, 60 mg/kg; Adagrasib, 100mg/kg	297.03±84.98	12.13	87.87	<0.001
7	Tipifarnib, 60 mg/kg; Sotorasib, 100mg/kg	333.81±118.97	13.63	86.37	<0.001
8	Compound (I), 15 mg/kg; Adagrasib, 100mg/kg	295.84±68.51	12.08	87.92	<0.001

Note: Bartlett's test was performed to test homogeneity of variance and normality, non-parametric test is run to compare groups. $P < 0.05$ vs. vehicle control is statistically significant.

Table 3. Anti-tumor Activity of Test Compounds in NCI-H2030 NSCLC Model

Group	Treatment	Tumor Volume on Day 24 (mm ³) (mean ± SEM)	T/C (%) on Day 24	TGI (%) on Day 24	p Value
1	Vehicle control	2050±166	-	-	-
2	Tipifarnib, 60 mg/kg	1266±93	61.75	45.36	0.0003
3	Compound (I), 15 mg/kg	1078±140	52.60	56.20	0.0002
4	Adagrasib, 100mg/kg	82±18	4.00	113.88	<0.001
5	Sotorasib, 100mg/kg	138±12	6.75	110.61	<0.001
6	Tipifarnib, 60 mg/kg; Adagrasib, 100mg/kg	24±3	1.15	117.21	<0.001
7	Tipifarnib, 60 mg/kg; Sotorasib, 100mg/kg	34±11	1.68	116.61	<0.001
8	Compound (I), 15 mg/kg; Adagrasib, 100mg/kg	14±2	0.70	117.79	<0.001

Note: One-tailed t-test was performed for p-values. $P < 0.05$ vs. vehicle control is statistically

significant.

[00159] All combination treatment groups showed tumor regressions, while all single agent treatment groups did not regress in both NCI-H2122 and LU2512 models (**FIGS. 4A-C** and **FIGS. 5A-C**). In the NCI-H2030 model, combination treatment groups had complete tumor regressions, while single agent adagrasib and sotorasib treatment groups began to relapse by Day 28 (**FIGS. 6A-C**). Additionally, in the NCI-H2030 model, a separate study was conducted to evaluate depth and durability of the combination of FTIs with the KRAS G12C inhibitor adagrasib. The combination treatment group showed deeper tumor regressions compared to single agent adagrasib treatment group (**FIG. 7A**). By Day 32, tumors in the adagrasib treatment group started to regrow, while the combination treatment group continued to regress. Even after treatment was stopped, combination-treated tumors continued to regress or stabilize until Day 46 (**FIG. 7B**). These results demonstrate that, in the NCI-H2030 model, the combination of FTI with adagrasib induces deep and durable anti-tumor responses compared to single agent treatment.

[00160] IHC on NCI-H2122 endpoint tumor samples showed an increase in the cell apoptosis marker cleaved caspase-3 (CC3) as well as decreases in both p-S6 (Ser235/236) and p-4EBP1 (Thr3746) signaling markers in the combination groups treated with tipifarnib and adagrasib (**FIG. 8A**) as well as Compound (I) and adagrasib (**FIG. 8B**). These results suggest mTOR pathway inhibition as a potential mechanism of action of combination of FTI with KRAS G12C inhibitor.

[00161] To study the mechanism of action of the FTI/KRAS G12C inhibitor combination in further detail, a pharmacodynamic study in the NCI-H2122 KRAS G12C NSCLC CDX model was conducted. Western blotting was used to assess important proteins involved in the mTOR and MAPK signaling pathways (**FIG. 9A**). The combination of FTI (Compound (I)) and KRAS G12C inhibitor (adagrasib) induced stronger inhibition of HER3 protein expression and phosphorylation of key MAPK signaling proteins (p90 RSK (S380) and S6 (S235/236)), and phosphorylation of mTOR substrates (S6 (S240/244) and 4EBP1 (S65 and T37/46)) relative to single agent exposure. Phosphorylation of Rb (S807/811), a marker of cell cycle arrest, was also reduced by the combination compared to single agents. IHC performed on the same tumor samples corroborated these findings (**FIGS. 9B** and **9C**). There was an overall trend of decrease in Ki67 (marker of proliferation) and increase in cleaved caspase 3 (CC3; marker of apoptosis) in

the combination treatment tumors compared to adagrasib single agent tumors as quantified by H-scores (superimposed on IHC images in **FIG. 9B**) or percent positive cells (**Table 4**). In addition, as shown in **FIG. 9B**, there were modest decreases in p-S6 and p-4EBP1 in the combination group compared to adagrasib single agent. There was an observable decrease in HER3 levels in the combination group compared to adagrasib single agent, while HER2 and EGFR levels seemed to be similar between combination and adagrasib single agent groups (**FIG. 9C**).

Table 4

% positive cells	Adagrasib	Combination
Ki67	59.3 ± 3.4	39.6 ± 9.7
Cleaved Caspase 3	2.2 ± 0.4	8.8 ± 2.1

[00162] Combinations of tipifarnib of Compound (I) with the KRAS G12D inhibitor, MRTX1133, were evaluated in models of KRAS G12D-mutant PDAC. For the combination treatment groups in KRAS G12D models PA0787 (PDX) (**FIG. 10A**) and SW1990 (CDX) (**FIG. 10B**), tipifarnib or Compound (I) in combination with MRTX1133 were able to delay tumor regrowth and enhanced inhibition of tumor growth over that observed with single agent MRTX1133 treatment. Specifically, in the PA0787 model, the combination of Compound (I) with MRTX1133 prevented tumor regrowth. *In vitro* signaling through immunoblotting was done to assess the mechanism of action of combination of FTI with KRAS G12D inhibitor. In the AsPC-1 KRAS G12D PDAC cell line, there was greater inhibition of HER3, p-ERK1/2 (T202/204), p-p90 RSK (S380), p-p70 S6K (T389), p-S6 (S235/236), p-S6 (S240/244), p-4EBP1 (S65), and p-Rb (S807/811) by 48 h of combination treatment with Compound (I) and MRTX1133 compared to MRTX1133 alone (**FIG. 11**). These results suggest that combination of an FTI with a KRAS G12D inhibitor can potentially inhibit various nodes within the mTOR pathway that would otherwise undergo feedback reactivation by single agent KRAS G12D inhibitor treatment.

