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(54) Benævnelse: **SAMTIDIG INDGIVELSE AF MIRDAMETINIB OG LIFIRAFENIB TIL ANVENDELSE TIL BEHANDLING AF KRÆFTFORMER**

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US-A1- 2014 155 372
Z. TANG ET AL: "BGB-283, a Novel RAF Kinase and EGFR Inhibitor, Displays Potent Antitumor Activity in BRAF-Mutated Colorectal Cancers", MOLECULAR CANCER THERAPEUTICS, vol. 14, no. 10, 24 July 2015 (2015-07-24) , pages 2187-2197, XP055451634, US ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-15-0262
YUAN XI ET AL: "RAF dimer inhibition enhances the antitumor activity of MEK inhibitors in K-RAS mutant tumors", MOLECULAR ONCOLOGY, vol. 14, no. 8, 18 May 2020 (2020-05-18), pages 1833-1849, XP055824012, ISSN: 1574-7891, DOI: 10.1002/1878-0261.12698

DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present disclosure relates to a combination of mirdametinib or a pharmaceutically acceptable salt form thereof, and lifirafenib or a pharmaceutically acceptable salt form thereof, for use in treating a patient having a solid tumor. Also disclosed are pharmaceutical compositions of mirdametinib or a pharmaceutically acceptable salt form thereof, and lifirafenib or a pharmaceutically acceptable salt form thereof, for use in such cancer treatment.

BACKGROUND

[0002] N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide ("Compound A", "mirdametinib", "PD-0325901") is a small molecule drug which has been designed to inhibit mitogen-activated protein kinase 1 ("MEK1") and mitogen-activated protein kinase 2 ("MEK2"). MEK1 and MEK2 are proteins that play key roles in the mitogen-activated protein kinase ("MAPK") signaling pathway. The MAPK pathway is critical for cell survival and proliferation, and inappropriate activation of this pathway has been shown to help enable tumor growth. Mirdametinib is a highly specific non-ATP-competitive inhibitor of MEK1 and MEK2. By virtue of this mechanism of action, mirdametinib significantly inhibits phosphorylation of the extracellular regulated MAP kinases ERK1 and ERK2, thereby leading to impaired growth of tumor cells both in culture and in vivo. In addition, evidence indicates that inflammatory cytokine-induced increases in MEK/ERK activity contribute to the inflammation, pain, and tissue destruction associated with rheumatoid arthritis and other inflammatory diseases. The use of mirdametinib in treating solid tumor is disclosed in US 2014/155372 A1.

[0003] 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyrdin-2(1H)-one ("Compound B", "lifirafenib", "BGB-283") is a novel, first-in-class, investigational RAF dimer inhibitor with potent, reversible inhibition of wild-type A-RAF, B-RAF, C-RAF, and B-RAFV600E, as well as EGFR and K-RAS, thereby enabling efficacy in a broad range of tumor types driven by mutations in the MAPK pathway, such as those with K-RAS driver mutations. The use of lifirafenib in treating solid tumor is disclosed in Z. Tang ET AL: Molecular Cancer Therapeutics, vol. 14, no. 10, 2015, p. 2187-2197.

[0004] Therapeutic agents targeting oncogenic B-RAF were developed within the past decade and clinical studies demonstrated unprecedented clinical responses over the then standard of care, dacarbazine (Chapman 2011), leading to the US FDA approval of 4 agents and 2 combination regimens targeting the MAPK pathway (Chapman 2011; Hauschild 2012; Larkin 2014; Long 2015). Importantly, early efforts focused on B-RAF inhibitor monotherapy; however, resistance developed quickly in most patients, with a progression-free survival ("PFS") of less than 6 months for these agents (Chapman 2011; Hauschild 2012). Insights gained from translational research highlighted

MAPK reactivation as a major resistance mechanism (Rizos 2014; Kwong 2015) and led to therapeutic strategies co-targeting B-RAF and MEK-leading to a near doubling in PFS (Larkin 2014; Long 2015). However, resistance still develops in the majority of patients, though a small fraction achieves long-term disease control (Flaherty 2012a; Flaherty 2012b; reviewed by Reddy 2016). Therefore, second-generation B-RAF inhibitors combined with MEK inhibitors are highly desirable as new combinations.

BRIEF DESCRIPTION OF FIGURES

[0005]

FIG. 1 shows average volume over time of Calu-6 tumors implanted in Balb/c nude mice treated with varying concentrations of Compound A and Compound B maleate.

FIG. 2 shows the body weight over time of mice implanted with Calu-6 tumors and treated with varying concentrations of Compound A and Compound B maleate.

FIG. 3 shows the percentage change in final volumes versus baseline for each of the individual Calu-6 tumors implanted in Balb/c nude mice treated with varying concentrations of Compound A and Compound B maleate.

FIG. 4 shows the best change (%) from baseline in tumor size (defined by the sum of the longest diameter of the target lesions) in advanced or refractory solid tumor patients having a mutation in a MAPK gene.

BRIEF SUMMARY OF THE INVENTION

[0006] In one aspect, the invention relates to a combination of Compound A (mirdametinib), or a pharmaceutically acceptable salt form thereof, and Compound B (lifirafenib), or a pharmaceutically acceptable salt form thereof for use in treating a patient having a solid tumor, wherein compound A and compound B are each to be administered in a therapeutically effective amount.

[0007] In another aspect, the invention relates to pharmaceutical composition comprising Compound A (mirdametinib), Compound B (lifirafenib), or a pharmaceutically acceptable salt form thereof; a filler; a disintegrant; and a lubricant.

[0008] Further embodiments of the invention are defined in the appended claims.

[0009] The references to the methods of treatment by therapy in this description are to be interpreted as references to compounds, pharmaceutical compositions and medicaments of the present invention for use in those methods.

[0010] In some aspects, the therapeutically effective amount of Compound A is about 1 mg to about 5 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 40 mg per day.

[0011] In some aspects, the therapeutically effective amount of Compound A is about 1 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 15 mg per day.

[0012] In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 35 mg per day.

[0013] In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 35 mg per day.

[0014] In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 35 mg per day.

[0015] In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 1 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day, In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically

acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg per day.

[0016] In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form of Compound B is a maleate salt. In some aspects, the maleate salt is a sesqui-maleate salt.

[0017] In some aspects, the therapeutically effective amount of Compound A is about 1 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 5 mg to about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 1 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 7 mg per day.

[0018] In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 10 mg to about 30 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 13 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 27 mg per day.

[0019] In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 15 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 34 mg per day.

[0020] In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 20 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 4 mg per

day and the therapeutically effective amount of Compound B as a maleate salt is about 27 mg per day.

[0021] In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 25 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 34 mg per day.

[0022] In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 1 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day, In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 13 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 7 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 13 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 7 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and

the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 13 mg per day.

[0023] In some aspects, Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in the same or different dosage forms. In some aspects, Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in the same dosage form. In some aspects, Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered orally.

[0024] In some aspects, the dosage form is a capsule.

[0025] In some aspects, Compound A is administered once per day. In some aspects, Compound B, or a pharmaceutically acceptable salt form thereof, is administered once per day.

[0026] In some aspects, the present disclosure provides a pharmaceutical composition comprising:

1. a. Compound A, or a pharmaceutically acceptable salt form thereof;
2. b. Compound B, or a pharmaceutically acceptable salt form thereof;
3. c. a filler;
4. d. a disintegrant; and
5. e. a lubricant.

[0027] In some aspects, the pharmaceutically acceptable salt of Compound B is the maleic acid salt of Compound B.

[0028] In some aspects, the pharmaceutical composition comprises about 0.8 mg to about 1.2 mg of Compound A. In some aspects, the pharmaceutical composition comprises Compound A about 1.5 mg to about 2.5 mg.

[0029] In some aspects, the pharmaceutical composition comprises about 6 mg to about 8 mg of Compound B as the maleic acid salt. In some aspects, the pharmaceutical composition comprises about 20 mg to about 35 mg of Compound B as the maleic acid salt.

[0030] In some aspects, the filler in the pharmaceutical composition is present at about 80 wt/wt % to about 90 wt/wt %. In some aspects, the filler in the pharmaceutical composition is present at about 72.5 wt/wt % to about 85 wt/wt %. In some aspects, the filler in the pharmaceutical composition is selected from the group consisting of microcrystalline cellulose, lactose, mannitol, starch, dibasic calcium phosphate, and combinations thereof. In some aspects, the filler comprises microcrystalline cellulose. In some aspects, the filler in the pharmaceutical composition comprises silicified microcrystalline cellulose.

[0031] In some aspects, the disintegrant in the pharmaceutical composition is present at about 3.5 wt/wt % to about 4.5 wt/wt %. In some aspects, the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, alginic acid, and combinations thereof. In some aspects, the disintegrant in the pharmaceutical composition comprises

croscarmellose sodium.

[0032] In some aspects, the lubricant in the pharmaceutical composition is present at about 1.5 wt/wt % to about 5.0 wt/wt %. In some aspects, the lubricant is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, glyceryl dibehenate, talc, and combinations thereof. In some aspects, the lubricant in the pharmaceutical composition comprises sodium stearyl fumarate. In some aspects, the lubricant in the pharmaceutical composition comprises magnesium stearate.

[0033] In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, is a tablet or capsule. In some aspects, the pharmaceutical composition comprising Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, is a capsule.

[0034] In some aspects, the capsule comprises about 1 mg of Compound A and about 7 mg of the maleic acid salt of Compound B, wherein each component of the capsule is as follows:

1. a. about 0.8 wt/wt % to about 1.2 wt/wt % of Compound A;
2. b. about 6 wt/wt % to about 8 wt/wt % of the maleic acid salt of Compound B;
3. c. about 80 wt/wt % to about 90 wt/wt % of silicified microcrystalline cellulose;
4. d. about 3.5 wt/wt % to about 4.5 wt/wt % of croscarmellose sodium;
5. e. about 1.5 wt/wt % to about 5.0 wt/wt % of sodium stearyl fumarate; and
6. f. a gelatin capsule which encapsulates components a-e.

[0035] In some aspects, the capsule comprises about 2 mg of Compound A and about 27 mg of the maleic acid salt of Compound B, wherein each component of the capsule is as follows:

1. a. about 0.8 wt/wt % to about 1.3 wt/wt % of Compound A;
2. b. about 12.3 wt/wt % to about 15.0 wt/wt % of the maleic acid salt of Compound B;
3. c. about 72.5 wt/wt % to about 85 wt/wt % of silicified microcrystalline cellulose;
4. d. about 3.5 wt/wt % to about 4.5 wt/wt % of croscarmellose sodium;
5. e. about 1.5 wt/wt % to about 5.0 wt/wt % of sodium stearyl fumarate; and
6. f. a gelatin capsule which encapsulates components a-e.

[0036] In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, are administered to treat a patient having a cancer. In some aspects, the cancer is a solid tumor. In some aspects, the solid tumor is selected from the group consisting of malignant peripheral nerve sheath tumor, biliary tract cancer, breast cancer, cholangiocarcinoma, urothelial cancer, uterine neoplasm, lung adenocarcinoma, squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, gastric cancer, sarcoma, bladder cancer, head and neck cancer, small cell lung cancer, endometrial cancer, esophageal cancer, adenoid cystic carcinoma, gallbladder cancer, colorectal cancer ("CRC"), thyroid cancer, hepatocellular cancer, prostate cancer, oral cancer, cervical cancer, pancreatic carcinoma, ovarian cancer, melanoma, and serous carcinoma to the peritoneum. In some aspects, the patient has non-small cell lung cancer. In some aspects, the patient has endometrial cancer. In some aspects, the

patient has ovarian cancer. In some aspects, the patient has low grade serous ovarian cancer. In some aspects, the patient has a confirmed mutation in one or more of KRAS, NRAS, HRAS, BRAF, NF1, MEK1, and MEK2. In some aspects, the patient has a confirmed mutation in RASA1 and/or RAF1.

[0037] In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising: (a) 21 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered; and (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) 21 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof are both administered; followed by (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 2 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof are administered; and (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 2 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered; followed by (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 3 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof are administered; and (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 3 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered; followed by (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a

pharmaceutically acceptable salt form thereof, is administered.

[0038] In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising: (a) 21 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof form, is administered; and (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising (a) 21 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered; followed by (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof is administered and (ii) 2 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is not administered; and (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered and (ii) 2 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered; followed by (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered and (ii) 3 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered; and (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a

pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is administered and (ii) 3 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered; followed by (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered.

[0039] In some aspects, the 28-day dosing cycle is repeated up to a total of 24 consecutive 28-day dosing cycles.

[0040] In some aspects, only Compound B, or a pharmaceutically acceptable salt form thereof, is administered for a lead-in period prior to the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is the same or lower than the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above.

[0041] In some aspects, one or both of Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, is administered for a lead-in period prior to the first of the 28-day dosing cycles discussed above at a lower dose than the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is the same as the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is lower than the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is the same as the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is lower than the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above.

[0042] In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 1 mg to about 5 mg per day. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period about 1 mg per day. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period about 2 mg per day. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period about 3 mg per day.

[0043] In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof,

administered in the lead-in period is about 5 mg to about 25 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg to about 20 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg to about 15 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 10 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 15 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 20 mg per day.

