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(54) **Title**: METHODS OF TREATMENT USING AN ERK INHIBITOR

(57) **Abstract**: The present invention provides methods of treating, stabilizing or lessening the severity or progression of a disease or disorder associated with one or both of ERK1 and ERK2.

METHODS OF TREATMENT USING AN ERK INHIBITOR

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. provisional application number 62/037,091, filed August 13, 2014, the entirety of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention provides methods of treating, stabilizing or lessening the severity or progression of a disease or disorder associated with one or both of ERK1 and ERK2.

BACKGROUND OF THE INVENTION

[0003] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is protein kinases.

[0004] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.).

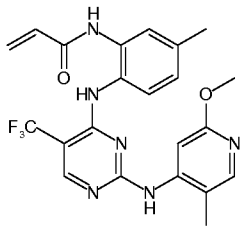
[0005] The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begins with activation of Ras. Activation of Ras leads to the recruitment and activation of Raf, a serine-threonine kinase. Activated Raf then phosphorylates and activates MEK1/2, which then phosphorylates and activates one or both of ERK1 and ERK2. When activated, one or both of ERK1 and ERK2 phosphorylates several downstream targets involved in a multitude of cellular events including cytoskeletal changes and transcriptional activation. The ERK/MAPK pathway

is one of the most important for cell proliferation, and human tumor data suggest that the ERK/MAPK pathway is frequently activated in many tumors. Ras genes, which are upstream of one or both of ERK1 and ERK2, are mutated in several cancers including, but not limited to, colorectal, melanoma, lung, breast and pancreatic tumors. High Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased RAF, MEK, and ERK kinase activity. Tumor types with the most frequent mutation in BRAF include melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers.

[0006] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0007] The present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2. In some aspects, the present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof a pharmaceutically acceptable composition comprising *N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide* **1**:



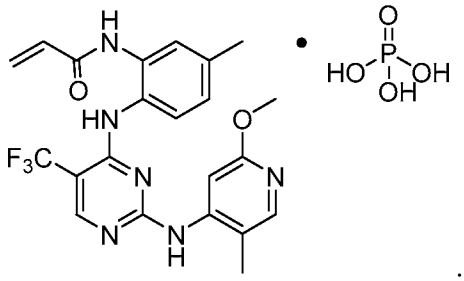
1

or a pharmaceutically acceptable salt thereof.

[0008] Compound **1**, N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide, is designated as compound number **I-90** in PCT patent application serial number PCT/US14/15256, filed February 7, 2014 and published as WO2014/124230 on August 14, 2014 (referred to herein as "the '230

publication,") the entirety of which is hereby incorporated by reference. The synthesis of compound **1** is described in detail at Example 94 of the '230 publication. Compound **1** is active in a variety of assays and therapeutic models demonstrating covalent, irreversible inhibition of one or both of ERK1 and ERK2 kinases (see, e.g., Table A of the '230 publication). Accordingly, Compound **1**, or a pharmaceutically acceptable salt thereof, is useful for treating one or more disorders associated with activity of one or both of ERK1 and ERK2, as described in detail herein, *infra*.

[0009] For instance, in certain embodiments, the present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof a pharmaceutically acceptable composition comprising a phosphate salt of Compound **1**, depicted below:



[0010] In some embodiments, the present invention provides methods of treating, stabilizing or lessening the severity or progression of a proliferative disorder, wherein the method comprises administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof. For instance, in some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, wherein the method comprises administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof.

[0011] In some embodiments, the cancer is a locally advanced cancer. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is recurring. In some embodiments, the cancer is refractory.

[0012] In certain embodiments, the cancer is a RAF inhibitor-resistant cancer. In some such embodiments, the RAF inhibitor-resistant cancer is a BRAF inhibitor-resistant cancer.

[0013] In certain embodiments, the cancer is a MEK inhibitor-resistant cancer.

[0014] In certain embodiments, the cancer is a MAPK pathway-mediated cancer.

[0015] In some embodiments, the cancer is a BRAF-mutated cancer. In certain embodiments, the BRAF-mutated cancer is a $BRAF^{V600}$-mutated cancer, such as $BRAF^{V600E}$ $BRAF^{V600K}$, $BRAF^{V600R}$, and $BRAF^{V600D}$.

[0016] In some embodiments, the cancer is a RAS-mutated cancer. In certain embodiments, the RAS-mutated involves codons 12, 13, or 61. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$. In certain embodiments, the RAS-mutated cancer is an NRAS-mutated cancer, including, but not limited to, $NRAS^{Q61R}$, $NRAS^{Q61K}$, $NRAS^{Q61L}$, or $NRAS^{Q61H}$. In certain embodiments, the RAS-mutated cancer is an HRAS-mutated cancer, including, but not limited to, $HRAS^{G12V}$, $HRAS^{Q61R}$, and $HRAS^{G12S}$.

[0017] In some embodiments, the cancer is selected from multiple myeloma, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung, bone, colon, thyroid, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma (including uveal melanoma) sarcoma, bladder carcinoma, liver carcinoma (e.g., hepatocellular carcinoma (HCC)) and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's disease, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colorectal carcinoma, large intestine, rectum, brain and central nervous system, endometrial, multiple myeloma (MM), prostate, acute myeloid leukemia (AML), and leukemia. In some such embodiments, the cancer is relapsed. In some embodiments, the cancer is refractory. In some embodiments, the cancer is locally advanced. In some embodiments, the cancer is metastatic.