[00163] The impact of combined FTI and MRTX1133 on tumor growth was also assessed in the KRAS G12D mutant CRC models. In the CR3262 PDX model, combined MRTX1133 and tipifarnib or Compound (I) slowed tumor growth compared to monotherapy (**FIG. 12A**). In the GP2D CDX model, in the first experiment, the combination of Compound (I) and MRTX1133 induced deeper tumor regressions than single agent exposure to either agent (**FIG. 12B**). The

combination of Compound (I) and MRTX1133 also better inhibited growth of CR1245 CRC PDX tumors compared to single agent treatment (**FIG. 12C**). Samples of GP2D CDX tumors treated with MRTX1133, Compound (I), or the combination were collected after 28 days treatment along with vehicle controls and lysed for immunoblot analysis. In combination treated tumors, phosphorylation of S6 and 4EBP1 was lower than in monotherapy-treated tumors, suggesting more potent mTOR inhibition (**FIG. 13**). Rb phosphorylation was lower in tumors treated with MRTX1133 and Compound (I), indicating diminished cell cycling/proliferation. For the second experiment, the anti-tumor efficacy of Compound (I) in combination with the pan-RAS inhibitor RMC-6236 or the KRAS^{G12D}-specific inhibitor MRTX1133 was evaluated in the KRAS^{G12D}-mutant colorectal cancer CDX model, GP2D. Compared to 10 mg/kg or 25 mg/kg RMC-6236 alone, the combination of RMC-6236 and Compound (I) resulted in greater inhibition of tumor growth (**Figure 12D**). The combination of 25 mg/kg RMC-6236 and 10 mg/kg Compound (I) induced tumor regressions. Response calls according to modified RECIST (mRECIST) criteria (BestResp and Best Avg Resp at t > 10 d; Gao et al. Nat. Med. 2015) indicated 88% stable disease (mSD) and 12% partial response (mPR) for RMC-6236, while the combination induced 88% mPR and 12% mSD. Treatment with single agent MRTX1133 only resulted in GP2D tumor stasis, while the combination of MRTX1133 with cetuximab or Compound (I) led to tumor regression (**Figure 12E**). The triplet of Compound (I) plus MRTX1133 plus cetuximab resulted in the deepest tumor regressions. Response calls were as shown in Table 5. The combination of Compound (I) and 20 mg/kg RMC-6236 also inhibited the growth of tumors in colorectal xenograft models CO-04-0002 (PDX), LoVo (CDX), and SW620 (CDX) to a greater degree than either agent alone.

Table 5.

Response	MRTX1133 n (%)	Compound (I) + MRTX1133 n (%)	MRTX1133 + cetuximab n (%)	Compound (I) + MRTX1133 + cetuximab n (%)
mPD	1 (12)	0 (0)	0 (0)	0 (0)
mSD	7 (88)	0 (0)	3 (38)	0 (0)
mPR	0 (0)	8 (100)	5 (62)	7 (88)
mCR	0 (0)	0 (0)	0 (0)	1 (12)

Per modified RESCIST criteria: mPD = progressive disease; mSD = stable disease; mPR = partial response; mCR = complete response

These results suggest that FTIs can enhance the efficacy of multiple RAS-targeted agents in

KRAS-mutant settings.

[00164] Additional *in vivo* tumor growth experiments were conducted in several additional models at the doses listed in the respective figures. Compound (I), adagrasib, and the combination were studied in the MIA PaCa-2 KRAS G12C PDAC model (**FIG. 14A**) and in the PA1383 KRAS G12C PDAC model (**FIG. 14B**). In a CR6256 KRAS G12C CRC model, two experiments were performed: (a) tipifarnib, Compound (I), sotorasib, tipifarnib and sotorasib, and Compound (I) and sotorasib (**FIG. 15A**); and (b) tipifarnib, Compound (I), adagrasib, tipifarnib and adagrasib, and Compound (I) and adagrasib (**FIG. 15B**); and additional studies were performed, (c) in a CR6243 KRAS G12C CRC model, with Compound (I), adagrasib, and the combination (**FIG. 15C**), and (d) in a SW837 KRAS G12C CRC model, with Compound (I), adagrasib, and the combination (**FIG. 15D**). In an NCI-H358 KRAS G12C NSCLC model, two experiments were performed: (a) tipifarnib, adagrasib (at two dose levels), and combinations thereof (**FIG. 16A**); and (b) tipifarnib, sotorasib (at two dose levels), and combinations thereof (**FIG. 16B**). The combination of Compound (I) and 100 mg/kg adagrasib also inhibited tumor growth to a greater degree than either agent alone in LU11693 PDX, LU6405 PDX, and SW1573 CDX KRAS G12C NSCLC models.