[0044] In some aspects, the Compound B administered in the lead-in period is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 5 mg to about 40 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 5 mg to about 30 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 5 mg to about 25 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 7 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 13 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 20 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 27 mg per day.

[0045] In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and/or the Compound B, or a pharmaceutically acceptable salt thereof, is administered daily during the lead-in period. In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and/or Compound B, or a pharmaceutically acceptable salt thereof, is administered once daily during the lead-in period. In some aspects, Compound A, or pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered orally during the lead-in period.

[0046] In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in the same or different dosage forms during the lead-in period. In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in the same dosage form during the lead-in period. In some aspects, the dosage form is a capsule.

[0047] In some aspects, Compound A, or a pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in different dosage forms during the lead-in period. In some aspects, Compound A is administered before, concomitantly, or subsequently to the administering of Compound B, or a pharmaceutically acceptable salt form thereof

during the lead-in period. In some aspects, the dosage form of Compound A, or a pharmaceutically acceptable salt thereof, is a capsule. In some aspects, he dosage form of Compound B, or a pharmaceutically acceptable salt form thereof, is a capsule

[0048] In some aspects, the lead-in period begins 21 days before the first 28-day dosing cycle. In some aspects, the lead-in period begins 14 days before the first 28-day dosing cycle. In some aspects, the lead-in period begins 10 days before the first 28-day dosing cycle. In some aspects, the lead-in period begins 7 days before the first 28-day dosing cycle.

[0049] In some aspects, methods of treating a patient having a solid tumor comprising administering once daily 2 mg Compound A as free base and 15 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

[0050] In some aspects, methods of treating a patient having a solid tumor comprising administering once daily 2 mg Compound A as free base and 20 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein

[0051] In some aspects, methods of treating a patient having a solid tumor comprising a 7 day cycle that comprises (a) administering once daily 3 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form for 5 consecutive days; followed by (b) administering no Compound A or Compound B for 2 consecutive days, are described herein.

[0052] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering once daily 3 mg Compound A free base and 10 mg Compound B, or a pharmaceutically acceptable salt form thereof, for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 3 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days, are described herein.

[0053] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering a total of 2 mg Compound A free base divided over two doses per day and 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering 1 mg of Compound A free base twice daily and 15 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein.

[0054] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically

acceptable salt form thereof, once daily for 14 consecutive days; followed by

2. (b) a 7 day treatment cycle that comprises (i) administering once daily 1 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein.

[0055] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 2 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein.

[0056] In some aspects, methods of treating a patient having a solid tumor comprising a 7 day cycle that comprises (a) administering once daily 4 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form for 5 consecutive days; followed by (b) administering no Compound A or Compound B for 2 consecutive days are described herein.

[0057] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 3 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are provided herein.

[0058] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 4 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein.

[0059] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering a total of 3 mg Compound A free base divided over two doses per day and 15 mg Compound B, or a pharmaceutically acceptable salt form

thereof, once daily, for 14 consecutive days; followed by

2. (b) a 7 day treatment cycle that comprises (i) administering once daily 3 mg of Compound A free base and 15 mg of Compound B, or a pharmaceutically acceptable salt form therefore, for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are provided herein.

[0060] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering a total of 4 mg Compound A free base divided over two doses per day and 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 4 mg of Compound A free base and 15 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein.

[0061] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 2 mg Compound A as free base and once daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

[0062] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 4 mg Compound A as free base and once daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

[0063] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 6 mg Compound A as free base and once daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

[0064] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 2 mg Compound A as free base and twice daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

[0065] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 4 mg Compound A as free base and twice daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

[0066] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 6 mg Compound A as free base and twice daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein.

Definitions

[0067] To facilitate understanding of the disclosure set forth herein, a number of terms are defined

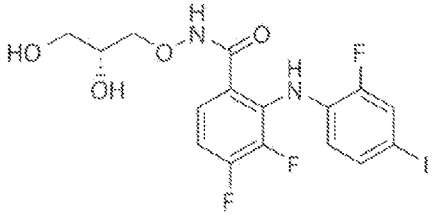
below.

[0068] Generally, the nomenclature used herein and the laboratory procedures in organic chemistry, medicinal chemistry, and pharmacology described herein are those well-known and commonly employed in the art. Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs.

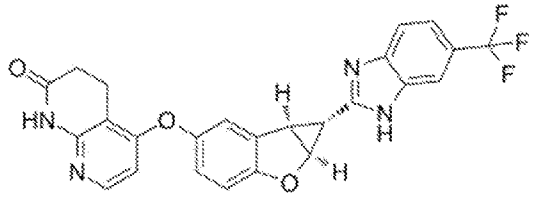
[0069] In this specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. The terms "a" (or "an"), as well as the terms "one or more," and "at least one" can be used interchangeably herein. In certain aspects, the term "a" or "an" means "single." In other aspects, the term "a" or "an" includes "two or more" or "multiple."

[0070] Furthermore, "and/or" where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term "and/or" as used in a phrase such as "A and/or B" herein is intended to include "A and B," "A or B," "A" (alone), and "B" (alone). Likewise, the term "and/or" as used in a phrase such as "A, B, and/or C" is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0071] The terms "Compound A", "mirdametinib", and "PD-0325901" refer to the single enantiomer N-[(2R)-2,3-dihydroxypropoxy]-3,4-difluoro-2-(2-fluoro-4-iodoanilino)benzamide. The structure of Compound A is as follows:



[0072] The terms "Compound B", "lifirafenib", and "BGB-283" refer to the single enantiomer 5-(((1R,1aS,6bR)-1-(6-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-5-yl)oxy)-3,4-dihydro-1,8-naphthyrdin-2(1H)-one. The structure of Compound B is below:



[0073] The term "subject" refers to an animal, including, but not limited to, a primate (e.g., human), cow, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms "subject" and "patient" are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject.

[0074] As used herein, the terms "treat," "treated," and "treating" mean both therapeutic treatment

and prophylactic or preventative measures wherein the object is to prevent or slow down (lessen) an undesired physiological condition, disorder, or disease, or obtain beneficial or desired clinical results. Thus, those in need of treatment include those already diagnosed with or suspected of having the disorder. Beneficial or desired clinical results include, but are not limited to, alleviation of symptoms; diminishment of the extent of a condition, disorder, or disease; stabilized (i.e., not worsening) state of condition, disorder, or disease; delay in onset or slowing of condition, disorder, or disease progression; amelioration of the condition, disorder, or disease state or remission (whether partial or total), whether detectable or undetectable; an amelioration of at least one measurable physical parameter, not necessarily discernible by the patient; or enhancement or improvement of condition, disorder, or disease. Treatment includes eliciting a clinically significant response without excessive levels of side effects. Treatment also includes prolonging survival as compared to expected survival if not receiving treatment. The term "therapeutically effective amount" is meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of a disorder, disease, or condition being treated. The term "therapeutically effective amount" also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician.

[0075] In certain aspects, a subject is successfully "treated" for cancer, *e.g.*, lung cancer or ovarian cancer, according to the methods of the present invention if the patient shows one or more of the following: a reduction in the number of or complete absence of cancer cells; relief of one or more symptoms associated with the specific cancer; reduced morbidity and mortality; improvement in quality of life; increased progression-free survival (PFS), disease-free survival (DFS), overall survival (OS), metastasis-free survival (MFS), complete response (CR), minimal residual disease (MRD), partial response (PR), stable disease (SD), a decrease in progressive disease (PD), an increased time to progression (TTP), or any combination thereof. In some aspects, nationally or internationally accepted standards of treatment outcomes in a given cancer can be used to determine whether the combination of effective amounts of mirdametinib and lifirafenib meets any of these particular endpoints (*e.g.*, CR, PFS, PR).

[0076] The terms "pharmaceutically acceptable carrier," "pharmaceutically acceptable excipient," "physiologically acceptable carrier," or "physiologically acceptable excipient" refer to a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material. In one aspect, each component is "pharmaceutically acceptable" in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. See Remington: The Science and Practice of Pharmacy, 21st Edition, Lippincott Williams & Wilkins: Philadelphia, PA, 2005; Handbook of Pharmaceutical Excipients, 5th Edition, Rowe et al., Eds., The Pharmaceutical Press and the American Pharmaceutical Association: 2005; and Handbook of Pharmaceutical Additives, 3rd Edition, Ash and Ash Eds., Gower Publishing Company: 2007; Pharmaceutical Preformulation and Formulation, Gibson Ed., CRC Press LLC: Boca Raton, FL, 2004. Excipients can include, for example: antiadherents, antioxidants, binders, coatings, compression aids, disintegrants, dyes (colors), emollients, emulsifiers, fillers (diluents), film formers or coatings, flavors, fragrances, glidants (flow enhancers), lubricants, preservatives, printing inks, sorbents, suspensing or dispersing agents, sweeteners, and waters of hydration. Exemplary excipients include, but are not limited to: butylated hydroxytoluene (BHT), calcium carbonate, calcium phosphate (dibasic), calcium stearate, croscarmellose, crosslinked

polyvinyl pyrrolidone, citric acid, crospovidone, cysteine, ethylcellulose, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, maltitol, mannitol, methionine, methylcellulose, methyl paraben, microcrystalline cellulose, polyethylene glycol, polyvinyl pyrrolidone, povidone, pregelatinized starch, propyl paraben, retinyl palmitate, shellac, silicon dioxide, sodium carboxymethyl cellulose, sodium citrate, sodium starch glycolate, sorbitol, starch (corn), stearic acid, sucrose, talc, titanium dioxide, vitamin A, vitamin E, vitamin C, and xylitol.

[0077] The term "pharmaceutical composition," as used herein, represents a composition containing a compound described herein formulated with a pharmaceutically acceptable excipient, and can be manufactured or sold with the approval of a governmental regulatory agency as part of a therapeutic regimen for the treatment of disease in a mammal. Pharmaceutical compositions can be formulated, for example, for oral administration in unit dosage form (e.g., a tablet, capsule, caplet, gelcap, or syrup); for topical administration (e.g., as a cream, gel, lotion, or ointment); for intravenous administration (e.g., as a sterile solution free of particulate emboli and in a solvent system suitable for intravenous use); for intrathecal injection; for intracerebroventricular injections; for intraparenchymal injection; or in any other pharmaceutically acceptable formulation.

[0078] The term "pharmaceutically-acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of Compound A or Compound B. These salts can be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting a purified compound of the invention in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed during subsequent purification. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, napthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", J. Pharm. Sci. 66:1-19).

[0079] The pharmaceutically acceptable salts of the subject compounds include the conventional nontoxic salts or quaternary ammonium salts of the compounds, e.g., from non-toxic organic or inorganic acids. For example, such conventional nontoxic salts include those derived from inorganic acids such as hydrochloride, hydrobromic, sulfuric, sulfamic, phosphoric, nitric, and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, palmitic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicyclic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like.

[0080] In certain aspects, the compounds of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically-acceptable salts" in these instances refers to the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention. These salts can likewise be prepared in situ in the administration vehicle or the dosage form manufacturing process, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine,

ethanolamine, diethanolamine, piperazine and the like. (See, e.g., Berge et al., supra).

[0081] The terms "about" or "approximately" means within a range of an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain aspects, the term "about" or "approximately" means within 1, 2, 3, or 4 standard deviations. In some aspects, the term "about" or "approximately" means a quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length that varies by as much as 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1% to a reference quantity, level, value, number, frequency, percentage, dimension, size, amount, weight or length.

[0082] As used herein, the term "administration" refers to the administration of a composition (e.g., a compound or a preparation that includes a compound as described herein) to a subject or system. Administration to an animal subject (e.g., to a human) can be by any appropriate route, such as one described herein.

[0083] The terms "drug," "therapeutic agent," and "chemotherapeutic agent" refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease.

[0084] The terms "co-administration", "co-administering", or "co-administered" refer to administering a combination of therapeutic agents, such as, for example, a combination of mirdametinib and lifirafenib. The combination can be administered as two separate entities, such as, for example, in separate capsules or tablets, or as a single combination entity, such as, for example, in the same capsule or tablet. One therapeutic agent (*e.g.*, Compound A, or a pharmaceutically acceptable salt form thereof) can be administered before, concomitantly, or subsequently to the administering of the other therapeutic agent (e.g., Compound B, or a pharmaceutically acceptable salt form thereof) to the subject.

[0085] It is understood that wherever aspects are described herein with the language "comprising," otherwise analogous aspects described in terms of "consisting of" and/or "consisting essentially of" are also provided.

[0086] The details of one or more aspects are set forth in the description below. Other features, objects, and advantages will be apparent from the description and from the claims.

DETAILED DESCRIPTION OF THE INVENTION

[0087] The present inventors have developed a method of treating certain cancers by co-administering mirdametinib and lifirafenib. Also disclosed are dosage forms comprising these compounds for co-administration.

[0088] In some aspects, the present disclosure provides a method of treating a patient having a solid tumor comprising co-administering to the patient a therapeutically effective amount of Compound A or a pharmaceutically acceptable salt form thereof, and a therapeutically effective amount of Compound B or a pharmaceutically acceptable salt form thereof.

[0089] In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt form thereof, is about 1 mg to about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt form thereof, is about 1 mg to about 12 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt form thereof, is about 1 mg to about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 1 mg to about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt form thereof, is about 1 mg, about 2 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 11 mg, about 12 mg, about 13 mg, about 14 mg, or about 15 mg.