[0018] In some embodiments, the cancer is selected from carcinoma, lymphoma, blastoma, sarcoma, and leukemia. In some embodiments, a sarcoma is a soft tissue sarcoma. In some embodiments, a lymphoma is non-Hodgkin's lymphoma. In some embodiments, a lymphoma is large cell immunoblastic lymphoma. In some embodiments, the cancer is selected from adenocarcinoma; adenoma; adrenocortical cancer; bladder cancer; bone cancer; brain cancer; breast cancer; cancer of the buccal cavity; cervical cancer; colon cancer; colorectal cancer; endometrial or uterine carcinoma; epidermoid carcinoma; esophageal cancer; eye cancer;

follicular carcinoma; gallbladder cancer; prostate, AML, multiple myeloma (MM), gastrointestinal cancer, such as, for example, gastrointestinal stromal tumor; cancer of the genitourinary tract; glioblastoma; hairy cell carcinoma; various types of head and neck cancer; hepatic carcinoma; hepatocellular cancer; Hodgkin's disease; keratoacanthoma; kidney cancer; large cell carcinoma; cancer of the large intestine; laryngeal cancer; liver cancer; lung cancer, such as, for example, adenocarcinoma of the lung, anaplastic carcinoma of the lung, papillary lung adenocarcinoma, small-cell lung cancer, squamous carcinoma of the lung, non-small cell lung cancer; melanoma and nonmelanoma skin cancer; lymphoid disorders; myeloproliferative disorders, such as, for example, polycythemia vera, essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), hypereosinophilic syndrome, systematic mast cell disease, atypical CML, AML, or juvenile myelomonocytic leukemia; plasmacytoma; multiple myeloma; neuroblastoma; ovarian cancer; papillary carcinoma; pancreatic cancer; cancer of the peritoneum; prostate cancer, including benign prostatic hyperplasia; rectal cancer; salivary gland carcinoma; sarcoma; seminoma; squamous cell cancer; small cell carcinoma; cancer of the small intestine; stomach cancer; testicular cancer; thyroid cancer; undifferentiated carcinoma; and vulval cancer. In some such embodiments, the cancer is relapsed. In some embodiments, the cancer is refractory. In some embodiments, the cancer is locally advanced. In some embodiments, the cancer is metastatic.

[0019] In certain embodiments, the cancer is selected from melanoma, pancreatic cancer, thyroid cancer, colorectal cancer, lung cancer (e.g., non-small cell lung cancer), breast cancer, endometrial cancer, prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), multiple myeloma (MM), and leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia. In certain embodiments, a leukemia is acute lymphoblastic leukemia.

[0020] In some embodiments, the cancer is selected from melanoma, colorectal cancer, lung cancer, or pancreatic.

[0021] In some embodiments, the cancer is melanoma. In certain embodiments, the melanoma is uveal melanoma. In some embodiments, the melanoma is a melanoma of the skin. In certain embodiments, the melanoma is locally advanced. In some embodiments, the

melanoma is metastatic. In some embodiments, the melanoma is recurring. In some embodiments, the melanoma is $BRAF^{v600}$-mutated melanoma. In certain embodiments, the melanoma is a RAS-mutated melanoma. In some embodiments, the melanoma is NRAS-mutated melanoma. In certain embodiments, the melanoma is wild type for KRAS, NRAS or BRAF. In certain embodiments, the melanoma is a BRAF inhibitor-resistant (e.g., Vemurfenib-resistant, dabrafenib-resistant, encorafenib-resistant, etc.) melanoma. In certain embodiments, the cancer is a VemR (i.e., Vemurfenib-resistant) BRAF-mutated melanoma. In some embodiments, the melanoma is relapsed. In some embodiments, the melanoma is refractory.

[0022] In some embodiments, the cancer is colorectal cancer. In certain embodiments, the colorectal cancer is locally advanced. In certain embodiments, the colorectal cancer is metastatic. In certain embodiments, the colorectal cancer is a BRAF-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a $BRAF^{v600}$-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a RAS-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a KRAS-mutated colorectal cancer. In some embodiments, the colorectal cancer is relapsed. In some embodiments, the colorectal cancer is refractory.

[0023] In some embodiments, the cancer is pancreatic cancer. In certain embodiments, the pancreatic cancer is locally advanced. In certain embodiments, the pancreatic cancer is metastatic. In certain embodiments, the pancreatic cancer is a pancreatic ductal adenocarcinoma (PDAC). In certain embodiments, the pancreatic cancer is a RAS-mutated pancreatic cancer. In certain embodiments, the pancreatic cancer is a KRAS-mutated pancreatic cancer. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$. In some embodiments, the pancreatic cancer is relapsed. In some embodiments, the pancreatic cancer is refractory.

[0024] In some embodiments, the cancer is a papillary thyroid cancer. In certain embodiments, the papillary thyroid cancer is locally advanced. In some embodiments, the papillary thyroid cancer is metastatic. In some embodiments, the papillary thyroid cancer is recurring. In some embodiments, the papillary thyroid cancer is BRAF-mutated papillary thyroid cancer. In some embodiments, the papillary thyroid cancer is $BRAF^{v600}$-mutated papillary thyroid cancer. In some embodiments, the papillary thyroid cancer is relapsed. In

some embodiments, the papillary thyroid cancer is refractory. In some embodiments, the papillary thyroid cancer may include undifferentiated or dedifferentiated histology.

[0025] In some embodiments, the cancer is lung cancer. In certain embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In certain embodiments, the lung cancer is locally advanced. In certain embodiments, the lung cancer is metastatic. In certain embodiments, the lung cancer is a RAS-mutated lung cancer. In certain embodiments, the lung cancer is KRAS-mutated lung cancer. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$. In some embodiments, the lung cancer is relapsed. In some embodiments, the lung cancer is refractory.