[00165] In the NCI-H2122 KRAS G12C NSCLC CDX model, the following arms were performed: adagrasib, Compound (I), RMC-4550 (a SHP2 inhibitor), BI-3406 (a SOS1 inhibitor that inhibits the SOS1-KRAS interaction), everolimus (an mTOR inhibitor), VT103 (a TEAD1 protein palmitoylation inhibitor), Compound (I) and adagrasib, RMC-4550 and adagrasib, BI-3406 and adagrasib, everolimus and adagrasib, and VT103 and adagrasib (**FIG. 17A**). An extract of the results showing the results from the adagrasib, Compound (I) and adagrasib, RMC-4550 and adagrasib, BI-3406 and adagrasib, everolimus and adagrasib, and VT103 and adagrasib arms is shown in **FIG. 17B**. Similar head-to-head studies were performed for 28 days comparing the combination of adagrasib and Compound (I) with combinations of adagrasib and RMC-4550 (**FIG. 17C**), BI-3406 (**FIG. 17D**), everolimus (**FIG. 17E**), or VT103 (**FIG. 17F**).

[00166] *In vivo* pretreatment studies: NCI-H2030 and NCI-H2122 KRAS^{G12C} NSCLC CDX models were treated with either KRAS^{G12C} inhibitors, adagrasib or sotorasib, for varying periods of time. Compound (I) was added to the treatment to assess the anti-tumor activity of the Compound (I)-adagrasib combination in this KRAS^{G12C} inhibitor pre-treated setting. Specifically, in the NCI-H2030 CDX model, addition of Compound (I) to the tumors progressing

on adagrasib monotherapy after Day 28 lead to tumor stasis (**FIG. 18A**). Addition of Compound (I) plus adagrasib to tumors progressing on sotorasib monotherapy in this CDX model may produce similar results. In the NCI-H2122 CDX model, addition of Compound (I) to tumors treated with adagrasib monotherapy for two weeks caused tumor regressions comparable to the upfront combination of Compound (I) with adagrasib (**FIG. 18B**). Similar tumor regressions were observed with combination of Compound (I) plus adagrasib after sotorasib single agent pretreatment for two weeks (**FIG. 18C**).

[00167] To determine the mechanism of action of the anti-tumor effects observed with the combination treatment of Compound (I) with adagrasib after prior KRAS^{G12C} inhibitor single agent treatment, changes in various proteins in the mTOR and MAPK signaling pathways were assessed. In the NCI-H2030 KRAS^{G12C} NSCLC CDX model, tumors treated with the combination of Compound (I) plus adagrasib after progression on adagrasib monotherapy showed a decrease in p-S6 (S235/236) and p-S6 (S240/244) levels that were comparable to that of upfront combination of Compound (I) plus adagrasib (**FIG. 19A**). In the NCI-H2122 KRAS^{G12C} NSCLC CDX model, tumors treated with the combination of Compound (I) plus adagrasib after two weeks pretreatment with either KRAS^{G12C} inhibitor showed a decrease in MAPK signaling at the level of p-p90 RSK and p-ERK1/2 (T202/204) as well as inhibition of mTOR signaling at the level of p-p70 S6K and p-4EBP1 (S65), compared to monotherapy (**FIG. 19B**). Switching from one KRAS^{G12C} inhibitor to another did not provide additional benefit; however, addition of Compound (I) with a switch from sotorasib to adagrasib was able to abolish p-S6 signaling at both phosphorylation sites. Additionally, a decrease in p-RB levels, suggesting cell cycle arrest, was observed only in groups treated with Compound (I). These results suggest that adding Compound (I) after pretreatment with a KRAS^{G12C} inhibitor can yield comparable combination benefit to xenograft tumors treated with an upfront combination of Compound (I) plus adagrasib by inhibiting mTOR signaling.

[00168] A similar *in vivo* study was conducted in the NCI-H2122 CDX model to determine the efficacy of Compound (I) in combination with a pan-RAS inhibitor, RMC-6236, after prior KRAS inhibitor treatment. After adagrasib single agent pretreatment for two weeks, tumor growth was inhibited with the addition of Compound (I) plus RMC-6236 compared to tumor stasis after switching to RMC-6236 monotherapy (**FIG. 18D**). The addition of Compound (I) to tumors progressing on RMC-6236 monotherapy caused tumor regressions comparable to upfront

combination of Compound (I) with RMC-6236 (**FIG. 18E**). These results demonstrate that Compound (I) can overcome adaptive resistance to KRAS inhibitors, such as KRAS G12C inhibitors and RAS inhibitors (e.g., pan-RAS inhibitors) even after pre-treatment with such agents.

[00169] Dose scheduling study: NCI-H2122 *KRAS*^{G12C} NSCLC CDX model was treated with various schedule regimens of the combination of Compound (I) with adagrasib. Results are shown in **FIG. 20**. Conclusions from this study are that weekly on/off dosing of Compound (I) with continuous dosing of adagrasib had comparable anti-tumor efficacy to continuous dosing of Compound (I) with adagrasib, weekly on/off dosing of Compound (I) whether with continuous dosing of adagrasib or synchronous on/off dosing of adagrasib had similar anti-tumor responses, and synchronous dosing of Compound (I) and adagrasib was needed for tumor regressions since nonsynchronous dosing only led to tumor stabilization. These results suggest the importance of treating both FTI and *KRAS*^{G12C} inhibitor simultaneously in order for Compound (I) to enhance the effects of adagrasib.