[0090] In some aspects, Compound A is in free base form.

[0091] In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 35 mg, about 5 mg to about 30 mg, about 5 mg to about 25 mg, about 5 mg to about 20 mg, about 5 mg to about 15 mg, or about 5 mg to about 10 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg to about 35 mg, about 10 mg to about 30 mg, about 10 mg to about 25 mg, about 10 mg to about 20 mg, or about 10 mg to about 15 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg to about 40 mg, about 15 mg to about 35 mg, about 15 mg to about 30 mg, about 15 mg to about 25 mg, or about 15 mg to about 20 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 40 mg, about 20 mg to about 35 mg, about 20 mg to about 30 mg, or about 20 mg to about 25 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 25 mg to about 40 mg, about 25 mg to about 35 mg, or about 25 mg to about 30 mg per day. In some aspects, the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 2 mg, about 3 mg, about 4 mg, about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, about 35 mg, about 36 mg, about 37 mg, about 38 mg, about 39 mg, or about 40 per day.

[0092] In some aspects, the therapeutically effective amount of Compound A is about 1 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 15 mg per day.

[0093] In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 35 mg per day.

[0094] In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form

thereof, is about 5 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 35 mg per day.

[0095] In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 35 mg per day.

[0096] In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg to about 40 mg per day.

[0097] In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 1 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day, In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 15 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a

pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 5 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 10 mg per day.

[0098] In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt. In some aspects, the maleate salt is a sesqui-maleate salt.

[0099] In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 5 mg to about 35 mg per day. In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 5 mg to about 30 mg, about 5 mg to about 25 mg, about 5 mg to about 20 mg, about 5 mg to about 15 mg, or about 5 mg to about 10 mg per day. In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 10 mg to about 30 mg, about 10 mg to about 25 mg, about 10 mg to about 20 mg, or about 10 mg to about 15 mg per day. In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 15 mg to about 30 mg, about 15 mg to about 25 mg, or about 15 mg to about 20 mg per day. In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 20 mg to about 30 mg or about 20 mg to about 25 mg per day. In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 25 mg to about 30 mg per day. In some aspects, the therapeutically effective amount of the maleate salt form of Compound B is about 5 mg, about 6 mg, about 7 mg, about 8 mg, about 9 mg, about 10 mg, about 11 mg, about 12 mg, about 13 mg, about 14 mg, about 15 mg, about 16 mg, about 17 mg, about 18 mg, about 19 mg, about 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, or about 35 mg.

[0100] In some aspects, the therapeutically effective amount of Compound A is about 1 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 5 mg to about 10 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 1 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 7 mg per day.

[0101] In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 10 mg to about 30 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 13 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 2 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 27 mg per day.

[0102] In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 15 mg to about 40

mg per day. In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 3 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 34 mg per day.

[0103] In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 20 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 4 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 27 mg per day.

[0104] In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 25 mg to about 40 mg per day. In some aspects, the therapeutically effective amount of Compound A is about 5 mg per day and the therapeutically effective amount of Compound B as a maleate salt is about 34 mg per day.

[0105] In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 1 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day, In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 2 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 3 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 4 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 13 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective

amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 7 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 8 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 13 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 7 mg per day. In some aspects, the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt thereof, is about 12 mg per day and the therapeutically effective amount of Compound B, or a pharmaceutically acceptable salt form thereof, is about 13 mg per day.

[0106] In some aspects, Compound A, or a pharmaceutically acceptable salt form thereof is administered once per day. In some aspects, Compound B, or a pharmaceutically acceptable salt form thereof, is administered once per day.

[0107] In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered in the same or different dosage forms. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered in different dosage forms. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, is administered before, concomitantly, or subsequently to the administering of Compound B or a pharmaceutically acceptable salt form thereof.

[0108] In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered in the same dosage form. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered orally. In some aspects, the dosage form comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is a capsule.

[0109] In some aspects, the present disclosure provides a pharmaceutical composition comprising:

1. a. Compound A, or a pharmaceutically acceptable salt form thereof;
2. b. Compound B, or a pharmaceutically acceptable salt form thereof;
3. c. a filler;
4. d. a disintegrant; and
5. e. a lubricant.

[0110] In some aspects, the pharmaceutical composition comprises about 0.8 mg to about 1.2 mg of Compound A. In some aspects, the pharmaceutical composition comprises about 1.5 mg to about 2.5 mg of Compound A. In some aspects, the pharmaceutical composition comprises about 0.8 mg, about 0.9 mg, about 1 mg, about 1.1 mg, about 1.2 mg, about 1.3 mg, about 1.4 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 2.1 mg, about 2.2 mg, about 2.3 mg, about 2.4 mg, or about 2.5 mg of Compound A.

[0111] In some aspects, the pharmaceutical composition comprises about 20 mg to about 35 mg of

the maleic acid salt of Compound B. In some aspects, the pharmaceutical composition comprises about 22 to about 34 mg of the maleic acid salt of Compound B. In some aspects, the pharmaceutical composition comprises about 23 mg to about 29 mg of the maleic acid salt of Compound B. In some aspects, the pharmaceutical composition comprises about 25 mg to about 28 mg of the maleic acid salt of Compound B. In some aspects, the pharmaceutical composition comprises 20 mg, about 21 mg, about 22 mg, about 23 mg, about 24 mg, about 25 mg, about 26 mg, about 27 mg, about 28 mg, about 29 mg, about 30 mg, about 31 mg, about 32 mg, about 33 mg, about 34 mg, or about 35 mg of the maleic acid salt of Compound B.

[0112] In some aspects, the pharmaceutical composition comprises a filler. In some aspects, the pharmaceutical composition comprises about 70 wt/wt% to about 90 wt/wt% filler. In some aspects, the pharmaceutical composition comprises about 72.5 wt/wt % to about 85 wt/wt % filler. In some aspects, the pharmaceutical composition comprises about 80 wt/wt % to about 90 wt/wt % filler. In some aspects, the pharmaceutical composition comprises about 70 wt/wt %, about 72.5 wt/wt %, about 75 wt/wt %, about 80 wt/wt %, about 85 wt/wt %, or about 90 wt/wt % filler.

[0113] In some aspects, the filler is selected from a group consisting of microcrystalline cellulose, lactose, mannitol, starch, dibasic calcium phosphate, and combinations thereof. In some aspects, the filler comprises microcrystalline cellulose. In some aspects, the microcrystalline cellulose is silicified microcrystalline cellulose. In some aspects, the pharmaceutical composition comprises about 70 wt/wt% to about 90 wt/wt% silicified microcrystalline cellulose. In some aspects, the pharmaceutical composition comprises about 72.5 wt/wt % to about 85 wt/wt % silicified microcrystalline cellulose. In some aspects, the pharmaceutical composition comprises about 80 wt/wt % to about 90 wt/wt % silicified microcrystalline cellulose. In some aspects, the pharmaceutical composition comprises about 70 wt/wt %, about 72.5 wt/wt %, about 75 wt/wt %, about 80 wt/wt %, about 85 wt/wt %, or about 90 wt/wt % silicified microcrystalline cellulose.

[0114] In some aspects, the pharmaceutical composition comprises about 3.5 wt/wt % to about 4.5 wt/wt % disintegrant. In some aspects, the pharmaceutical composition comprises about 3.5 wt/wt %, about 4.6 wt/wt %, about 3.7 wt/wt %, about 3.8 wt/wt %, about 3.9 wt/wt %, about 4 wt/wt %, about 4.1 wt/wt %, about 4.2 wt/wt %, about 4.3 wt/wt %, about 4.4 wt/wt %, or about 4.5 wt/wt % disintegrant.

[0115] In some aspects, the disintegrant sis selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, alginic acid, and combinations thereof. In some aspects, the disintegrant comprises croscarmellose sodium. In some aspects, the pharmaceutical composition comprises about 3.5 wt/wt % to about 4.5 wt/wt % croscarmellose sodium. In some aspects, the pharmaceutical composition comprises about 3.5 wt/wt %, about 4.6 wt/wt %, about 3.7 wt/wt %, about 3.8 wt/wt %, about 3.9 wt/wt %, about 4 wt/wt %, about 4.1 wt/wt %, about 4.2 wt/wt %, about 4.3 wt/wt %, about 4.4 wt/wt %, or about 4.5 wt/wt % croscarmellose sodium.

[0116] In some aspects, the pharmaceutical composition comprises about 1.5 wt/wt % to about 5 wt/wt % lubricant. In some aspects, the pharmaceutical composition comprises about 1.5 wt/wt %, about 2 wt/wt %, about 2.5 wt/wt %, about 3 wt/wt %, about 3.5 wt/wt %, about 4 wt/wt %, about 4.5 wt/wt %, or about 5 wt/wt % lubricant.

[0117] In some aspects, the lubricant is selected from the group consisting of sodium stearyl fumarate, magnesium stearate, glyceryl dibehenat, talc, and combinations thereof. In some aspects, the lubricant comprises sodium stearyl fumarate or magnesium stearate. In some aspects, the

pharmaceutical composition comprises about 1.5 wt/wt %, about 2 wt/wt %, about 2.5 wt/wt %, about 3 wt/wt %, about 3.5 wt/wt %, about 4 wt/wt %, about 4.5 wt/wt %, or about 5 wt/wt % sodium stearyl fumarate. In some aspects, the pharmaceutical composition comprises about 1.5 wt/wt %, about 2 wt/wt %, about 2.5 wt/wt %, about 3 wt/wt %, about 3.5 wt/wt %, about 4 wt/wt %, about 4.5 wt/wt %, or about 5 wt/wt % magnesium stearate.

[0118] In some aspects, the pharmaceutical composition to be orally administered. In some aspects, the pharmaceutical composition is a tablet or capsule. In some aspects, the pharmaceutical composition is a capsule.

[0119] In some aspects, the capsule comprises about 1 mg of Compound A and about 7 mg of the maleic acid salt of Compound B, wherein each component of the capsule is as follows:

1. a. about 0.8 wt/wt % to about 1.2 wt/wt % of Compound A;
2. b. about 6 wt/wt % to about 8 wt/wt % of the maleic acid salt of Compound B;
3. c. about 80 wt/wt % to about 90 wt/wt % of silicified microcrystalline cellulose;
4. d. about 3.5 wt/wt % to about 4.5 wt/wt % of croscarmellose sodium;
5. e. about 1.5 wt/wt % to about 5.0 wt/wt % of sodium stearyl fumarate; and
6. f. a gelatin capsule which encapsulates components a-e.

[0120] In some aspects, the capsule comprises about 2 mg of Compound A and about 27 mg of the maleic acid salt of Compound B, wherein each component of the capsule is as follows:

1. a. about 0.8 wt/wt % to about 1.3 wt/wt % of Compound A;
2. b. about 12.3 wt/wt % to about 15.0 wt/wt % of the maleic acid salt of Compound B;
3. c. about 72.5 wt/wt % to about 85 wt/wt % of silicified microcrystalline cellulose;
4. d. about 3.5 wt/wt % to about 4.5 wt/wt % of croscarmellose sodium;
5. e. about 1.5 wt/wt % to about 5.0 wt/wt % of sodium stearyl fumarate; and
6. f. a gelatin capsule which encapsulates components a-e.

[0121] In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered to treat a patient having a solid tumor. In some aspects, the solid tumor is selected from the group consisting of malignant peripheral nerve sheath tumor, biliary tract cancer, breast cancer, cholangiocarcinoma, urothelial cancer, uterine neoplasm, lung adenocarcinoma, squamous non-small cell lung cancer, non-squamous non-small cell lung cancer, gastric cancer, sarcoma, bladder cancer, head and neck cancer, small cell lung cancer, endometrial cancer, esophageal cancer, adenoid cystic carcinoma, gallbladder cancer, colorectal cancer, thyroid cancer, hepatocellular cancer, prostate cancer, oral cancer, cervical cancer, pancreatic carcinoma, ovarian cancer, melanoma, and serous carcinoma to the peritoneum. In some aspects, the patient has non-small cell lung cancer. In some aspects, the patient has endometrial cancer. In some aspects, the patient has ovarian cancer. In some aspects, the patient has low grade serous ovarian cancer. In some aspects, the patient has a confirmed mutation in one or more of KRAS, NRAS, HRAS, BRAF, NF1, MEK1, and MEK2. In some aspects, the patient has a confirmed mutation in RASA1 and/or RAF1.

[0122] In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising: (a) 21 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered; and (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) 21 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof are both administered; followed by (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 2 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof are administered; and (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 2 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered; followed by (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 3 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof are administered; and (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered. In some aspects, Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, are both administered and (ii) 3 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered; followed by (b) 7 days in which neither Compound A or a pharmaceutically acceptable salt form thereof, nor Compound B or a pharmaceutically acceptable salt form thereof, is administered.

[0123] In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt

form thereof, is administered on a 28-day dosing cycle comprising: (a) 21 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof form, is administered; and (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising (a) 21 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered; followed by (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof is administered and (ii) 2 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is not administered; and (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 5 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered and (ii) 2 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered; followed by (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered and (ii) 3 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is administered; and (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is not administered. In some aspects, the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is administered on a 28-day dosing cycle comprising (a) three 7-day periods each comprising (i) 4 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form of thereof, is administered and (ii) 3 days in which the pharmaceutical composition comprising

Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered; followed by (b) 7 days in which the pharmaceutical composition comprising Compound A or a pharmaceutically acceptable salt form thereof, and Compound B or a pharmaceutically acceptable salt form thereof, is not administered.