[0026] In certain embodiments, the cancer is a leukemia. In some embodiments, a leukemia is a chronic leukemia. In certain embodiments, a leukemia is chronic myeloid leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia (AML). In certain embodiments, a leukemia is acute monocytic leukemia (AMoL, or AML-M5). In certain embodiments, a leukemia is acute lymphoblastic leukemia (ALL). In certain embodiments, a leukemia is acute T cell leukemia. In certain embodiments, a leukemia is myelomonoblastic leukemia. In certain embodiments, a leukemia is human B cell precursor leukemia. In certain embodiments, a leukemia has a Flt3 mutation or rearrangement. In some embodiments, the leukemia is relapsed. In some embodiments, the leukemia is refractory.

[0027] In some embodiments, the cancer is a CNS cancer, for instance CNS tumors. In certain embodiments, a CNS tumor is a glioblastoma or glioblastoma multiforme (GBM). In some embodiments, the present invention relates to a method of treating stomach (gastric) and esophageal tumors and cancers.

[0028] In some embodiments, the cancer is multiple myeloma (MM). In certain embodiments, the multiple myeloma is locally advanced. In certain embodiments, the multiple myeloma is metastatic. In certain embodiments, the multiple myeloma is a RAS-mutated multiple myeloma. In certain embodiments, the multiple myeloma is KRAS-mutated multiple myeloma. In certain embodiments, the RAS-mutated multiple myeloma is a KRAS-mutated multiple myeloma, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$, or $KRAS^{Q61L/H/R}$.

In some embodiments, the multiple myeloma is relapsed. In some embodiments, the multiple myeloma is refractory.

[0029] In some embodiments, the cancer is hepatocellular carcinoma (HCC). In certain embodiments, the HCC is locally advanced. In certain embodiments, the HCC is metastatic. In certain embodiments, the cancer is a RAS-mutated HCC. In certain embodiments, the cancer is KRAS-mutated HCC. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$, or $KRAS^{Q61L/H/R}$. In some embodiments, the hepatocellular carcinoma is relapsed. In some embodiments, the hepatocellular carcinoma is refractory.

[0030] In some embodiments, provided methods comprise orally administering to a patient compositions comprising Compound **1**, or a pharmaceutically acceptable salt thereof. In certain embodiments, provided methods comprise orally administering to a patient compositions comprising the phosphate salt of Compound **1**. In some embodiments, such compositions are capsule formulations.

[0031] In general, provided methods comprise administering a composition which comprises Compound **1**, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, such as, for example, one or more solubilizers, surfactants/wetting agents, dispersing agents, fillers, disintegrants, glidants and lubricants. In certain embodiments, provided methods comprise administering a composition which comprises the phosphate salt of Compound **1**, and one or more pharmaceutically acceptable excipients, such as, for example, one or more solubilizers, surfactants/wetting agents, dispersing agents, fillers, disintegrants, glidants and lubricants.

[0032] In some embodiments, the present invention also provides dosing regimens and protocols for the administration of Compound **1**, or a pharmaceutically acceptable salt thereof, to patients in need thereof. In certain embodiments, the present invention also provides dosing regimens and protocols for the administration of the phosphate salt of Compound **1** to patients in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] **Figure 1** depicts an XRPD pattern of Form A of the phosphate salt of Compound **1**.

[0034] **Figure 2** depicts an XRPD pattern of Form B of the phosphate salt of Compound **1**.

[0035] **Figure 3** depicts an XRPD pattern of Form C of the phosphate salt of Compound **1**.

[0036] **Figure 4** depicts an XRPD pattern of Form D of the phosphate salt of Compound **1**.

[0037] **Figure 5** depicts graphically the regression of LOX IMVI (melanoma) tumor xenografts when treated with the phosphate salt of Compound **1**. Reductions in tumor volume averaging 93% to 95% (compared with vehicle controls) were observed on Day 20 at doses of 60.5 mg/kg and 121 mg/kg, respectively, administered for seven consecutive days beginning on day 13 after tumor cell implantation.

[0038] **Figure 6** depicts graphically the in vivo inhibition of HCT-116 ($KRAS^{G13D}$ mutant CRC) xenografts by Compound **1**. Tumor growth inhibition with Compound **1** varied from 57% (compared to vehicle control) at 12.5 mg/kg BID to 77% inhibition at doses of 100 mg/kg QD. Animals were treated for 21 consecutive days.

[0039] **Figure 7A** depicts in vitro assays of Compound **1** against Panc-1 (a.k.a PANC-1) pancreatic cancer cells.

[0040] **Figure 7B** depicts in vitro assays of Compound **1** against MIA PaCa-2 (a.k.a. Mia PaCa, a.k.a. MiaPaCa) pancreatic cancer cells.

[0041] **Figure 7C** depicts in vitro assays of Compound **1** against HS294T melanoma.

[0042] **Figure 8** depicts the phase overall study design.

[0043] **Figure 9A** depicts a first in vitro assay of Compound **1** against HCT-116 colorectal cancer cells. As shown in Figure 9A, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1321.30 nM.

[0044] **Figure 9B** depicts a second in vitro assay of Compound **1** against HCT-116 colorectal cancer cells. As shown in Figure 9B, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1169.50 nM

[0045] **Figure 10** depicts an in vitro assay of Compound **1** against KRAS-mutant q61H NCI-H460 lung cancer cells. As shown in Figure 10, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 6839.12 nM.

[0046] **Figure 11** depicts an in vitro assay of Compound **1** against KRAS-unknown NCI-H522 lung cancer cells. As shown in Figure 11, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 2338.84 nM.