Further Examples

[00170] The combination of Compound (I) and divarasib, another *KRAS*^{G12C} inhibitor, exhibited enhanced anti-tumor activity over each agent alone in the NCI-H2122 *KRAS*^{G12C} NSCLC CDX model (**FIG. 21**). The combination of Compound (I) and BI-2493, a pan-KRAS inhibitor, exhibited enhanced anti-tumor activity over each agent alone in *KRAS* G12V PDAC models (**FIG. 22**). Addition of Compound (I) plus BI-2493 in *KRAS* WT-amplified gastric cancer models produces similar results. Compound (I) may enhance activity of *KRAS* inhibitors in xenograft models of CRC, PDAC, and NSCLC, including G12C, G12D, and G12V mutant subtypes.

Clinical Trial Study

[00171] A Phase 1, first-in-human, open-label clinical study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of Compound (I) when administered in combination with a *KRAS* G12C inhibitor, e.g., adagrasib, in adult patients with *KRAS* G12C-mutant, locally advanced or metastatic, non-small cell lung cancer is conducted. In some aspects, patients have received at least one prior systemic therapy.

Compound (I) is dosed once daily on days 1-7 and 15-21 in 28-day cycles. Adagrasib is dosed once daily in 28-day cycles.

7.1 EXEMPLARY EMBODIMENTS

[00172] One or more than one (including for instance all) of the following exemplary Embodiments may comprise each of the other embodiments or parts thereof.

[00173] A1. A method of treating cancer in a subject comprising administering to the subject an FTI.

[00174] A2. A method of treating a *KRAS*-dependent cancer in a subject comprising administering to the subject an FTI.

[00175] A3. A method of delaying emergence of resistance to a *KRAS* inhibitor for a cancer in a subject or overcoming resistance to a *KRAS* inhibitor for a cancer in a subject previously treated with a *KRAS* inhibitor, comprising administering to the subject an FTI; optionally administering to the subject a *KRAS* inhibitor in combination with the FTI; optionally wherein the subject was previously treated with the same or a different *KRAS* inhibitor.

[00176] A4. A method of treating pancreatic cancer, pancreatic ductal adenocarcinoma, lung cancer, non-small cell lung cancer, or colorectal cancer in a subject comprising administering to the subject Compound (I) or a pharmaceutically acceptable form thereof.

[00177] A5. The method of any one of Embodiments A1 to A4, comprising administering to the subject a *KRAS* inhibitor.

[00178] A6. The method of any one of Embodiments A1 to A5, wherein the cancer is lung cancer, pancreatic cancer, gynecologic cancer, gastrointestinal cancer, breast cancer, neoplasm (metastatic neoplasm, germ cell cancer, plasma cell neoplasm, or myelodysplastic/myeloproliferative neoplasm), carcinoma of unknown primary (CUP), or leukemia.

[00179] A7. The method of Embodiment A6, wherein the lung cancer is non-small cell lung cancer (NSCLC), non-squamous NSCLC, squamous NSCLC, or lung adenocarcinoma.

[00180] A8. The method of Embodiment A6, wherein the gastrointestinal cancer is colorectal cancer (CRC), colon cancer, pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), biliary tract cancer, appendiceal cancer, small bowel cancer, stomach cancer, cholangiocarcinoma, ampullary cancer, gallbladder cancer, gastric cancer, gastric

adenocarcinoma, esophageal cancer, esophageal adenocarcinoma, urinary tract cancer, GI-neuroendocrine tumor, or gastroesophageal junction adenocarcinoma.

[00181] A9. The method of Embodiment A6, wherein the gynecological cancer is ovarian cancer, endometrial cancer, peritoneal cancer, or cervical cancer.

[00182] A10. The method of any of the preceding Embodiments, wherein the cancer is lung cancer, colorectal cancer, or pancreatic cancer.

[00183] A11. The method of Embodiment A10, wherein the cancer is non-small lung cancer, colorectal cancer, or pancreatic ductal adenocarcinoma.

[00184] A12. The method of any of the preceding Embodiments, wherein the cancer comprises a *KRAS* mutation or a *KRAS* amplification, or a combination thereof.

[00185] A13. The method of any of the preceding Embodiments, wherein the cancer comprises a *KRAS* mutation.

[00186] A13A. The method of any of the preceding Embodiments, wherein the *KRAS* inhibitor is a *KRAS* G12C inhibitor, a *KRAS* G12D inhibitor, a *KRAS* G12S inhibitor, a *KRAS* G12V inhibitor, a *KRAS* G12R inhibitor, a *KRAS* G13D inhibitor, a pan-*KRAS* inhibitor, or a pan-RAS inhibitor.

[00187] A14. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation is a *KRAS* G12C mutation and wherein the method comprises administering a *KRAS* inhibitor, the *KRAS* inhibitor is a *KRAS* G12C inhibitor.

[00188] A14A. The method of Embodiment A14, wherein the cancer is NSCLC, lung adenocarcinoma, non-squamous NSCLC, squamous NSCLC, CRC, pancreatic cancer, PDAC, CUP, endometrial cancer, ovarian cancer, cervical cancer, gastric cancer, gastric adenocarcinoma, cholangiocarcinoma, esophageal cancer, stomach cancer, small bowel cancer, appendiceal cancer, biliary tract cancer (BTC), ampullary cancer, gallbladder cancer, breast cancer, or metastatic neoplasm.

[00189] A15. The method of Embodiment A14, wherein the *KRAS* G12C inhibitor is adagrasib (KRAZATI[®], MRTX849, Amgen), sotorasib (LUMAKRAS[™], AMG-510, Amgen), divarasib (GDC-6036, Genentech), linperlisib (YL-15293), RM007, D-1553 (InvestisBio), JDQ443 (Novartis), LY3537982 (Eli Lilly), LY3499446, ERAS-601, ERAS-007, BI 1823911 (Boehringer Ingelheim), JAB-21822, MK-1084, MK-1086, MK-1087, L-15293, D3S-001, RMC-6291 (Revolution), HBI-2438, FMC-376 (Frontier), BBO-8520 (BridgeBio), ZG19018

(Suzhou Zelgen), UCT-001024 (1200 Pharma), TEB-17231 (280Bio unit of Yingli Pharma), HYP-2A (Sichuan Huiyu), ABSK071 (Abbisko), IBI351 (GFH925; Innovent/Genfleet), ARS-853, ARS-1620, or JNJ-74699157 (ARS-3248).