[0124] In some aspects, the 28-day dosing cycle is repeated up to a total of 24 consecutive 28-day dosing cycles.

[0125] In some aspects, only Compound B, or a pharmaceutically acceptable salt form thereof, is administered for a lead-in period prior to the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is the same or lower than the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above.

[0126] In some aspects, one or both of Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, is administered for a lead-in period prior to the first of the 28-day dosing cycles discussed above at a lower dose than the therapeutically effective amount of Compound A, or a pharmaceutically acceptable salt form thereof, and Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is the same as the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is lower than the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is the same as the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is lower than the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered during the first of the 28-day dosing cycles discussed above.

[0127] In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 1 mg to about 5 mg per day. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period about 1 mg per day. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period about 2 mg per day. In some aspects, the amount of Compound A, or a pharmaceutically acceptable salt thereof, administered in the lead-in period about 3 mg per day.

[0128] In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg to about 25 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg to about 20 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg to about 15

mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 5 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 10 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 15 mg per day. In some aspects, the amount of Compound B, or a pharmaceutically acceptable salt thereof, administered in the lead-in period is about 20 mg per day.

[0129] In some aspects, the Compound B administered in the lead-in period is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 5 mg to about 40 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 5 mg to about 30 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 5 mg to about 25 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 7 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 13 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 20 mg per day. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 27 mg per day.

[0130] In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and/or the Compound B, or a pharmaceutically acceptable salt thereof, is administered daily during the lead-in period. In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and/or Compound B, or a pharmaceutically acceptable salt thereof, is administered once daily during the lead-in period. In some aspects, Compound A, or pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered orally during the lead-in period.

[0131] In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in the same or different dosage forms during the lead-in period. In some aspects, the Compound A, or a pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in the same dosage form during the lead-in period. In some aspects, the dosage form is a capsule.

[0132] In some aspects, Compound A, or a pharmaceutically acceptable salt thereof, and Compound B, or a pharmaceutically acceptable salt form thereof, are administered in different dosage forms during the lead-in period. In some aspects, Compound A is administered before, concomitantly, or subsequently to the administering of Compound B, or a pharmaceutically acceptable salt form thereof during the lead-in period. In some aspects, the dosage form of Compound A, or a pharmaceutically acceptable salt thereof, is a capsule. In some aspects, he dosage form of Compound B, or a pharmaceutically acceptable salt form thereof, is a capsule

[0133] In some aspects, the lead-in period begins 21 days before the first 28-day dosing cycle. In

some aspects, the lead-in period begins 14 days before the first 28-day dosing cycle. In some aspects, the lead-in period begins 10 days before the first 28-day dosing cycle. In some aspects, the lead-in period begins 7 days before the first 28-day dosing cycle.

[0134] In some aspects, methods of treating a patient having a solid tumor comprising administering once daily 2 mg Compound A as free base and 15 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is administered as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, is about 20 mg.

[0135] In some aspects, methods of treating a patient having a solid tumor comprising administering once daily 2 mg Compound A as free base and 20 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is administered as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg

[0136] In some aspects, methods of treating a patient having a solid tumor comprising a 7 day cycle that comprises (a) administering once daily 3 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form for 5 consecutive days; followed by (b) administering no Compound A or Compound B for 2 consecutive days, are described herein. In some aspects, the Compound B is administered as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg

[0137] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering once daily 3 mg Compound A free base and 10 mg Compound B, or a pharmaceutically acceptable salt form thereof, for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 3 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days, are described herein. In some aspects, the Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 13 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 27 mg

[0138] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering a total of 2 mg Compound A free base divided

over two doses per day and 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by

2. (b) a 7 day treatment cycle that comprises (i) administering 1 mg of Compound A free base twice daily and 15 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein. In some aspects, the Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 13 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 20 mg

[0139] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 1 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein. In some aspects, the Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 20 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 27 mg

[0140] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 2 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein. In some aspects, Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt,

administered in the lead-in period is about 20 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 27 mg.

[0141] In some aspects, methods of treating a patient having a solid tumor comprising a 7 day cycle

that comprises (a) administering once daily 4 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form for 5 consecutive days; followed by (b) administering no Compound A or Compound B for 2 consecutive days are described herein. In some aspects, the Compound B is administered as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, is about 27 mg

[0142] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 3 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are provided herein. In some aspects, Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 20 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 27 mg

[0143] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 4 mg of Compound A free base and 20 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein. In some aspects, Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 20 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 27 mg.

[0144] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering a total of 3 mg Compound A free base divided over two doses per day and 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily, for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 3 mg of Compound A free base and 15 mg of Compound B, or a pharmaceutically acceptable salt form therefore, for

5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are provided herein. In some aspects, Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 13 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 20 mg.

[0145] In some aspects, methods of treating a patient having a solid tumor comprising:

1. (a) a lead-in period that comprises administering a total of 4 mg Compound A free base divided over two doses per day and 15 mg Compound B, or a pharmaceutically acceptable salt form thereof, once daily for 14 consecutive days; followed by
2. (b) a 7 day treatment cycle that comprises (i) administering once daily 4 mg of Compound A free base and 15 mg of Compound B, or a pharmaceutically acceptable salt form therefore, once daily for 5 consecutive days; followed by (ii) administering no Compound A or Compound B for 2 consecutive days are described herein. In some aspects, Compound B is administered in both the lead-in period and treatment cycle as a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt, which can be a sesqui-maleate salt. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the lead-in period is about 13 mg. In some aspects, the amount of Compound B as a maleate salt, which can be a sesqui-maleate salt, administered in the treatment period is about 20 mg.

[0146] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 2 mg Compound A as free base and once daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt which can be a sesqui-maleate salt. In some aspects, the amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg.

[0147] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 4 mg Compound A as free base and once daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt which can be a sesqui-maleate salt. In some aspects, the amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg.

[0148] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 6 mg Compound A as free base and once daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt which can be a sesqui-maleate salt. In some aspects, the amount of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg.

[0149] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 2 mg Compound A as free base and twice daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt which can be a sesqui-maleate salt. In some aspects, each dose of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg.

[0150] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 4 mg Compound A as free base and twice daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt which can be a sesqui-maleate salt. In some aspects, each dose of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg

[0151] In some aspects, methods of treating a patient having a solid tumor comprising administering twice daily 6 mg Compound A as free base and twice daily 5 mg Compound B, or a pharmaceutically acceptable salt thereof, are described herein. In some aspects, Compound B is a pharmaceutically acceptable salt form. In some aspects, the pharmaceutically acceptable salt form is a maleate salt which can be a sesqui-maleate salt. In some aspects, each dose of Compound B, as a maleate salt, which can be a sesqui-maleate salt, is about 7 mg

EXAMPLES

[0152] It is understood that the examples and aspects described herein are for illustrative purposes only.

Example 1: Combination Effect of Compound A and Compound B in KRAS Mutant NSCLC Cell Lines

[0153] A cell viability assay was carried out for combinatorial treatment of Compound A (mirdametinib) and Compound B (lifirafenib maleate) in human non-small cell lung cancer and colorectal cancer cell lines harboring K-RAS mutations (A549, NCI-H2122, NCI-H23, Sk-Lu-1, Calu-1, NCI-H1299, NCI-H358).

[0154] The mutant cell lines used were grown according to standard cell culture techniques, with varying concentrations from 0-10 μM of mirdametinib and lifirafenib diluted with dimethyl sulfoxide (54686.500, biomol). Cell lines were grown in RPMI1640 medium (22400-089, GIBCO®), McCoy's 5a (16600-082, GIBCO®) or, DMEM (11965-092, GIBCO®), each with 10% fetal bovine serum (SH30084.03, Hyclone™) and 1% penicillin-streptomycin (15140-148, Invitrogen).

[0155] Briefly, for each experiment, about 3,000 cells were plated in each well of a 96-well plate and the plates were incubated overnight. Varying levels of mirdametinib and lifirafenib were added to each well, and cells were incubated for three days. Cell viability was determined according to manufacturer

instructions using CellTiter-Glo® Luminescent Cell Viability Assay (G7570, Promega™), with a BMG LABTECH PERAstar FS plate reader.

Results

[0156] Compound A (mirdametinib) and Compound B maleate (lifirafenib maleate) synergistically inhibited the proliferation of multiple non-small cell lung cancer and colorectal cell lines harboring K-RAS mutations. In 7 of the 8 cell lines evaluated, the combination of mirdametinib and lifirafenib maleate demonstrated synergistic cell killing activity versus either compound alone.

Table 1

Cell line	KRAS Mutation	Maximum EC_{50} shift
Calu-6	Q61K	59 fold decrease
A549	G12S	11 fold decrease
NCI-H2122	G12C	21 fold decrease
NCI-H23	G12C	22 fold decrease
Sk-Lu-1	G12D	32 fold decrease
NCI-H1299	Q61K	16 fold decrease
NCI-H358	G12C	18 fold decrease
Calu-1	G12C	No shift

[0157] No shift: less than 2 fold EC_{50} shift was detected by combining Compound B maleate with Compound A in the indicated cell line.

Example 2: Efficacy Study of Compound A and Compound B in Calu-6 K-RAS Mutated Human Xenograft Lung Adenocarcinoma Model in Balb/c Nude Mice

1. Study Objective

[0158] To determine the effects of Compound B Maleate and Compound A, alone or in combination, on growth of subcutaneous Calu-6 tumors which harbor a K-RAS mutation in Balb/c nude mice in an Efficacy Study.

2. Study Design

[0159] Experimental designs for the Efficacy study are illustrated in Table 2.

Table 2. Experimental groups in the Efficacy Study.

Group	Mouse	Compound B maleate* (mg/kg)	Compound A (mg/kg)	Route/Vol	Frequency	Initiation	Termination
1	10	0	0	p.o./10 ml/kg	BID**	120-150 mm3	<2000 mm^3 in Veh***
2	10	2.5	0	p.o./10 ml/kg	BID**	120-150 mm3	<2000 mm^3 in Veh***
3	10	1.25	0.5	p.o./10 ml/kg	BID**	120-150 mm3	<2000 mm^3 in Veh***
4	10	1.25	1.5	p.o./10 ml/kg	BID**	120-150 mm3	<2000 mm^3 in Veh***
5	10	1.25	5	p.o./10 ml/kg	BID**	120-150 mm3	<2000 mm^3 in Veh***

*Dose for Compound B maleate is based on the free base form.
**For both compounds
**Mean tumor volume of the vehicle-treated group (Group 1)

3. Materials

3.1 Animals and Housing Condition

[0160] 6-8 week old female Balb/c nude mice with a mean body weight of about 18 g were housed under standard laboratory conditions and given free access to sterile food and water.

3.2 Cells

[0161] Calu-6 cell lines were cultured in Minimal Essential Medium (ThermoFisher, #11095080), with phosphate buffered saline (Gibco®, #C20012500BT), non-essential amino acids (ThermoFisher, #11140-050), fetal bovine serum (ExCell™ Bio, #FND500), Matrigel® (Corning, #354234) and penicillin/streptomycin (ThermoFisher, #15140122).

3.4 Formulation Method

[0162] The required amount of methylcellulose was slowly added to purified water (approximately 60% to 80% of total volume) with continuous stirring until a clear solution was obtained by visual inspection. Next, purified water was added to reach the final volume and the mixture was stirred until a homogenous solution was obtained by visual inspection. This solution was autoclaved. Tween-80 was then be added to achieve final concentration of 1% (v/v) and solution was stored at 4°C.

[0163] Formulation of dosing solutions for Group 1 to Group 5 is illustrated in Table 3 below. Both compounds were formulated as homogenous suspension and prepared once weekly, and stored at 4°C in dark. Required amount of test article was added to a volume slightly smaller than the calculated volumes of vehicle solution with stirring. Vehicle solution was added to reach the final volume and the mixture was stirred for at least 10 minutes until a homogenous suspension was obtained by visual inspection. The homogenous dosing solution for each group was aliquoted for each dosing day. On the day of dosing, the tubes with aliquoted dosing solutions were vortexed or inverted until a homogenous suspension was achieved before each dosing.

Table 3. Formulation of dosing solutions

Group	Drug Doses	Dosing Solution**	Dosing Volume	Frequency
1	vehicle solution	vehicle solution	10 ml/kg	BID
2	0.25 mg/ml Compound B	0.34 mg/ml Compound B maleate**	10 ml/kg	BID
3	0.125 mg/ml Compound B* + 0.05 mg/ml Compound A	0.17 mg/ml Compound B maleate** + 0.05 mg/ml Compound A	10 ml/kg	BID
4	0.125 mg/ml Compound B* + 0.15 mg/ml Compound A	0.17 mg/ml Compound B maleate** + 0.15 mg/ml Compound A	10 ml/kg	BID
5	0.125 mg/ml Compound B* + 0.5 mg/ml Compound A	0.17 mg/ml Compound B maleate** + 0.5 mg/ml Compound A	10 ml/kg	BID

*The required dose of the free base form of Compound B
**The calculated concentration of Compound B maleate in the dosing solution = Dose of free base x 652.52/478.43

4. Experimental Methods and Procedures:

4.1 Cell Culture

[0164] Calu-6 tumor cells were cultured in MEM medium supplemented with 10% FBS, 1% NEAA, 1x penicillin/streptomycin at 37 °C in an atmosphere of 5% CO_2. Tumor cells were routinely sub-cultured twice weekly per ATCC instruction.