[0047] **Figure 12** depicts an in vitro assay of Compound **1** against p.G469A NCI-H1755 lung cancer cells. As shown in Figure 12, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 722.77 nM.

[0048] **Figure 13** depicts an in vitro assay of Compound **1** against KRAS-mutant p.G12V NCI-H727 lung cancer cells. As shown in Figure 13, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 762.08 nM.

[0049] **Figure 14** depicts an in vitro assay of Compound **1** against KRASunknown NCI-H522 lung cancer cells. As shown in Figure 14, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 3006.08 nM.

[0050] **Figure 15A** depicts a second in vitro assay of Compound **1** against Mia PaCa-2 pancreatic cancer cells. As shown in Figure 15A, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1238.80 nM.

[0051] **Figure 15B** depicts a third in vitro assay of Compound **1** against Mia PaCa-2 pancreatic cancer cells. As shown in Figure 15B, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1534.62 nM

[0052] **Figure 16** depicts a second in vitro assay of Compound **1** against HS294T melanoma cells. As shown in Figure 16, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1202.26 nM.

[0053] **Figure 17A** depicts a growth inhibition assay of Compound **1** against NRAS and BRAF mutant vemurafenib-resistant melanoma cell lines. As shown in Figure 17A, Compound **1** inhibits growth of both NRAS and BRAF mutant vemurafenib-resistant melanoma cell lines with an average GI50 of 290 nM.

[0054] **Figure 17B** depicts an in vitro assay of Compound **1** against NRAS and BRAF mutant vemurafenib-resistant melanoma cell lines. Compound **1** induced cell death in all NRAS and BRAF mutant vemurafenib-resistant melanoma cell lines except in line 4 (in which the effect was cytostatic) at 10 μM.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0055] As used herein, a "disease or disorder associated with one or both of ERK1 and ERK2" means any disease or other deleterious condition in which one or both of ERK1 and

ERK2, or a mutant thereof, is known or suspected to play a role. As described further herein, one of ordinary skill in the art will appreciate that ERK1 and ERK2 are downstream targets within the MAPK pathway. Thus, without wishing to be bound by any particular theory, a disease or disorder associated with one or both of ERK1 and ERK2 includes those in which activation of the MAPK pathway at any level (Ras-Raf-Mek-ERK) is known or suspected to play a role, including one or both of ERK1 and ERK2 as well as other nodes in the MAPK pathway upstream from ERK (such as Ras, Raf and Mek).Accordingly, another embodiment of the present invention relates to preventing, treating, stabilizing or lessening the severity or progression of one or more diseases in which one or both of ERK1 and ERK2, or a mutant thereof, is known or suspected to play a role. In some embodiments, the present invention relates to a method of treating or lessening the severity of a proliferative disorder, wherein said method comprises administering to a patient in need thereof Compound **1**, or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable composition thereof.

[0056] As used herein, the term "irreversible" or "irreversible inhibitor" refers to an inhibitor (i.e. a compound) that is able to be covalently bonded to a target protein kinase in a substantially non-reversible manner. That is, whereas a reversible inhibitor is able to bind to (but is generally unable to form a covalent bond to) the target protein kinase, and therefore can become dissociated from the target protein kinase, an irreversible inhibitor will remain substantially bound to the target protein kinase once covalent bond formation has occurred. Irreversible inhibitors usually display time dependency, whereby the degree of inhibition increases with the time with which the inhibitor is in contact with the enzyme. Methods for identifying if a compound is acting as an irreversible inhibitor are known to one of ordinary skill in the art. Such methods include, but are not limited to, enzyme kinetic analysis of the inhibition profile of the compound with the protein kinase target, the use of mass spectrometry of the protein drug target modified in the presence of the inhibitor compound, discontinuous exposure, also known as "washout," experiments, and the use of labeling, such as radiolabeled inhibitor, to show covalent modification of the enzyme, as well as other methods known to one of skill in the art.

[0057] As used herein, a "therapeutically effective amount" means an amount of a substance (*e.g.*, a therapeutic agent, composition, and/or formulation) that elicits a desired biological response. In some embodiments, a therapeutically effective amount of a substance is an amount that is sufficient, when administered as part of a dosing regimen to a subject suffering from or

susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the disease, disorder, and/or condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a substance may vary depending on such factors as the desired biological endpoint, the substance to be delivered, the target cell or tissue, *etc.* For example, the effective amount of compound in a formulation to treat a disease, disorder, and/or condition is the amount that alleviates, ameliorates, relieves, inhibits, prevents, delays onset of, reduces severity of and/or reduces incidence of one or more symptoms or features of the disease, disorder, and/or condition. In some embodiments, a "therapeutically effective amount" is at least a minimal amount of a compound, or composition containing a compound, which is sufficient for treating one or more symptoms of a disease or disorder associated with one or both of ERK1 and ERK2.

[0058] The term "subject", as used herein, means a mammal and includes human and animal subjects, such as domestic animals (e.g., horses, dogs, cats, etc.).

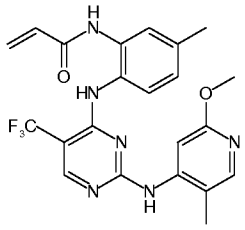
[0059] The terms "treat" or "treating," as used herein, refers to partially or completely alleviating, inhibiting, delaying onset of, preventing, ameliorating and/or relieving a disease or disorder, or one or more symptoms of the disease or disorder. As used herein, the terms "treatment," "treat," and "treating" refer to partially or completely alleviating, inhibiting, delaying onset of, preventing, ameliorating and/or relieving a disease or disorder, or one or more symptoms of the disease or disorder, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In some embodiments, the term "treating" includes preventing or halting the progression of a disease or disorder. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence. Thus, in some embodiments, the term "treating" includes preventing relapse or recurrence of a disease or disorder.