[00190] A16. The method of Embodiment A14 or Embodiment A15, wherein the KRAS G12C inhibitor is adagrasib or sotorasib.

[00191] A17. The method of any one of Embodiments A14 to A16, wherein the cancer is non-small cell lung cancer or colorectal cancer.

[00192] A18. The method of Embodiment A17, wherein the cancer is non-small cell lung cancer.

[00193] A19. The method of Embodiment A17, wherein the cancer is colorectal cancer.

[00194] A20. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation is a *KRAS* G12D mutation and wherein the method comprises administering a KRAS inhibitor, the KRAS inhibitor is a KRAS G12D inhibitor.

[00195] A20A. The method of Embodiment A20, wherein the cancer is pancreatic cancer, PDAC, CRC, NSCLC, non-squamous NSCLC, CUP, endometrial cancer, ovarian cancer, small bowel adenocarcinoma, appendiceal adenocarcinoma, gastric cancer, gastric adenocarcinoma, or cholangiocarcinoma.

[00196] A21. The method of Embodiment A20, wherein the KRAS G12D inhibitor is MRTX1133 (Mirati), TH-Z827, TH-Z835, KD-8, BI-KRAS12D1-3, BI-KRASG12D3, RMC-9805 (Revolution), ASP3082, ASP4396, LY3962673, INCB161734, HRS-4642, or QTX3046 (Quanta).

[00197] A22. The method of Embodiment A20, wherein the KRAS G12D inhibitor is MRTX1133.

[00198] A23. The method of any one of Embodiments A20 to A22, wherein the cancer is pancreatic ductal adenocarcinoma, non-small cell lung cancer, colorectal cancer, or gastric cancer.

[00199] A24. The method of Embodiment A23, wherein the cancer is pancreatic ductal adenocarcinoma.

[00200] A25. The method of Embodiment A23, wherein the cancer is non-small cell lung cancer.

[00201] A26. The method of Embodiment A23, wherein the cancer is colorectal cancer.

- [00202] A27. The method of Embodiment A23, wherein the cancer is gastric cancer.
- [00203] A28. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation is a *KRAS* G12V mutation and wherein the method comprises administering a KRAS inhibitor, the KRAS inhibitor is a KRAS G12V inhibitor.
- [00204] A28A. The method of Embodiment A28, wherein cancer is CRC, NSCLC, non-squamous NSCLC, PDAC, CUP, endometrial cancer, ovarian cancer, cholangiocarcinoma, small bowel adenocarcinoma, appendiceal adenocarcinoma, gastrointestinal cancer, esophageal cancer, and stomach cancer.
- [00205] A29. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation is a *KRAS* G12R mutation and wherein the method comprises administering a KRAS inhibitor, the KRAS inhibitor is a KRAS G12R inhibitor.
- [00206] A29A. The method of Embodiment A29, wherein the cancer is pancreatic cancer, PDAC, or CUP.
- [00207] A30. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation is a *KRAS* G12S mutation and wherein the method comprises administering a KRAS inhibitor, the KRAS inhibitor is a KRAS G12S inhibitor.
- [00208] A31. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation is a *KRAS* G13D mutation and wherein the method comprises administering a KRAS inhibitor, the KRAS inhibitor is a KRAS G13D inhibitor.
- [00209] A31A. The method of Embodiment A31, wherein the cancer is CRC, non-squamous NSCLC, or endometrial cancer.
- [00210] A32. The method of Embodiment A13 or Embodiment A13A, wherein the *KRAS* mutation comprises at least two *KRAS* mutations selected from *KRAS* G12C, G12D, G12V, G12R, and G13D mutations, and wherein the method comprises administering a KRAS inhibitor, the KRAS inhibitor is a pan-KRAS inhibitor.
- [00211] A33. The method of Embodiment A32, wherein the pan-KRAS inhibitor is BI-2852, BI-pan-KRAS1-4 (BI1701963), RSC-1255, RMC-6236, RSC-1255, QTX3034 (Quanta), JAB-23425 (Beijing Jacobio), BI-2493, LY4066434, or VRTX-153 (VRise).
- [00212] A34. The method of any of the preceding Embodiments, wherein the cancer comprises a *KRAS* amplification.
- [00213] A35. The method of any one of the preceding Embodiments, wherein the cancer is a

solid tumor, in remission, early stage, advanced, locally advanced, relapsed, metastatic, refractory, recurrent, or a combination thereof.

[00214] A36. The method of any one of the preceding Embodiments, wherein the cancer has been previously treated with a first-line therapy and optionally a second-line therapy.

[00215] A37. The method of any one of the preceding Embodiments, wherein the administering comprises administering the FTI before, after, or simultaneously with the KRAS inhibitor, optionally during one or more treatment cycles, such as one or more 28-day cycles.

[00216] A38. The method of any one of the preceding Embodiments, comprising administering the FTI and the KRAS inhibitor concurrently or sequentially, and independently, continuously or in cycles.