4.2 Mycoplasma Test and Short Tandem Repeat (STR) Analysis

[0165] STR and mycoplasma tests were performed to ensure the authenticity and quality of tumor cells. Results indicated that the Calu-6 cells used in this study were STR correct and mycoplasma negative.

4.3 Tumor Cell Inoculation and Mouse Grouping

[0166] Each mouse was inoculated subcutaneously at the right flank with Calu-6 tumor cells (5×10^6 cells in 0.1 ml 50% Matrigel® in MEM). Tubes containing suspended cells and syringes were kept on ice to avoid solidification of Matrigel®. 2x overage was implemented for cell injection. When mean tumor volume reached the indicated sizes in Table 2, animals were randomly assigned to the indicated groups in Table 2 and received the first dosing.

4.4 Dosing

[0167] Test articles and vehicle solution were administrated by oral gavage ("p.o.") twice daily (BID, ≥8h interval between two dosings in one day). Dosing solution was prepared as described in Table 3 once weekly and as complete homogenous suspension before each dosing. Dosing volumes were given based on results from the previous mouse body weight measurement. Animals were treated either throughout the study per parameters described in Table 2.

4.5 Tumor Measurements and Collection

[0168] Tumor volumes and mouse body weights were measured three times weekly after tumors became palpable and before randomization and grouping. Afterwards, tumor volumes and mouse body weights were measured twice weekly to termination, in two dimensions using a caliper, and the tumor volumes were expressed in mm^3 using the formula: $V = 0.5\ L \times W^2$, where L and W were the long and short diameters of the tumor, respectively. The TGI value for the drug A-treated group at Day X was calculated as following: where mTV represented mean tumor volume.

4.6 Statistical Analysis

[0169] A two-way ANOVA was performed to compare tumor volumes among different treatment groups. $AP < 0.05$ was considered statistically significant.

5. Summary of Results

[0170] Compared to the vehicle control, treatment with Compound B maleate and Compound A at all tested doses, alone or in combination, resulted in significant inhibition of Calu-6 tumor growth (FIGs. 1 and 3). Increasing doses of Compound A added to a consistent dose of Compound B maleate led to dose-dependent improvements in tumor growth inhibition, consistent with the in vitro data that demonstrated cell killing synergy between the two compounds in K-RAS mutated cancer cell lines. The greatest tumor growth inhibition in this experiment was observed at a dose 1.25 mg/kg Compound B maleate and 5 mg/kg Compound A.

[0171] FIG. 2 demonstrates a relatively stable mouse body weight over time, with marginal differences

between Groups, suggesting that the combination of Compound A and Compound B maleate was well tolerated.

Example 3: Synergistic Effective Between Compound A and Compound B

[0172] We applied BIGL methods with Highest Single Agent (**HSA**) null model to evaluate synergy effect of the combination of a BRAF inhibitor (BGB-283, lifirafenib) and a MEK inhibitor (PD-0325901, mirdametinib) in multiple KRAS mutant cell lines. HSA model does not attempt to model interaction effects and the predicted effect of a combination is the minimum of both monotherapy curves.

[0173] Data were collected from 3 plates with identical layout that includes negative and positive controls, 8 doses of each single agent, and 8 × 8 = 64 combined doses. The raw signals were normalized by controls before pooling for analysis. Both raw data and normalized were shown in data plots.

[0174] The presence of synergistic or antagonistic effects were evaluated by statistical tests. Two types of tests were conducted

- **Overall test** (meanR): that evaluates how the predicted response surface differs from the observed one. If the null hypothesis is rejected, this test suggests that at least some dose combinations may exhibit either synergistic or antagonistic behaviour.
- **Dose combination test** (maxR): that evaluates presence of synergistic or antagonistic effects for each dose combination and as such provides a point-by-point classification.

[0175] Both of the above test statistics have a well specified null distribution under a set of assumptions, namely normality of Z-scores. If this assumption is not satisfied, distribution of these statistics can be estimated using bootstrap. The results based on both normal and bootstrapping errors were provided.

[0176] More statistics analysis details can be found at Van der Borght, K., et al., Sci Rep 7:17935 (2017) and the methodology vignette.

Table 4

Cell Line	RAS mutation	Overall test p-value *	Percentage of combinations show synergistic effect **	Maximum EC_{50} shift for mirdametinib
HCT116	K-RAS^{G13D}	<0.0001	34%	**>100 fold ↓**
LU65	K-RAS^{G12C}	<0.0001	31%	**>100 fold ↓**
H2122	K-RAS^{G12C}	<0.0001	23%	**>100 fold ↓**
MiaPaCa-2	K-RAS^{G12C}	<0.0001	19%	2 fold ↓
Calu-1	K-RAS^{G12C}	<0.0001	13%	NA
Sk-Mel-2	K-RAS^{Q61R}	<0.0001	13%	No shift
SW837	K-RAS^{G12C}	<0.0001	6%	3 fold

Cell Line	RAS mutation	Overall test p-value *	Percentage of combinations show synergistic effect **	Maximum EC_{50} shift for mirdametinib
NCI-H358	K-RAS^{G12C}	<0.0001	5%	2 fold
NCI-H2030	K-RAS^{G12C}	<0.0001	2%	NA
NCI-H23	K-RAS^{G12C}	0.036	2%	NA
SW620	K-RAS^{G12V}	<0.0001	2%	NA
A549	K-RAS^{G12S}	<0.0001	0%	15 fold ↓
HCT15	K-RAS^{G13D}	1.000	0%	NA
Sk-Mel-119	K-RAS^{Q61K}	0.036	0%	No shift
SK-Mel-285	K-RAS^{G12C}	0.929	0%	NA
Sk-Mel-30	K-RAS^{Q61K}	0.143	0%	NA
SW1573	K-RAS^{G12C}	<0.0001	0%	NA
SW480	K-RAS^{G12V}	0.679	0%	NA

* p-values for the hypothesis that at least one of the considered dose combinations exhibits either synergistic or antagonistic behavior.
** The percentage of the considered dose combinations with synergy at significance level 0.05.
No shift: less than 2 fold EC_{50} shift was detected
NA: cell line is not sensitive to miradametib alone or in combination with lifirafenib, and no dose dependent curve can be generated

Example 4: Antiproliferation effect by combining Compound B with different MEK inhibitors in K/N-RAS mutated NSCLC and CRC cell

[0177] The antiproliferative activity of compounds in a panel of RAS mutant NSCLC and CRC cell line has been determined using CellTiter-Glo luminescent cell viability assay (Promega). See, Yuan et al., Molecular Oncology 14 (2020) 1833-1849. The number of cells seeded per well of a 96-well plate was optimized for each cell line to ensure logarithmic growth over the three-day treatment period. Cells were incubated for 16 h and then treated with a 10-point dilution series in duplicate. Following a 3-day exposure to compounds, a volume of CellTiter-Glo reagent equal to the volume of cell culture medium was added into each well. Mixture was mixed on an orbital shaker for 2 min to allow cell lysing, followed by 10-min incubation at RT to allow development and stabilization of luminescent signal. Luminescent signal was measured using PHERAstar FS reader (BMG Labtech).

[0178] Excess over Highest Single Agent (EOHSA) is a standard criterion for evaluating drug combinatorial effects on cell growth inhibition. EOHSA was used to analyze the excess inhibition effects produced by the drug combination over the larger effects produced by two single agents at corresponding concentrations. For analysis purpose, it is assumed that the log of the difference of each raw measurement/positive control and the negative control follows a normal distribution with

different means but the same variance. The model is fitted by the maximum-likelihood method, and the EOHSA for each dose combination was calculated by applying the fitted model to the EOHSA calculation formula.

[0179] Tables 5-7 provide the inhibition observed in multiple cell lines for combinations of Compound B and various MEK inhibitors. The p-values (*) were calculated using the testing procedure described in Perone et al., JAm Stat Assoc. 99:1002-14. The calculations were applied to control the false discovery exceedance at 5%, for the hypothesis that at least one of the considered dose combinations has synergy per EOHSA. Tables 5-7 provide the percentage of the considered dose combinations with synergy (**) using the Pacifico approach at significance level 0.05. No shift is defined as less than 2-fold EC50 shift detected after combination of Compound B with the MEK inhibitor.

Table 5. Inhibition of the proliferation of multiple NSCLC cell lines harboring K/N-RAS mutations with a combination of Compound A and Compound B.

Cell Line	EOHSA		Maximum EC_{50} shift for PD-0325901
	p-value*	Percentage**	
NSCLC:			
Calu-6	0.0001	0.17	**59 fold ↓**
A549	<0.0001	0.17	**11 fold ↓**
NCI-H2122	<0.0001	0.16	**21 fold ↓**
NCI-H23	<0.0001	0.22	**22 fold ↓**
SW1573	<0.0001	0.27	**97 fold ↓**
NCI-H358	0.2361	0.00	18 fold ↓
NCI-H1299	<0.0001	0.14	**16 fold ↓**
Calu-1	0.8944	0.00	No shift
Sk-Lu-1	0.0015	0.09	**32 fold ↓**

Table 6. Inhibition of the proliferation of multiple NSCLC and CRC cell lines harboring K/N-RAS mutations with a combination of Compound B and MEK inhibitor pimarsertib

Cell Line	EOHSA		Maximum EC_{50} shift for pimarsertib
	p-value*	Percentage	
NSCLC:			
Calu-6	<0.0001	0.42	**12 fold ↓**
A549	<0.0001	0.30	**42 fold ↓**
NCI-H2122	<0.0001	0.09	**6 fold ↓**
NCI-H23	<0.0001	0.44	**20 fold ↓**
SW1573	<0.0001	0.25	**>100 fold ↓**
NCI-H358	0.0001	0.41	**>100 fold**
NO-HI 299	<0.0001	0.27	**45 fold ↓**
Calu.1	0.0001	0.11	**7 fold ↓**
Sk-Lu-1	<0.0001	0.17	**9 fold ↓**
CRC:			
LS174T	<0.0001	0.16	**15 fold ↓**

CRC:			
Lovo	<0.0001	0.19	**18 fold ↓**
T84	<0.0001	0.27	**44 fold ↓**
DLD-1	<0.0001	0.36	**>100 fold ↓**
HCT8	<0.0001	0.12	**54 fold ↓**
HCC2998	<0.0001	0.2	**31 fold ↓**
SW480	<0.0001	0.17	No shift

Table 7. Inhibition of the proliferation of multiple NSCLC cell lines harboring K/N-RAS mutations with a combination of Compound B and MEK inhibitor RO5126766

Cell Line	EOHSA		Maximum EC_{50} shift for RO5126766
	p-value*	Percentage**	
NSCLC:			
Calu-6	<0.0001	0.08	5 fold ↓
A549	<0.0001	0.16	*2 fold* ↓
NCI-H2122	0.0350	0.02	3 fold ↓
NCI-H23	<0.0001	0.20	4 fold ↓
SW1573	0.0005	0.12	5 fold ↓
NCI-H358	<0.0001	0.20	No shift
NCI-H1299	<0.0001	0.17	No shift
Calu-1	<0.0001	0.28	No shift
Sk-Lu-1	<0.0001	0.33	5 fold ↓

Example 5: Human Clinical Trials

[0180] Part 1 (Phase 1b dose escalation) of lifirafenib and mirdametinib has, to date, included 26 patients with advanced, metastatic or unresectable solid cancers. The patients were treated in four sequential dose cohorts. The first two dose cohorts (DL1 and DL2) evaluated lifirafenib and mirdametinib given once daily on the continuous dosing schedule, where the DL1 cohort included 15 mg of lifirafenib combined with 2 mg of mirdametinib in 6 subjects and the DL2 cohort evaluated 20 mg of lifirafenib combined with 2 mg of mirdametinib in 8 subjects. The latter two dose cohorts (DL3a and DL4a) evaluated lifirafenib and mirdametinib on an intermittent dosing schedule (once daily for 5 days followed by 2 days off in every week), where the DL3a cohort included 20 mg of lifirafenib combined with 3 mg of mirdametinib in 6 subjects and the DL4a cohort evaluated 20 mg of lifirafenib combined with 4 mg of mirdametinib in 6 subjects. One treatment cycle in all dose cohorts was 28 days. Initial results in patients having advanced solid cancers (e.g., ovarian, CRC, NSCLC, endometrial) are provided in FIG. 4.

[0181] After the completion of dose cohort 4a, Part 1 (Phase 1b dose escalation) will continue in two parallel dose escalation arms (arm b and arm c). In both arms, lifirafenib and mirdametinib will be evaluated in sequential dose escalation cohorts on an intermittent dosing schedule (5 days followed by 2 days off in every week). One treatment cycle will be 28 days. In both arms, the lifirafenib dose will be

fixed across all dose escalation cohorts. In arm b, lifirafenib will be given as the lead-in dose of 15 mg once daily during the first 2 weeks (14 days) followed by the target dose of 20 mg once daily during the 28-day treatment period. In arm c, lifirafenib will be given as the lead-in dose of 10 mg once daily during the first 2 weeks (14 days) followed by the target dose of 15 mg once daily during the 28-day treatment period. The starting dose cohort in arm b (DL3b) will evaluate 15 mg and 20 mg of lifirafenib once daily (lead in and target dose, respectively) combined with 3 mg of mirdametinib once daily. The starting dose cohort in arm c (DL3c) will evaluate 10 mg and 15 mg of lifirafenib once daily (lead in and target dose, respectively) combined with 2 mg of mirdametinib twice daily. In subsequent dose escalation cohorts, mirdametinib dose will be escalated by 1-2 mg once daily (arm b) and 1-2 mg twice daily (arm b) if tolerated.