[0060] The expression "unit dosage form" as used herein refers to a physically discrete unit of inventive formulation appropriate for the subject to be treated. It will be understood, however, that the total daily usage of the compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose

level for any particular subject or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of specific active agent employed; specific composition employed; age, body weight, general health, sex and diet of the subject; time of administration, and rate of excretion of the specific active agent employed; duration of the treatment; drugs and/or additional therapies used in combination or coincidental with specific compound(s) employed, and like factors well known in the medical arts.

Compound 1

[0061] As described above and herein, in certain embodiments, the present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, depicted below:



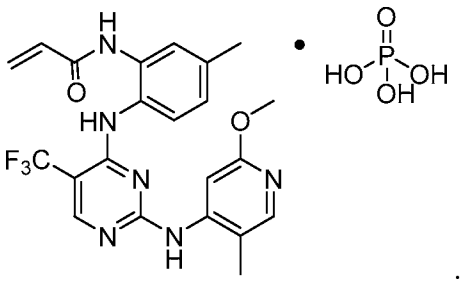
1

or a pharmaceutically acceptable salt thereof.

[0062] Compound **1**, N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide, is designated as compound number **I-90** in PCT patent application serial number PCT/US14/15256, filed February 7, 2014 and published as WO 2014/124230 on August 14, 2014 (referred to herein as "the '230 publication," the entirety of which is hereby incorporated by reference). Ths synthesis of compound **1** is described in detail at Example 94 of the '230 publication. Compound **1** is active in a variety of assays and therapeutic models demonstrating covalent, irreversible inhibition of one or both of ERK1 and ERK2 kinases (see, e.g., Table A of the '230 publication).

[0063] For instance, in certain embodiments, the present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need

thereof a pharmaceutically acceptable composition comprising a phosphate salt of Compound **1**, depicted below:



[0064] The present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutically acceptable composition is an oral dosage form. In some such embodiments, the pharmaceutically acceptable composition is formulated as a capsule. Such methods, dosing regimens and protocols for the administration of pharmaceutically acceptable compositions comprising Compound **1**, or a pharmaceutically acceptable salt thereof, are described in further detail, below.

Methods of Treatment

[0065] Compound **1** and compositions described herein are generally useful for the inhibition of protein kinase activity of one or more enzymes. Examples of kinases that are inhibited by Compound **1** and compositions described herein and against which the methods described herein are useful include one or both of ERK1 and ERK2, or a mutant thereof.

[0066] The classical Mitogen-Activated Protein Kinase (MAPK) Pathway is a three-tiered, kinase cascade (RAF-MEK-ERK) with a central role in regulating proliferation, differentiation, and cell cycle progression in response to a variety of extracellular signals. Aberrant activation of the MAPK pathway is a frequent event in human cancer and pathway activity in treatment naïve tumors is often the result of activating mutations involving either the *RAS* family of proto-oncogenes or the B isoform of *RAF* (BRAF). Activating mutations in *RAS* are reported in approximately 30% of human cancers (McArthur GA, Lancet 2012 Volume 13, Issue 8, August 2012, Pages 744-745; Baines AT et al. Future Med. Chem. 2011 October; 3(14): 1787–1808; J.

Clin. Oncol. 22(8) 1430-1438). Somatic point mutations in *RAS* are most commonly localized to one of three codons (12, 13 and 61), which impair GTP hydrolysis, thus promoting formation of constitutively activated, GTP-bound RAS. RAS can also be activated in human tumors by aberrant upstream activation of receptor tyrosine kinases (RTKs) or by loss of function of the NF-1 tumor suppressor, which normally down regulates RAS activity in a negative feedback loop. Approximately 70-90% of pancreatic ductal adenocarcinomas (PDACs), 40% of colorectal carcinomas and 20-30% of lung adenocarcinomas exhibit activating mutations of *KRAS* and approximately 10-15% of primary melanomas exhibit mutations in *NRAS* (Neuzillet, C. et al. 2013 Cancer Metastasis Rev. 2013 June, 32(1-2):147-62; Riely G.J. et al. 2009 Proc. Am. Thorac. Soc. 2009 Apr 15, 6(2):201-5.; Martin P et al. J. Thorac. Oncol. 2013 May, 8(5):530-42.; Fedorenko I.V. Oncogene. 2013 June 20, 32(25):3009-18).

[0067] Somatic point mutations involving the serine-threonine kinase BRAF, typically involve exons 11 (the P-loop) and 15 (the activation segment) of the kinase domain and more than 90% involve a single amino acid substitution (V600E or K) (Brose et al, 2002 Cancer Res. 2002 Dec 1; 62(23):6997-7000; Davies, H. et al. 2002 Nature June 27, 417(6892):949-54 ; Pratilas, C. et al. Curr. Top. Micrbiol. Immunol. 2012, 355:83-98; De Luca et al., 2012 Expert Opin. Ther. Targets. 2012 April, 16 Suppl 2:S17-27). MAPK pathway activation in *BRAF* mutated tumors occurs independently of RTK signaling or RAS and does not require the formation of RAF dimers (Poulikakos, P. I. et al. Sci. Signal. 2011 Mar 29, 4(166):pe16).). Activating mutations in *BRAF* have been identified in 8% of human cancers, and are most commonly found in hairy cell leukemias (in virtually all cases), metastatic melanomas (50-60%), papillary thyroid carcinomas (approximately 45%) and colorectal cancers (5-8%) (Pratilas, C. 2012; Xing 2005 docr Relat. Cancer. 2005 Jun;12(2):245-62; Samuel J. N. Engl. J. Med. 2014 Jan 16, 370(3):286-8). The downstream substrates for oncogenic BRAF are MEK1 and MEK2, which are activated through phosphorylation.