[00217] A39. The method of any of the preceding Embodiments, comprising administering a daily dose of the FTI selected from about 0.1-2.5 mg, 0.5-5 mg, 0.5-10 mg, 0.5-25 mg, 0.5-50 mg, 0.5-75 mg, 0.5-100 mg, 0.5-300 mg, 0.5-600 mg, 0.5-1200 mg, 1-5 mg, 1-10 mg, 1-25 mg, 1-50 mg, 1-75 mg, 1-100 mg, 1-300 mg, 1-600 mg, 1-1200 mg, 1-2400 mg, 20-100 mg, 40-75 mg, 50-75 mg, 50-100 mg, 50-150 mg, 75-100 mg, 100-200 mg, 125-200 mg, 150-300 mg, 200-250 mg, 200-400 mg, 300-600 mg, 250-500 mg, 400-600 mg, 500-750 mg, 600-900 mg, 700-100 mg, 650-1000 mg, 800-1200 mg, 900-1500 mg, 1000-1600 mg, 1000-2000 mg, 1200-1600 mg, 1500-2000 mg, 1500-2400 mg, 1800-2400 mg and 2000-2400 mg per day (free base equivalent); or the daily dose of the FTI is about 0.5 mg, about 1.5 mg, about 1.6 mg, about 1.7 mg, about 1.8 mg, about 1.9 mg, about 1 mg, about 2 mg, about 2.5 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg,

about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, or about 2400 mg per day (free base equivalent).

[00218] A40. The method of Embodiment A39, wherein the daily dose of the FTI is administered across one or two doses per day.

[00219] A41. The method of any of the preceding Embodiments, wherein the FTI is administered once or twice per day on days 1-7, days 1-7 and 15-21, days 1-14, days 1-21, or each day (*i.e.*, days 1-28) of a 28-day cycle, for one or more cycles.

[00220] A42. The method of any of the preceding Embodiments, comprising administering the KRAS inhibitor at a daily dose of 10-2000 mg per day, or about 10-300 mg, about 50-400 mg, about 200-400 mg, about 500-1500 mg, about 800-1200 mg, or about 1100-1500 mg per day, or about 1200 mg (*e.g.*, about 600 mg twice daily), or about 960 mg.

[00221] A43. The method of any of the preceding Embodiments, wherein the FTI is tipifarnib, lonafarnib, FTI277, BMS214662, or Compound (I), or a pharmaceutically acceptable form thereof.

[00222] A44. The method of any one of Embodiments A1 to A43, wherein the FTI is Compound (I) or a pharmaceutically acceptable form thereof.

[00223] A45. The method of Embodiment A44, wherein the FTI is the free base of Compound (I).

[00224] A46. The method of Embodiment A44, wherein the FTI is a pharmaceutically acceptable salt of Compound (I).

[00225] A47. The method of Embodiment A45 or A46, wherein the FTI is a solvate of the free base or pharmaceutically acceptable salt of Compound (I).

[00226] A48. The method of any one of Embodiments A3 or A5-A47, wherein the KRAS inhibitor administered in combination with the FTI to the subject previously treated with a KRAS inhibitor is the same KRAS inhibitor.

[00227] A49. The method of any one of Embodiments A3 or A5-A47, wherein the KRAS inhibitor administered in combination with the FTI to the subject previously treated with a KRAS inhibitor is a different KRAS inhibitor.

[00228] B1. A pharmaceutical composition comprising (a) an FTI, (b) a KRAS inhibitor, and (c) a pharmaceutically acceptable excipient.

[00229] B2. A pharmaceutical composition for use in a method of any of Embodiments A1 to

A49 comprising an FTI and a pharmaceutically acceptable excipient.

[00230] B3. The pharmaceutical composition for use of Embodiment B2, comprising a KRAS inhibitor.

[00231] B4. A pharmaceutical composition comprising (a) Compound (I) or a pharmaceutically acceptable form thereof, (b) a KRAS inhibitor, and (c) a pharmaceutically acceptable excipient.

[00232] B5. The pharmaceutical composition of any of the preceding Embodiments, wherein the KRAS inhibitor is a KRAS G12C inhibitor, a KRAS G12D inhibitor, a KRAS G12S inhibitor, a KRAS G12V inhibitor, a KRAS G12R inhibitor, a KRAS G13D inhibitor, a pan-KRAS inhibitor, or a pan-RAS inhibitor, optionally wherein the KRAS inhibitor is a *KRAS* G12C inhibitor.

[00233] B6. The pharmaceutical composition of Embodiment B5, wherein the KRAS G12C inhibitor is adagrasib (KRAZATI[®], MRTX849, Amgen), sotorasib (LUMAKRAS[™], AMG-510, Amgen), divarasisib (GDC-6036, Genentech), loperlisib (YL-15293), RM007, D-1553 (InvestisBio), JDQ443 (Novartis), LY3537982 (Eli Lilly), LY3499446, ERAS-601, ERAS-007, BI 1823911 (Boehringer Ingelheim), JAB-21822, MK-1084, MK-1086, MK-1087, L-15293, D3S-001, RMC-6291 (Revolution), HBI-2438, FMC-376 (Frontier), BBO-8520 (BridgeBio), ZG19018 (Suzhou Zelgen), UCT-001024 (1200 Pharma), TEB-17231 (280Bio unit of Yingli Pharma), HYP-2A (Sichuan Huiyu), ABSK071 (Abbisko), IBI351 (GFH925; Innovent/Genfleet), ARS-853, ARS-1620, or JNJ-74699157 (ARS-3248).

[00234] B7. The pharmaceutical composition of Embodiment B5, wherein the KRAS G12C inhibitor is adagrasib or sotorasib.

[00235] B8. The pharmaceutical composition of any of Embodiments B1 to B4, wherein the KRAS inhibitor is a KRAS G12D inhibitor.