[0182] A standalone Phase 1b / 2a dose finding study will be conducted to evaluate lifirafenib and mirdametinib patients with advanced, metastatic or unresectable solid cancers. Part 1 (Phase 1b dose escalation) of this study will include two parallel dose escalation arms (arm a and arm b). In both arms, lifirafenib and mirdametinib will be evaluated in 3 sequential dose escalation cohorts. Both drugs will be given on the continuous dosing schedule and one treatment cycle will be 28 days. In both arms, the lifirafenib dose will be fixed across dose escalation cohorts. In arm a, lifirafenib will be given at the dose of 5 mg once daily and in arm b, lifirafenib will be given at the dose of 5 mg twice daily. The starting dose cohort in arm a (DL1a) will evaluate 5 mg of lifirafenib once daily combined with 2 mg of mirdametinib twice daily. The starting dose cohort in arm b (DL1b) will evaluate 5 mg of lifirafenib twice daily combined with 2 mg of mirdametinib twice daily. The dose escalation may proceed in additional 2 sequential cohorts (DL2a-DL3a in arm and DL2b-DL3b in arm b). This means that after the starting dose cohort (DL1a and DL1b), two subsequent dose escalation cohorts in respective arms will evaluate the same lifirafenib doses (5 mg once daily in arm and 5 mg twice daily in arm b), combined with mirdametinib doses escalated by 2 mg twice daily in each escalation step in both arms (4 mg twice daily in DL2a and DL2b and 6 mg twice daily in DL3a and Dl3b).

Example 4: Capsule Formulations

[0183]

	Compound A/Compound B (1/5 mg)		Compound A/Compound B (2/20 mg)	
Component	**%**	**mg/capsule**	**%**	**mg/capsule**
Compound A	1.00%	1.00	1.00%	2.00
Compound B (Maleic acid salt)	6.82%	6.82	13.64%	27.28
SMCC50	85.93%	85.93	79.11%	158.22
Croscarmellose sodium	4.00%	4.00	4.00%	8.00
Sodium Stearyl Fumarate (intra)	2.00%	2.00	2.00%	4.00
Sodium Stearyl Fumarate (extra)	0.25%	0.25	0.25%	0.50
Total	100%	100.00	100%	200.00

	Compound A/Compound B (1/5 mg)		Compound A/Compound B (2/20 mg)	
Component	**%**	**mg/capsule**	**%**	**mg/capsule**
Gelatin capsule				

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Patentkrav

1. Kombination af Forbindelse A (mirdametinib), eller en farmaceutisk acceptabel saltform deraf, og Forbindelse B (lifirafenib), eller en farmaceutisk acceptabel saltform deraf til anvendelse til behandling af en patient med en fast tumor, hvor forbindelse A og forbindelse B hver skal indgives i en terapeutisk effektiv mængde.

2. Kombinationen til anvendelsen ifølge krav 1, hvor den terapeutisk effektive mængde af Forbindelse A er ca. 1 mg til ca. 5 mg per dag; og/eller den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 5 mg til ca. 40 mg per dag.

3. Kombinationen til anvendelsen ifølge krav 1, hvor:

(i) a) den terapeutisk effektive mængde af Forbindelse A er ca. 1 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 5 mg til ca. 15 mg per dag, fortrinsvis ca. 20 mg per dag;

(ii) a) den terapeutisk effektive mængde af Forbindelse A er ca. 2 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 5 mg til ca. 40 mg per dag, eventuelt ca. 20 mg til ca. 35 mg per dag, fortrinsvis ca. 20 mg per dag, eller ca. 15 mg per dag;

(iii) a) den terapeutisk effektive mængde af Forbindelse A er ca. 3 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 5 mg til ca. 40 mg per dag, eventuelt ca. 20 mg til ca. 35 mg per dag, fortrinsvis ca. 20 mg per dag, eller ca. 15 mg per dag;

(iv) a) den terapeutisk effektive mængde af Forbindelse A er ca. 4 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 10 mg til ca. 40 mg per dag, eventuelt ca. 20 mg til ca. 35 mg per dag, fortrinsvis ca. 20 mg per dag, ca. 15 mg per dag, ca. 10 mg per dag, eller ca. 5 mg per dag;

(v) a) den terapeutisk effektive mængde af Forbindelse A er ca. 5 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en

farmaceutisk acceptabel saltform deraf, er ca. 10 mg til ca. 40 mg per dag, eventuelt ca. 20 mg til ca. 40 mg per dag;

(vi) a) den terapeutisk effektive mængde af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, er ca. 8 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 5 mg per dag, eller ca. 10 mg per dag; eller

(vii) a) den terapeutisk effektive mængde af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, er ca. 12 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 5 mg per dag, eller ca. 10 mg per dag.

4. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 1-3, hvor Forbindelse B er en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt.

5. Kombinationen til anvendelsen ifølge krav 4, hvor:

(i) a) den terapeutisk effektive mængde af Forbindelse A er ca. 1 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 5 mg til ca. 10 mg per dag, fortrinsvis ca. 7 mg per dag;

(ii) a) den terapeutisk effektive mængde af Forbindelse A er ca. 2 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 10 mg til ca. 30 mg per dag, fortrinsvis ca. 13 mg per dag, ca. 20 mg per dag, eller ca. 27 mg per dag;

(iii) a) den terapeutisk effektive mængde af Forbindelse A er ca. 3 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 15 mg til ca. 40 mg per dag, fortrinsvis ca. 20 mg per dag, ca. 27 mg per dag, eller ca. 34 mg per dag;

(iv) a) den terapeutisk effektive mængde af Forbindelse A er ca. 4 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 20 mg til ca. 40 mg

per dag, fortrinsvis ca. 27 mg per dag, ca. 20 mg per dag, ca. 13 mg per dag, eller ca. 7 mg per dag;

(v) den terapeutisk effektive mængde af Forbindelse A er ca. 5 mg per dag og den terapeutisk effektive mængde af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 25 mg til ca. 40 mg per dag, fortrinsvis ca. 34 mg per dag;

(vi) a) den terapeutisk effektive mængde af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, er ca. 8 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 7 mg per dag, eller ca. 13 mg per dag; eller

(vii) a) den terapeutisk effektive mængde af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, er ca. 12 mg per dag og b) den terapeutisk effektive mængde af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, er ca. 7 mg per dag eller ca. 13 mg per dag.

6. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 1-5, hvor Forbindelse A; og/eller Forbindelse B skal indgives en gang per dag.

7. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 1-6, hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives i en dosiscyklus på 28 dage omfattende:

I. (a) 21 dage hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, begge indgives; og (b) 7 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives;

II. (a) 21 dage hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf begge indgives; efterfulgt af (b) 7 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives;

III. (a) tre perioder på 7 dage, som hver omfatter (i) 5 dage hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, begge indgives og (ii) 2 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf indgives; og

(b) 7 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives;

IV. (a) tre perioder på 7 dage, som hver omfatter (i) 5 dage hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, begge indgives og (ii) 2 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives; efterfulgt af (b) 7 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives;

V. (a) tre perioder på 7 dage, som hver omfatter (i) 4 dage hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, begge indgives og (ii) 3 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf indgives; og (b) 7 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives; eller

VI. (a) tre perioder på 7 dage, som hver omfatter (i) 4 dage hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, begge indgives og (ii) 3 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives; efterfulgt af (b) 7 dage hvor hverken Forbindelse A eller Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives,

eventuelt hvor dosiscyklussen på 28 dage gentages i op til ialt 24 konsekutive dosiscyklusser på 28 dage.

8. Kombinationen til anvendelsen ifølge krav 6 eller krav 7, hvor kun Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives i en indkøringsperiode forud for en første dosiscyklus på 28 dage, eventuelt hvor mængden af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, indgivet i indkøringsperioden er den samme eller lavere end mængden af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, indgivet i løbet af den første dosiscyklus på 28 dage; og/eller hvor Forbindelsen B, eller et farmaceutisk acceptabelt salt deraf, indgives dagligt i løbet af indkøringsperioden fortrinsvis en gang dagligt i løbet af indkøringsperioden.

9. Kombinationen til anvendelsen ifølge krav 6 eller krav 7, hvor en eller begge af Forbindelse A, eller en farmaceutisk acceptabel saltform deraf, og Forbindelse B,

eller en farmaceutisk acceptabel saltform deraf, indgives i en indkøringsperiode forud for en første dosiscyklus på 28 dage i en lavere dosis end den terapeutisk effektive mængde af Forbindelse A, eller en farmaceutisk acceptabel saltform deraf, og Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, indgives i løbet af den første cyklus på 28 dage;
eventuelt hvor mængden af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, indgivet i indkøringsperioden er i) den samme som mængden af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, indgivet i løbet af den første dosiscyklus på 28 dage; eller ii) lavere end mængden af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, indgivet i løbet af den første dosiscyklus på 28 dage.

10. Kombinationen til anvendelsen ifølge krav 9, hvor

(A) mængden af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, indgivet i indkøringsperioden er ca. 1 mg til ca. 5 mg per dag, eventuelt hvor mængden af Forbindelse A, eller et farmaceutisk acceptabelt salt deraf, indgivet i indkøringsperioden er ca. 1 mg per dag, ca. 2 mg per dag, eller ca. 3 mg per dag; og/eller

(B) mængden af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, indgivet i indkøringsperioden er

(i) den samme som mængden af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, indgivet i løbet af den første dosiscyklus på 28 dage;

(ii) lavere end mængden af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, indgivet i løbet af den første dosiscyklus på 28 dage;

(iii) ca. 5 mg til ca. 25 mg per dag, ca. 5 mg til ca. 20 mg per dag, ca. 5 mg til ca. 15 mg per dag; eller

(iv) ca. 5 mg per dag, ca. 10 mg per dag, ca. 15 mg per dag, eller ca. 20 mg per dag.

11. Kombinationen til anvendelsen ifølge krav 9 eller krav 10, hvor Forbindelsen B indgivet i indkøringsperioden er en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt, mere fortrinsvis hvor mængden af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, indgivet i indkøringsperioden er

(i) ca. 5 mg til ca. 40 mg per dag, ca. 5 mg til ca. 30 mg per dag, eller ca. 5 mg til ca. 25 mg per dag; eller
(ii) ca. 7 mg per dag, ca. 13 mg per dag, ca. 20 mg per dag, eller ca. 27 mg per dag.

12. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 9-11, hvor indkøringsperioden begynder 21 dage, 14 dage, 10 dage eller 7 dage før den først dosiscyklus på 28 dage.

13. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 9-12, hvor Forbindelsen A, eller et farmaceutisk acceptabelt salt deraf, og Forbindelse B, eller et farmaceutisk acceptabelt salt deraf, hver indgives dagligt i løbet af indkøringsperioden, fortrinsvis en gang dagligt i løbet af indkøringsperioden.

14. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 1-13, hvor Forbindelse A er tilvejebragt i en farmaceutisk acceptabel saltform; eller i form af en fri base.

15. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib), til anvendelse til behandling af en patient med en fast tumor, hvor patienten skal indgives en gang dagligt 2 mg af Forbindelse A som fri base og 15 mg af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf;
eventuelt hvor Forbindelsen B indgives som en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt og, eventuelt hvor mængden af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 20 mg.

16. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib), til anvendelse til behandling af en patient med en fast tumor omfattende, hvor patienten skal indgives en gang dagligt 2 mg af Forbindelse A som fri base og 20 mg af Forbindelse B, eller et farmaceutisk acceptabelt salt deraf.

17. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib) til anvendelse til behandling af en patient med en fast tumor, hvilken behandling omfatter en cyklus på 7 dage, som omfatter:

I. (a) indgivelse en gang dagligt af 3 mg Forbindelse A fri base og 20 mg Forbindelse B, eller en farmaceutisk acceptabel saltform i 5 konsekutive dage; efterfulgt af (b) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage; eller

II. (a) indgivelse en gang dagligt af 4 mg Forbindelse A fri base og 20 mg Forbindelse B, eller en farmaceutisk acceptabel saltform i 5 konsekutive dage; efterfulgt af (b) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage.

18. Kombinationen til anvendelsen ifølge krav 16 eller krav 17, hvor Forbindelsen B indgives som en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt og, eventuelt hvor mængden af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 27 mg.

19. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib) til anvendelse til behandling af en patient med en fast tumor, hvilken behandling omfatter:

(a) en indkøringsperiode som omfatter indgivelse en gang dagligt af 3 mg Forbindelse A fri base og 10 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, i 14 konsekutive dage; efterfulgt af

(b) en behandlingscyklus på 7 dage som omfatter (i) indgivelse en gang dagligt af 3 mg af Forbindelse A fri base og 20 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage;

eventuelt hvor Forbindelsen B indgives både i indkøringsperioden og behandlingscyklussen som en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt og, eventuelt hvor mængden af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, indgivet i indkøringsperioden er ca. 13 mg eller ca. 27 mg.

20. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib) til anvendelse til behandling af en patient med en fast tumor, hvilken behandling omfatter:

I. (a) en indkøringsperiode som omfatter indgivelse af 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage, som omfatter (i) indgivelse en gang dagligt af 1 mg af Forbindelse A fri base og 20 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage;

II. (a) en indkøringsperiode som omfatter indgivelse af 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage , som omfatter (i) indgivelse en gang dagligt af 2 mg af Forbindelse A fri base og 20 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage;

III. (a) en indkøringsperiode som omfatter indgivelse af 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage, som omfatter (i) indgivelse en gang dagligt af 3 mg af Forbindelse A fri base og 20 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage; eller

IV. (a) en indkøringsperiode som omfatter indgivelse af 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage, som omfatter (i) indgivelse en gang dagligt af 4 mg af Forbindelse A fri base og 20 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage;

eventuelt hvor Forbindelsen B indgives i både indkøringsperioden og behandlingscyklussen som en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt og, eventuelt hvor mængden af Forbindelse B som et maleatsalt, som

kan være et sesqui-maleatsalt, indgivet i indkøringsperioden er ca. 20 mg eller ca. 27 mg.

21. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib) til anvendelse til behandling af en patient med en fast tumor, hvilken behandling omfatter:

I. (a) en indkøringsperiode som omfatter indgivelse af ialt 2 mg Forbindelse A fri base fordelt over to doser per dag og 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage, som omfatter (i) indgivelse af 1 mg af Forbindelse A fri base to gange dagligt og 15 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage;

II. (a) en indkøringsperiode som omfatter indgivelse af ialt 3 mg Forbindelse A fri base fordelt over to doser per dag og 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt, i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage som omfatter (i) indgivelse en gang dagligt af 3 mg af Forbindelse A fri base og 15 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage; eller

III. (a) en indkøringsperiode som omfatter indgivelse af ialt 4 mg Forbindelse A fri base fordelt over to doser per dag og 15 mg Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 14 konsekutive dage; efterfulgt af (b) en behandlingscyklus på 7 dage som omfatter (i) indgivelse en gang dagligt af 4 mg af Forbindelse A fri base og 15 mg af Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, en gang dagligt i 5 konsekutive dage; efterfulgt af (ii) ingen indgivelse af Forbindelse A eller Forbindelse B i 2 konsekutive dage;

eventuelt hvor Forbindelsen B indgives i både indkøringsperioden og behandlingscyklussen som en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt og, eventuelt hvor mængden af Forbindelse B som et maleatsalt, som kan være et sesqui-maleatsalt, indgivet i indkøringsperioden er ca. 13 mg, eller

ca. 20 mg.

22. Kombination af Forbindelse A (mirdametinib) og Forbindelse B (lifirafenib) til anvendelse til behandling af en patient med en fast tumor, hvilken behandling omfatter:

(i) indgivelse to gange dagligt af 2 mg Forbindelse A som fri base og en gang dagligt af 5 mg Forbindelse B, eller et farmaceutisk acceptabelt salt deraf;

(ii) indgivelse to gange dagligt af 4 mg Forbindelse A som fri base og en gang dagligt af 5 mg Forbindelse B, elle et farmaceutisk acceptabelt salt deraf;

(iii) indgivelse to gange dagligt af 6 mg Forbindelse A som fri base og en gang dagligt af 5 mg Forbindelse B, eller et farmaceutisk acceptabelt salt deraf;

(iv) indgivelse to gange dagligt af 2 mg Forbindelse A som fri base og to gange dagligt af 5 mg Forbindelse B, eller et farmaceutisk acceptabelt salt deraf;

(v) indgivelse to gange dagligt af 4 mg Forbindelse A som fri base og to gange dagligt af 5 mg Forbindelse B, eller et farmaceutisk acceptabelt salt deraf; eller

(vi) indgivelse to gange dagligt af 6 mg Forbindelse A som fri base og to gange dagligt af 5 mg Forbindelse B, eller et farmaceutisk acceptabelt salt deraf;

eventuelt hvor Forbindelse B er en farmaceutisk acceptabel saltform, fortrinsvis hvor den farmaceutisk acceptable saltform er et maleatsalt, som kan være et sesqui-maleatsalt og, eventuelt hvor hver dosis af Forbindelse B, som et maleatsalt, som kan være et sesqui-maleatsalt, er ca. 7 mg.

23. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 9-13 eller 15-22, hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, i indkøringsperioden og/eller behandlingsperioden indgives

(i) i den samme eller forskellige dosisformer;

(ii) i den samme dosisform og dosisformen er en kapsel; eller

(iii) i forskellige dosisformer, eventuelt hvor Forbindelse A indgives før, samtidigt eller efter indgivelsen af Forbindelse B, eller en farmaceutisk

acceptabel saltform deraf, og/eller hvor dosisformen af Forbindelse A; og/eller Forbindelse B er en kapsel.

24. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 9-23, hvor Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives oralt.

25. Farmaceutisk sammensætning omfattende:

a. Forbindelse A (mirdametinib);

b. Forbindelse B (lifirafenib), eller en farmaceutisk acceptabel saltform deraf;

c. et fyldstof;

d. et desintegreringsmiddel; og

e. et smøremiddel.

26. Den farmaceutiske sammensætning ifølge krav 25, hvor:

(i) Forbindelse A er til stede i ca. 0,8 mg til ca. 1,2 mg, eller 1,5 mg til ca. 2,5 mg;

(ii) det farmaceutisk acceptable salt af Forbindelse B er maleinsyresaltet, som kan være et sesqui-maleatsalt, af Forbindelse B og er til stede i ca. 6 mg til ca. 8 mg, eller ca. 20 mg til ca. 35 mg;

(iii) fyldstoffet er til stede i ca. 80 vægt/vægt-% til ca. 90 vægt/vægt-%, eller ca. 72,5 vægt/vægt-% til ca. 85 vægt/vægt-%;

(iv) desintegreringsmidlet er til stede i ca. 3,5 vægt/vægt-% til ca. 4,5 vægt/vægt-%; og/eller

(v) smøremidlet er til stede i ca. 1,5 vægt/vægt-% til ca. 5,0 vægt/vægt-%.

27. Den farmaceutiske sammensætning ifølge krav 25 eller krav 26, hvor

(i) fyldstoffet er valgt fra gruppen bestående af mikrokrystallinsk cellulose, lactose, mannitol, stivelse, dibasisk calciumphosphat og kombinationer deraf, fortrinsvis mikrokrystallinsk cellulose, yderligere fortrinsvis hvor den mikrokrystallinske cellulose er silicificeret mikrokrystallinsk cellulose;

(ii) desintegreringsmidlet er valgt fra gruppen bestående af croscarmellose, natriumstivelsesglycolat, crospovidon, alginsyre og kombinationer deraf, fortrinsvis croscarmellosenatrium;
(iii) smøremidlet er valgt fra gruppen bestående af natriumstearylfumarat, magnesiumstearat, glyceryldibehenat, talkum eller kombinationer deraf, fortrinsvis natriumstearylfumarat eller magnesiumstearat.

28. Den farmaceutiske sammensætning ifølge et hvilket som helst af kravene 25-27, hvor den farmaceutiske sammensætning er en tablet eller kapsel, fortrinsvis en kapsel.

29. Den farmaceutiske sammensætning ifølge krav 28, hvor kapslen omfatter:
I. ca. 1,0 mg af Forbindelse A og ca. 7 mg af maleinsyresaltet af Forbindelse B, som kan være et sesqui-maleatsalt, hvor hver komponent af kapslen er som følger:
a. ca. 0,8 vægt/vægt-% til ca. 1,2 vægt/vægt-% af Forbindelse A;
b. ca. 6 vægt/vægt-% til ca. 8 vægt/vægt-% af maleinsyresaltet af Forbindelse B, som kan være et sesqui-maleatsalt;
c. ca. 80 vægt/vægt-% til ca. 90 vægt/vægt-% af silicificeret mikrokrystallinsk cellulose;
d. ca. 3,5 vægt/vægt-% til ca. 4,5 vægt/vægt-% croscarmellosenatrium;
e. ca. 1,5 vægt/vægt-% til ca. 5,0 vægt/vægt-% natriumstearylfumarat; og
f. en gelatinekapsel som indkapsler komponenterne a-e; eller
II. ca. 2.0 mg af Forbindelse A og ca. 27 mg af maleinsyresaltet, som kan være et sesqui-maleatsalt, af Forbindelse B, hvor hver komponent af kapslen er som følger:
a. ca. 0,8 vægt/vægt-% til ca. 1,3 vægt/vægt-% af Forbindelse A;
b. ca. 12,3 vægt/vægt-% til ca. 15,0 vægt/vægt-% af maleinsyresaltet af Forbindelse B, som kan være et sesqui-maleatsalt;
c. ca. 72,5 vægt/vægt-% til ca. 85 vægt/vægt-% silicificeret mikrokrystallinsk cellulose;
d. ca. 3,5 vægt/vægt-% til ca. 4,5 vægt/vægt-% croscarmellosenatrium;
e. ca. 1,5 vægt/vægt-% til ca. 5,0 vægt/vægt-% natriumstearylfumarat; og

f. en gelatinekapsel som indkapsler komponenterne a-e.

30. Farmaceutisk sammensætning ifølge et hvilket som helst af kravene 25-29 til anvendelse til behandling af en patient med en fast tumor.

31. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 1-25, eller den farmaceutiske sammensætning til anvendelsen ifølge krav 30, hvor den faste tumor er valgt fra gruppen bestående af malign tumor i den perifere nervekappe, galdegangskræft, brystkræft, cholangiokarcinom, urotelial kræft, livmoderneoplasme, lungeadenokarcinom, pladecellet ikke-småcellet lungekræft, ikke-pladecellet ikke-småcellet lungekræft, gastrisk kræft, sarkom, blærekræft, hoved- og halskræft, småcellet lungekræft, endometriekræft, spiserørskræft, adenoidt cystisk karcinom, galdeblærekræft, kolorektal kræft, skjoldbruskkirtelkræft, hepatocellulær kræft, prostatakræft, mundkræft, livmoderhalskræft, bugspytkirtelkarcinom, æggestokkræft, melanom og serøst karcinom i peritoneum;
fortrinsvis hvor patienten har ikke-småcellet lungekræft, endometriekræft, æggestokkræft eller lavgrad serös æggestokkræft.

32. Kombinationen til anvendelsen ifølge et hvilket som helst af kravene 1-25 eller 31, eller den farmaceutiske sammensætning til anvendelsen ifølge krav 30 eller krav 31, hvor patienten har en bekræftet mutation i en eller flere af KRAS, NRAS, HRAS, BRAF, NF1, MEK1 og MEK2; og/eller en bekræftet mutation i RASA1 og/eller RAF1.

33. Den farmaceutiske sammensætning til anvendelsen ifølge et hvilket som helst af kravene 30-32, hvor den farmaceutiske sammensætning indgives i en dosiscyklus på 28 dage omfattende:

I. (a) 21 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf form, indgives; og (b) 7 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives;

II. (a) 21 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform

deraf, indgives; efterfulgt af (b) 7 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives;

III. (a) tre perioder på 7 dage som hver omfatter (i) 5 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives og (ii) 2 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives; og (b) 7 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives;

IV. (a) tre perioder på 7 dage som hver omfatter (i) 5 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives og (ii) 2 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives; efterfulgt af (b) 7 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives;

V. (a) tre perioder på 7 dage som hver omfatter (i) 4 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives og (ii) 3 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives; og (b) 7 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives; eller

VI. (a) tre perioder på 7 dage som hver omfatter (i) 4 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives og (ii) 3 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives; efterfulgt af (b) 7 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives, eventuelt

hvor dosiscyklussen på 28 dage gentages i op til ialt 24 konsekutive dosiscyklusser på 28 dage.

34. Den farmaceutiske sammensætning til anvendelsen ifølge et hvilket som helst af kravene 30-32, hvor den farmaceutiske sammensætning indgives i en dosiscyklus på 7 dage omfattende (a) 5 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, indgives; efterfulgt af (b) 2 dage hvor den farmaceutiske sammensætning omfattende Forbindelse A og Forbindelse B, eller en farmaceutisk acceptabel saltform deraf, ikke indgives.