[0068] MEK1 and MEK2 are tyrosine and serine/threonine dual-specificity kinases that are very substrate specific and have no known targets other than ERK proteins. ERK (extracellular signal-regulated kinase) 1 and ERK 2 function as the major MAPK effector of the RAS and BRAF oncoproteins. Activated ERK phosphorylates a multitude of downstream targets including RSK (p90 ribosomal S6 kinase). RSK in turn, phosphorylates several cytoplasmic targets and transcriptional regulators. ERK nuclear substrates include the Ternary Complex Factor (TCF)

transcription factors, which play a major role in inducing *IEG (Immediate Early Gene)* expression. The *IEG* products, such as c-Fos and c-Myc in turn, activate late response genes that promote cell survival, proliferation and motility. (Mendoza, M.C. et al. Trends Biochem. Sci. 2011 Trends Biochem Sci. Jun 36(6):320-8. doi).

[0069] To date, efforts to down-regulate the activity of mutant RAS directly have been largely unsuccessful. Most efforts have focused on the inhibition of post-translational modifications of RAS such as carboxyterminal prenylation (e.g. tipifarnib) required for anchoring of RAS or the development of compounds that compete for RAS binding to the inner leaflet of the plasma membrane (e.g. salisarib). The clinical development of these drug candidates in patient populations with RAS mutated tumors has generally not led to clinically-meaningful improvement in outcomes [Baines, A. et al. Future Med. Chem. 2011 Oct 3(14):1787-808; Van Cutsem E et al. 2004).

[0070] In contrast, the successful clinical development of small molecule inhibitors of mutant BRAF and MEK have validated MAPK pathway inhibition as a viable therapeutic approach. The inhibitors of mutant BRAF, vemurafenib (Roche/Genentech, So. San Francisco, CA) and dabrafenib (Glaxo Smith-Klein, city, state) have been approved by the U.S. FDA, European Medicines Agency and Australian TGA for the treatment of locally-advanced or metastatic melanoma in patients with $BRAF^{V600}$ mutations, based on compelling improvements in response rates, progression-free and overall survival compared with dacarbazine chemotherapy (McArthur, G.A. et al. Lancet Oncology, 2014; Hauschild, A. et al. Lancet, 2012, Jul 28, 380(9839):358-65; Lancet Oncol. 2012 Nov 13(11):1087-95). Additionally, Flaherty et al (Flaherty K et al. N Engl. J. Med. 2012 Jul 12;367(2):107-14) reported significant improvements in progression-free and overall survival in association with trametinib, an allosteric oral MEK 1/2 inhibitor, compared with chemotherapy (dacarbazine or paclitaxel) in patients with $BRAF^{V600}$-mutated melanoma, as the basis for its FDA approval. Results associated with MEK inhibitor therapy were not as compelling as those observed among patients treated with BRAF inhibitor therapy, owing at least in part, to the higher therapeutic index of vemurafenib or dabrafenib (which affects BRAF in a mutant-specific manner) compared with MEK inhibitors (McArthur, G.A. et al. Lancet Oncology, 2014; Hauschild, A. et al. Lancet, 2012 Jul 28, 380(9839):358-65; and Lancet Oncol. 2012 Nov 13(11):1087-95). Additionally, Flaherty et al. (Flaherty K et al. N. Engl. J. Med. 2012 Jul 12 367(2):107-14).

[0071] Despite encouraging rates of response, response durations have proven to be short-lived (typically 6-7 months) when these agents are administered as monotherapies owing to the emergence of drug resistance. Several mechanisms mediating resistance to BRAF inhibitors have been described including reactivation of the MAPK pathway via expression of cancer Osaka thyroid (COT) kinase, the occurrence of *de novo* NRAS or MEK mutations and the occurrence of variant splice mutants or amplification of mutant BRAF, among others (Solit, D. & Rosen, N. "Towards a Unified Model of RAF Inhibitor Resistance" Cancer Disc. 2014 Cancer Discov. 2014 Jan 4(1):27-30.; Flaherty K et al NEJM 2012)).

[0072] Activating mutations in MEK 1 and MEK 2 have been described as mechanisms of resistance to MEK inhibitor therapy. Thus, given the above findings , reactivation of the MAPK pathway signaling is an important and most common mechanism of resistance to treatment with BRAF or MEK inhibitors in a majority of melanomas biopsied at progression. (Shi H et al Cancer Discovery 2014. doi: 10.1158/2159-8290.CD-13-0642. Epub 2013 Nov 21; Van Allen et al 2014 Cancer Discov. 2014 Jan, 4(1):94-109).

[0073] A randomized Phase 2 study of the BRAF inhibitor dabrafenib combined with the MEK inhibitor trametinib in patients with BRAF V600 mutant metastatic melanoma demonstrated a higher rate and duration of response and longer progression free survival compared to dabrafenib alone, suggesting that the combination of BRAF and MEK inhibitor therapy may postpone but perhaps not prevent the emergence of resistance (Flaherty KT et al NEJM 2012; Wagle N Cancer Discovery 2013).