[00236] B9. The pharmaceutical composition of Embodiment B8, wherein the KRAS G12D inhibitor is MRTX1133 (Mirati), TH-Z827, TH-Z835, KD-8, BI-KRAS12D1-3, BI-KRASG12D3, RMC-9805 (Revolution), ASP3082, ASP4396, LY3962673, INCB161734, HRS-4642, or QTX3046 (Quanta).

[00237] B10. The pharmaceutical composition of Embodiment B8, wherein the KRAS G12D inhibitor is MRTX1133.

[00238] B11. The pharmaceutical composition of any of Embodiments B1 to B4, wherein the

KRAS inhibitor is a KRAS G12V inhibitor, a KRAS G12R inhibitor, a KRAS G12S inhibitor, a KRAS G13D inhibitor, or a pan-KRAS inhibitor, or wherein the KRAS inhibitor is a pan-RAS inhibitor.

[00239] B12. The pharmaceutical composition of Embodiment B11, wherein the pan-KRAS inhibitor is BI-2852, BI-pan-KRAS1-4 (BI1701963), RSC-1255, RMC-6236, RSC-1255, QTX3034 (Quanta), JAB-23425 (Beijing Jacobio), BI-2493, LY4066434, or VRTX-153 (VRise), or wherein the pan-KRAS inhibitor is a pan-RAS inhibitor, optionally wherein the KRAS inhibitor is RMC-6236 or wherein the KRAS inhibitor is RSC-1255.

[00240] B13. The pharmaceutical composition of any one of Embodiments B1 to B12, wherein the FTI is tipifarnib, lonafarnib, FTI277, BMS214662, or Compound (I), or a pharmaceutically acceptable form thereof.

[00241] B14. The pharmaceutical composition of any one of Embodiments B1 to B12, wherein the FTI is Compound (I) or a pharmaceutically acceptable form thereof.

[00242] B15. The pharmaceutical composition of Embodiment B14, wherein the FTI is the free base of Compound (I).

[00243] B16. The pharmaceutical composition of Embodiment B14, wherein the FTI is a pharmaceutically acceptable salt of Compound (I).

[00244] B17. The pharmaceutical composition of Embodiment B15 or B16, wherein the FTI is a solvate of the free base or pharmaceutically acceptable salt of Compound (I).

[00245] C1. A pharmaceutical kit or packaging comprising: (i) (a) a pharmaceutical composition comprising Compound (I) or a pharmaceutically acceptable form thereof, and a pharmaceutically acceptable excipient, and optionally (b) a pharmaceutical composition comprising a KRAS inhibitor and a pharmaceutically acceptable excipient, or (ii) the pharmaceutical composition of any of Embodiments B1-B17.

[00246] The embodiments described herein are intended to be merely exemplary, and those skilled in the art will recognize, or are able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the invention and are encompassed by the appended claims.

INCORPORATION BY REFERENCE

[00247] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference in their entireties to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference in its entirety. In case of conflict, the present application, including any definitions herein, will control.

What is claimed is:

1. A method of treating a *KRAS*-dependent cancer in a subject comprising administering to the subject an FTI and a *KRAS* inhibitor.
2. The method of claim 1, wherein the cancer is lung cancer, pancreatic cancer, gynecologic cancer, gastrointestinal cancer, breast cancer, neoplasm (metastatic neoplasm, germ cell cancer, plasma cell neoplasm, or myelodysplastic/myeloproliferative neoplasm), carcinoma of unknown primary (CUP), or leukemia.
3. The method of claim 2, wherein the lung cancer is non-small cell lung cancer (NSCLC), non-squamous NSCLC, squamous NSCLC, or lung adenocarcinoma.
4. The method of claim 1, wherein the gastrointestinal cancer is colorectal cancer (CRC), colon cancer, pancreatic cancer, pancreatic ductal adenocarcinoma (PDAC), biliary tract cancer, appendiceal cancer, small bowel cancer, stomach cancer, cholangiocarcinoma, ampullary cancer, gallbladder cancer, gastric cancer, gastric adenocarcinoma, esophageal cancer, esophageal adenocarcinoma, urinary tract cancer, GI-neuroendocrine tumor, or gastroesophageal junction adenocarcinoma.
5. The method of claim 2, wherein the gynecological cancer is ovarian cancer, endometrial cancer, peritoneal cancer, or cervical cancer.
6. The method of claim 2, wherein the cancer is lung cancer, colorectal cancer, or pancreatic cancer.
7. The method of claim 6, wherein the cancer is non-small lung cancer, colorectal cancer, or pancreatic ductal adenocarcinoma.
8. The method of any one of claims 1 to 7, wherein the cancer comprises a *KRAS* mutation or a *KRAS* amplification, or a combination thereof.
9. The method of claim 8, wherein the cancer comprises a *KRAS* mutation.
10. The method of claim 9, wherein the *KRAS* mutation is a *KRAS* G12C mutation and the *KRAS* inhibitor is a *KRAS* G12C inhibitor.
11. The method of claim 10, wherein the *KRAS* G12C inhibitor is adagrasib (KRAZATI[®], MRTX849, Amgen), sotorasib (LUMAKRAS[™], AMG-510, Amgen), divarasib (GDC-6036, Genentech), linperlisib (YL-15293), RM007, D-1553 (InvestisBio), JDQ443 (Novartis), LY3537982 (Eli Lilly), LY3499446, ERAS-601, ERAS-007, BI 1823911 (Boehringer

Ingelheim), JAB-21822, MK-1084, MK-1086, MK-1087, L-15293, D3S-001, RMC-6291 (Revolution), HBI-2438, FMC-376 (Frontier), BBO-8520 (BridgeBio), ZG19018 (Suzhou Zelgen), UCT-001024 (1200 Pharma), TEB-17231 (280Bio unit of Yingli Pharma), HYP-2A (Sichuan Huiyu), ABSK071 (Abbisko), IBI351 (GFH925; Innovent/Genfleet), ARS-853, ARS-1620, or JNJ-74699157 (ARS-3248).