DRAWINGS

Drawing

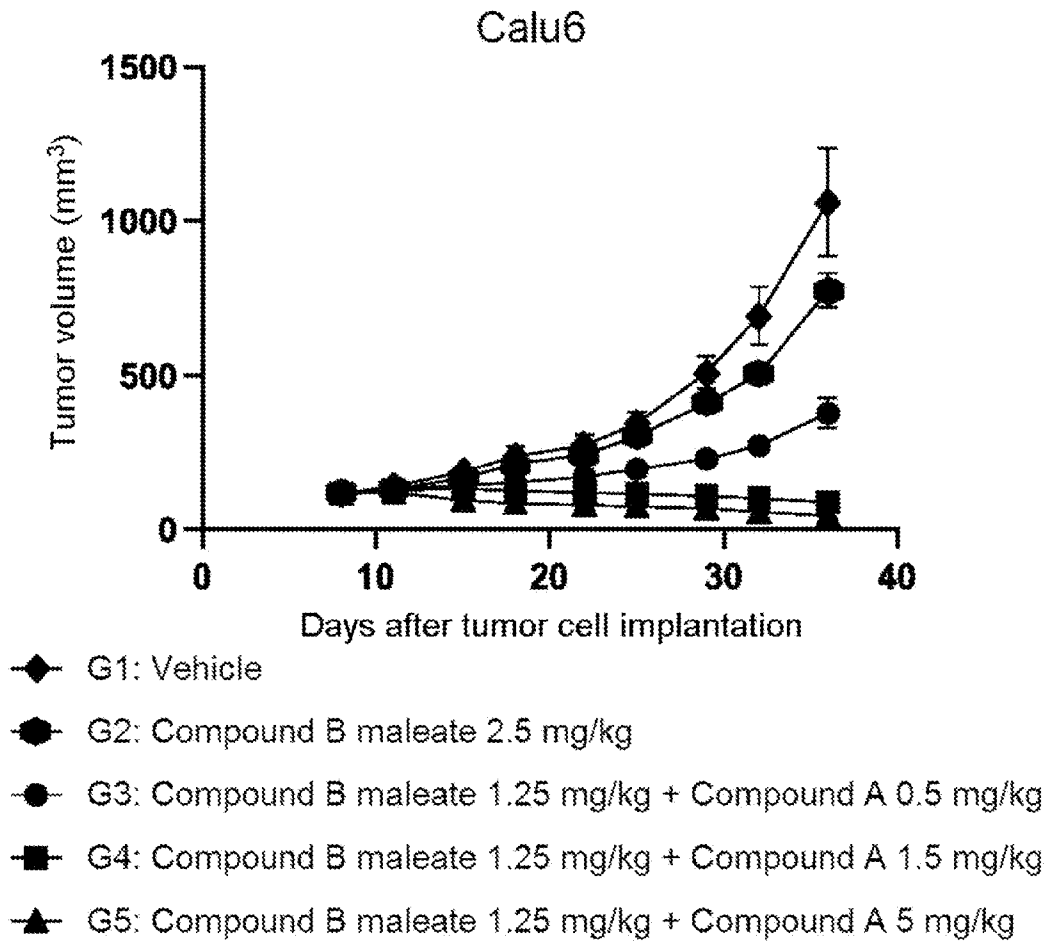

Fig. 1

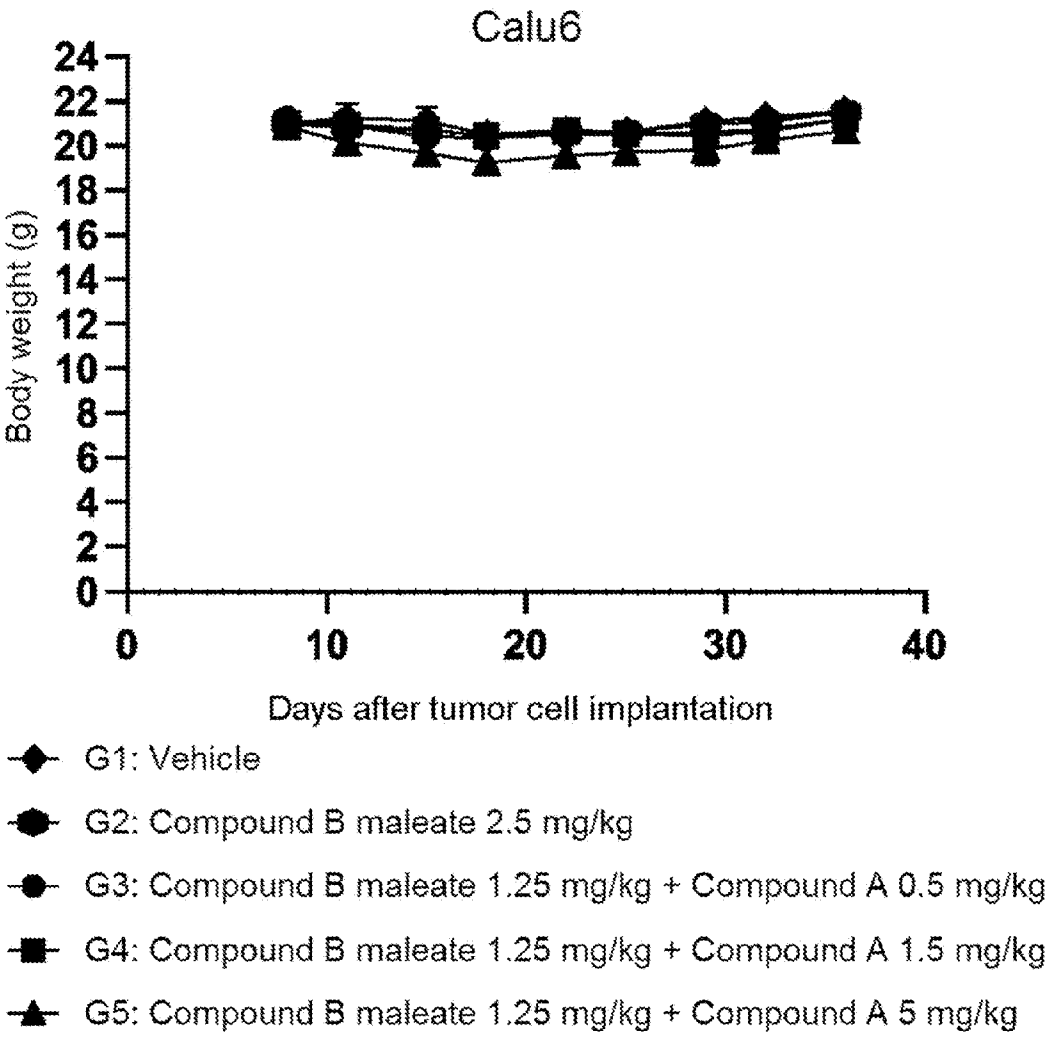
Calu6
Body weight (g)
24
22
20
18
16
14
12
10
8
6
4
2
0
0
10
20
30
40
Days after tumor cell implantation
G1: Vehicle
G2: Compound B maleate 2.5 mg/kg
G3: Compound B maleate 1.25 mg/kg + Compound A 0.5 mg/kg
G4: Compound B maleate 1.25 mg/kg + Compound A 1.5 mg/kg
G5: Compound B maleate 1.25 mg/kg + Compound A 5 mg/kg

Fig. 2

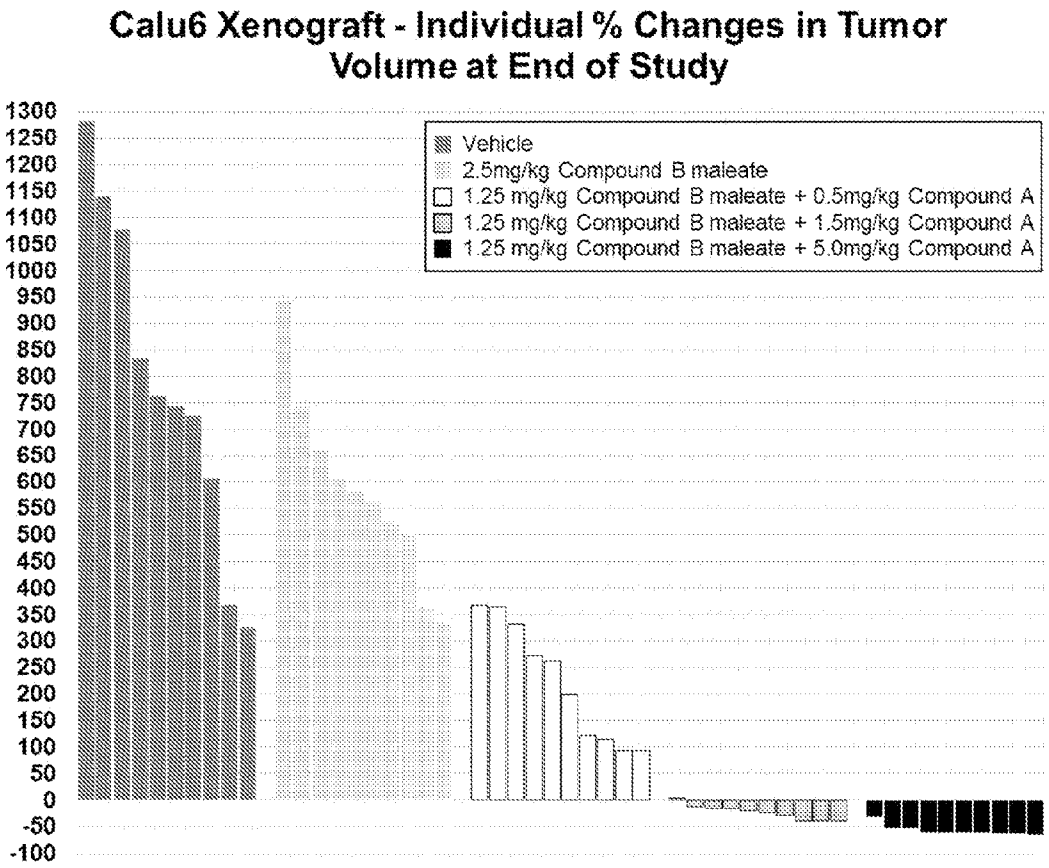
Calu6 Xenograft - Individual % Changes in Tumor Volume at End of Study
1300
1250
1200
1150
1100
1050
1000
950
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
-50
-100
Vehicle
2.5mg/kg Compound B maleate
1.25 mg/kg Compound B maleate + 0.5mg/kg Compound A
1.25 mg/kg Compound B maleate + 1.5mg/kg Compound A
1.25 mg/kg Compound B maleate + 5.0mg/kg Compound A

Fig. 3

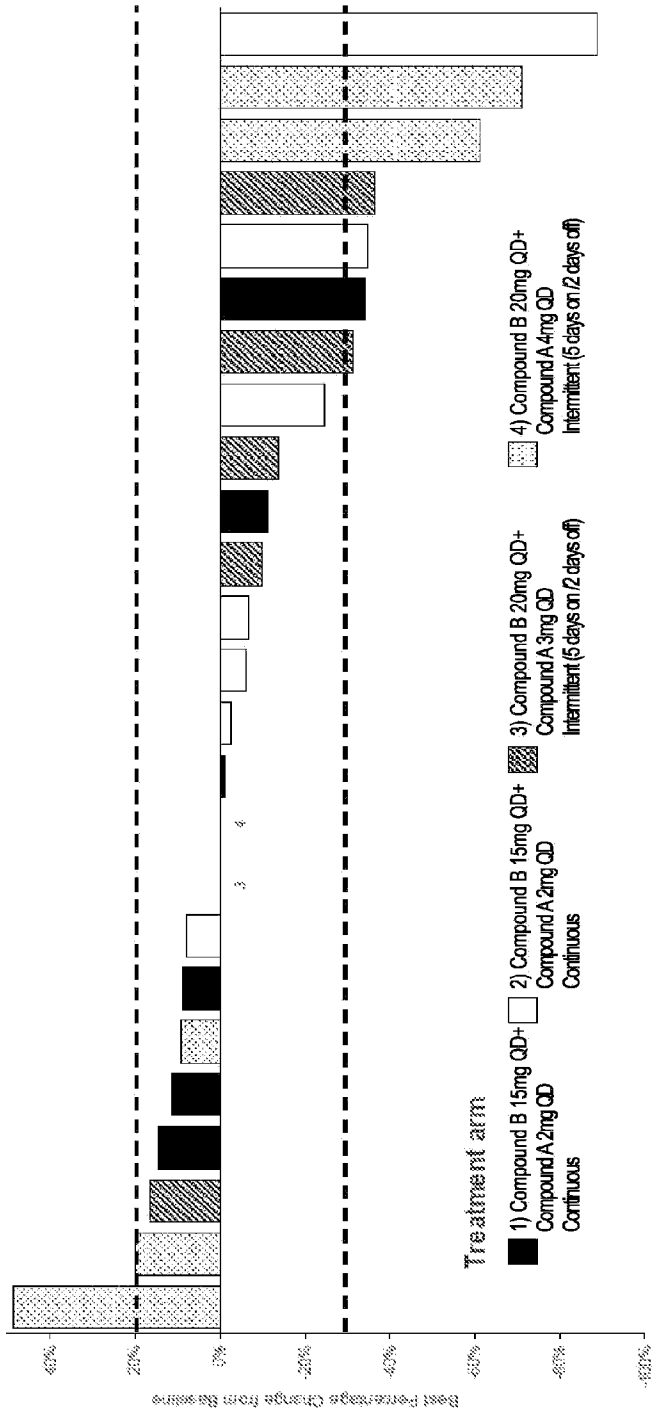
Best Percentage Change from Baseline
40%
20%
0%
-20%
-40%
-60%
-80%
Treatment arm
1) Compound B 15mg QD+ Compound A 2mg QD Continuous
2) Compound B 15mg QD+ Compound A 2mg QD Continuous
3) Compound B 20mg QD+ Compound A 3mg QD Intermittent (5 days on /2 days off)
4) Compound B 20mg QD+ Compound A 4mg QD Intermittent (5 days on /2 days off)

Fig. 4