[0074] Several recent observations have focused attention on the potential for direct pharmacologic inhibition of ERK as a means to abrogate MAPK pathway activity both in RAS-driven tumors as well as in the setting of resistance to BRAF/MEK inhibition:

[0075] 1.) Hatzivassilou et al. (Mol Cancer Ther. AACR 2-12, 11(5); 1143–54) showed that three RAS mutant cell lines (the basal-like, breast carcinoma cell line MDA-MB-231 and two colorectal cell lines—HCT-116 and LoVo) that were rendered resistant to MEK inhibition remained "addicted" to MAPK pathway activation and that ERK inhibition could overcome MEK inhibitor resistance, suggesting that ERK inhibition may constitute a therapeutic option in the setting of resistance to MEK (and potentially BRAF) inhibitor therapy.

[0076] 2.) Xenograft studies of a selective, highly potent (IC_{50}: 1-4 nanomolar) inhibitor of ERK 1/2 (SCH772984) in nude mice bearing $BRAF^{V600}$ mutant melanomas (LOX IMVI) or

KRAS mutant pancreatic adenocarcinoma (MiaPaCa) showed dose dependent, tumor volume reductions in both models. In the LOX IMVI model, tumor reduction was accompanied by robust inhibition of pERK expression in tumor tissue. Separately, SCH772984 was able to effectively reduce pERK and pRSK expression and inhibit proliferation in a $BRAF^{V600}$ mutant melanoma cell line (A101D) that was rendered dually resistant to BRAF and MEK inhibition. (Cancer Discov; AACR, 2013 3(7); 742–50).

[0077] 3.) In the first report of resistance mechanisms to combined BRAF/MEK inhibitor therapy, Wagle et al. showed that in 5 resistant melanomas subjected to whole exome and RNA sequencing, 3 harbored apparent resistant mechanisms that re-engaged MAPK pathway effectors (one novel MEK2 mutation, one BRAF splice isoform and one BRAF amplification), further suggesting that selective ERK inhibition may afford an opportunity for overcoming BRAF/MEK inhibitor refractory disease in the setting of renewed ERK signaling. (Cancer Discov. 2014 Jan 4(1):61-8. doi: 10.1158/2159-8290.CD-13-0631. Epub 2013 Nov 21).

[0078] Compound **1** is a potent inhibitor of the kinase activities of ERK1 and ERK2 with IC_{50} in the 10-20 nM range. Compound **1** irreversibly inhibits ERK 1 and 2 through formation of a covalent adduct with critical cysteine residues (amino acid 183 in ERK1 and 166 in ERK2) in the vicinity of the ATP binding pocket. In an analysis of 258 kinases, Compound **1** was shown to exhibit good overall kinase selectivity profile.

[0079] Compound **1** has demonstrated potent *in vitro* anti-proliferative activity against a large number of cancer cell lines of various tissue origins. Bioinformatic analyses indicate that tumors with activating mutations of BRAF are enriched within the set of sensitive cell lines to Compound **1**: of the 27 BRAF-mutant cancer cell lines tested, 25 (93%) demonstrated sensitivity to Compound **1** inhibition (GI_{50} <1μM). In the same cancer cell panel screening, 28 of 37 (76%) KRAS-mutant cancer cell lines were sensitive to Compound **1**. Compound **1** exhibits inhibitory activity against A375 melanoma cells that have acquired *in vitro* resistance to BRAF and MEK inhibition. This is of particular importance as resistance to BRAF inhibition has been commonly observed in the clinic and patients whose tumors demonstrated resistance to BRAF inhibitors can be cross-resistant to MEK inhibitors. Under these circumstances, ERK inhibitors may provide effective therapy in tumors resistant to inhibitors of BRAF or MEK.

Rationale for Treating Select Tumor Types

Pancreatic Ductal Adenocarcinoma (PDAC)

[0080] A model for PDAC oncogenesis in which mutational activation of KRAS followed by loss of CDKN2A, TP53 and SMAD4 tumor suppressor genes defines the key genetic steps in the progression from normal epithelium through the various stages of pancreatic intraductal neoplasia to invasive PDAC (Hezel AF, Kimmelman AC, Stanger BZ et al., Genes & Development 2006; 20:1218-49; Yeh JJ, Der C., Expert Opin Ther Targets 2007; 11(5):673-94..). The frequent and early mutation of KRAS in this progression has been particularly well-defined. The completion of whole exome sequencing (WES) of 24 pancreatic cancers, confirmed the most frequently mutated genes and cell signaling pathway aberrations (most of which had previously been identified from in vitro studies). Results of this analysis confirm that aberrant KRAS represents a key driver mutation for pancreatic cancer (Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P., Science 2008;321(5897):1801 6.; Baines AT, Xu D, Der CJ., Future Med Chem 2011; 3(14):1787-1808).

[0081] Morris reported tumor regressions in a MiaPaCa (KRAS-mutant pancreatic cancer) xenograft model in association with treatment of test animals with two doses (25 and 50 mg/kg BID) of SCH772984, a selective, reversible, ATP-competitive inhibitor of ERK 1/2. No significant body weight changes or drug-related lethality was observed at either dose (Morris EJ, Jha S, Restaino CR et al., Cancer Discovery 2013;3:742-50).

Locally Advanced or Metastatic Colorectal Cancer (CRC)

[0082] Activating mutations in KRAS account for approximately 40% of CRC; these involve almost exclusively codons 12 and 13 (Neumann J, Zeindl-Eberhart E, Kirchner T, Jung A., Pathology – Research and Practice 2009; 205:858-62). As for PDAC, mutations in KRAS are an early event in the genetic progression from early foci of intestinal crypt dysplasia to invasive CRC. Gene sequencing studies of 11 colorectal tumors revealed that KRAS was the most frequently mutated oncogene and second only to TP53 mutations for all mutated genes (Baines AT, Xu D, Der CJ., Future Med Chem 2011; 3(14):1787-1808).