12. The method of claim 11, wherein the KRAS G12C inhibitor is adagrasib or sotorasib.

13. The method of any one of claims 10 to 12, wherein the cancer is non-small cell lung cancer or colorectal cancer.

14. The method of claim 9, wherein the *KRAS* mutation is a *KRAS* G12D mutation and the KRAS inhibitor is a KRAS G12D inhibitor or a pan-KRAS inhibitor or a pan-RAS inhibitor.

15. The method of claim 14, wherein the KRAS G12D inhibitor is MRTX1133 (Mirati), TH-Z827, TH-Z835, KD-8, BI-KRAS12D1-3, BI-KRASG12D3, RMC-9805 (Revolution), ASP3082, ASP4396, LY3962673, INCB161734, HRS-4642, or QTX3046 (Quanta).

16. The method of claim 14, wherein the KRAS G12D inhibitor is MRTX1133.

17. The method of any one of claims 14 to 16, wherein the cancer is pancreatic ductal adenocarcinoma, non-small cell lung cancer, colorectal cancer, or gastric cancer.

18. The method of claim 9, wherein:

- (a) the *KRAS* mutation is a *KRAS* G12V mutation and the KRAS inhibitor is a KRAS G12V inhibitor; or
- (b) the *KRAS* mutation is a *KRAS* G12R mutation and the KRAS inhibitor is a KRAS G12R inhibitor; or
- (c) the *KRAS* mutation is a *KRAS* G12S mutation, and the KRAS inhibitor is a KRAS G12S inhibitor; or
- (d) the *KRAS* mutation is a *KRAS* G13D mutation and the KRAS inhibitor is a KRAS G13D inhibitor.

19. The method of claim 9, wherein the *KRAS* mutation comprises at least two *KRAS* mutations selected from *KRAS* G12C, G12D, G12V, G12R, and G13D mutations, and the KRAS inhibitor is a pan-KRAS inhibitor.

20. The method of claim 19, wherein the pan-KRAS inhibitor is BI-2852, BI-pan-KRAS1-4 (BI1701963), RSC-1255, RMC-6236, RSC-1255, QTX3034 (Quanta), JAB-23425 (Beijing Jacobio), BI-2493, LY4066434, or VRTX-153 (VRise), or wherein the pan-KRAS inhibitor is a

pan-RAS inhibitor, optionally wherein the KRAS inhibitor is RMC-6236, or optionally wherein the KRAS inhibitor is RSC-1255.

21. The method of any one of claims 1 to 20, wherein the cancer comprises a *KRAS* amplification.
22. The method of any one of claims 1 to 21, wherein the FTI is tipifarnib, lonafarnib, FTI277, BMS214662, or Compound (I), or a pharmaceutically acceptable form thereof.
23. The method of claim 22, wherein the FTI is Compound (I) or a pharmaceutically acceptable form thereof.
24. A method of delaying emergence of resistance to a KRAS inhibitor for a cancer in a subject or overcoming resistance to a KRAS inhibitor for a cancer in a subject previously treated with a KRAS inhibitor, comprising the method of any one of claims 1 to 23.
25. A method of treating pancreatic cancer, pancreatic ductal adenocarcinoma, lung cancer, non-small cell lung cancer, or colorectal cancer in a subject comprising administering to the subject (a) Compound (I) or a pharmaceutically acceptable form thereof and (b) a KRAS inhibitor.
26. The method of claim 24 or claim 25, wherein the cancer comprises a *KRAS* G12C mutation or a *KRAS* G12D mutation.
27. The method of any of the preceding claims, comprising administering to the subject an additional anticancer agent, optionally selected from an immunotherapy agent, an anti-EGFR monoclonal antibody, an inhibitor of the EGFR signaling pathway, cetuximab, panitumumab, chemotherapy, a platinum-based anticancer agent (e.g., cisplatin or carboplatin), leucovorin, fluorouracil, a topoisomerase inhibitor (e.g., irinotecan or topotecan), a taxane (e.g., paclitaxel, docetaxel, or nab-paclitaxel), gemcitabine, etoposide, pemetrexed, vinorelbine, a VEGF inhibitor (e.g., bevacizumab or ramucirumab), an EGFR inhibitor (e.g., osimertinib, afatinib, erlotinib, dacomitinib, gefitinib, or amivantamab), an ALK inhibitor (e.g., alectinib, brigatinib, lorlatinib, ceritinib, or crizotinib), a ROS1 inhibitor, and a BRAF inhibitor (e.g., dabrafenib, trametinib, or vemurafenib), and combinations thereof, each optionally in combination with radiation.
28. A pharmaceutical composition comprising (a) Compound (I) or a pharmaceutically acceptable form thereof, (b) a KRAS inhibitor, and (c) a pharmaceutically acceptable excipient.
29. A pharmaceutical kit or packaging comprising: (i) (a) a pharmaceutical composition comprising Compound (I) or a pharmaceutically acceptable form thereof, and a pharmaceutically

acceptable excipient, and (b) a pharmaceutical composition comprising a KRAS inhibitor and a pharmaceutically acceptable excipient, or (ii) the pharmaceutical composition of claim 27.