[0083] The prognostic significance of *KRAS* mutation in CRC is unclear. Multivariate analyses of large patient series suggest that prognosis may vary for those patient harboring mutations in codon 12 versus 13, with the latter group exhibiting a greater risk of relapse and

shorter overall survival (Yokota T., Anti-cancer Agents in Medicinal Chemistry 2012; 12:163-71). Thus, the biological significance of different mutations involving KRAS is likely to be heterogeneous.

[0084] Approximately 8-10% of unselected CRC patients have tumors that exhibit $BRAF^{V600}$ mutations, with this proportion rising to more than 60% of tumors with high microsatellite instability due to reduced expression of mismatch repair enzymes (Connolly K, Brungs D, Szeto E, Epstein RJ., Curr Oncol 2014; 21:e151-e154.). Mutations in KRAS and BRAF occur mutually exclusively. Certain clinicopathologic features are more prevalent in BRAF mutated than non-BRAF mutated tumors: they more commonly involve the right hemicolon, are more often associated with peritoneal metastasis, and more often poorly differentiated adenocarcinomas or mucinous carcinomas. The negative prognostic significance of BRAF mutation in CRC is well-established (Yokota T., Anti-cancer Agents in Medicinal Chemistry 2012; 12:163-71). In contrast to the high response rates observed in melanoma patients treated with BRAF inhibitors (60-80%), responses have been reported in fewer than 10% of patients with BRAF mutated CRC (Kopetz S, Desai J, Chan E, et al., J Clin Oncol 2010; 28:15s (abstract 3534)); Falchook GS, Long GV, Kurzock R, et al., Lancet 2012; 379:1893-1901). Lack of responsiveness to BRAF inhibition in CRC appears to be the result of de-repression of EGFR-dependent activation of downstream signaling in response to BRAF inhibitor mediated, MAPK pathway suppression (Corcoran RB, Hiromichi E, Turke AB, et al., Cancer Discov 2012; 2(3):227-35; Prahallad A, Sun C, Huang S et al., Nature 2012; 483:100-4).

[0085] Patients whose tumors harbor a KRAS or $BRAF^{V600}$ mutation do not generally benefit from chemotherapy regimens that include anti-EGFR (e.g. cetuximab) therapy (Yokota T., Anti-cancer Agents in Medicinal Chemistry 2012; 12:163-71; Di Nicolantonio F, Martini M, Molinari F, et al., J Clin Oncol 2008; 26:5705-12; Loupakis F, Ruzzo A, Cremolini C et al., Brit J Cancer 2009; 101:715-21). Most such patients are treated for metastatic CRC in the first-line setting with chemotherapy that generally consists of bolus plus infusional 5-fluorouracil (5-FU) and leucovorin (or capcitabine) plus either oxaliplatin (FOLFOX; CAPOX) or irinotecan (FOLFIRI) with bevacizumab. Although there is no clear consensus regarding optimal therapy in second-line, treatment at progression or first relapse often includes a trial of irinotecan (for patients who received oxaliplatin in first-line) or oxaliplatin (for patients treated with irinotecan in first-line) with or without additional 5-FU or investigational therapy.

Locally Advanced or Metastatic Melanoma

[0086] Over 50% of melanomas harbor a common mutation of BRAF kinase in the classical MAPK pathway ($BRAF^{V600}$) and most respond to inhibitors of mutant BRAF and MEK kinases. Numerous resistance mechanisms to single-agent BRAF and MEK inhibitor therapy have been reported based on both in vitro studies as well as interrogation of BRAF/MEK inhibitor-treated melanomas at the time of progression/relapse. Indeed, different resistance mechanisms have been reported in the same progressing tumor in some instances. Most (but not all) mechanisms of resistance appear to re-engage the classical MAPK pathway, as evidenced by the re-expression of pERK and other downstream markers (Solit DB, Rosen N., Cancer Discovery 2014; 4:27-30; Van Allen EM, Wagle N, Sucker A, et al. The genetic landscape of clinical resistance to RAF inhibition in metastatic melanoma. Cancer Discovery 2014; 4(1):94-109). As noted, tumor cell lines with acquired resistance to BRAF and/or MEK inhibition demonstrate retained sensitivity to ERK inhibition (Morris EJ, Jha S, Restaino CR et al., Cancer Discovery 2013;3:742-50; Hatzivassiliou G, Liu B, O'Brien C et al., Mol Cancer Ther 2012; 11:1143-54).

Methods of Treatment

[0087] As described generally above, Compound **1**, and pharmaceutically acceptable salts thereof described herein, is an inhibitor of one or both of ERK1 and ERK2. One of ordinary skill in the art will recognize that ERK is one of the key components in the RAS-RAF-MEK-ERK MAPK pathway and that ERK1 and ERK2 are downstream nodes within the MAPK pathway. Without wishing to be bound by theory, because of the downstream location of ERK1 and ERK1 in the MAPK pathway, an ERK inhibitor can treat disease or disorders in which activation of the MAPK pathway at any level (Ras-Raf-Mek-ERK) is known or suspected to play a role, including one or both of ERK1 and ERK2 as well as other nodes in the MAPK pathway upstream from ERK (such as Ras, Raf and Mek). Furthermore, because ERK is a downstream target, ERK inhibitors are believed to be able to overcome, in some instances, drug resistance induced by inhibitors of targets upstream of ERK within the MAPK pathway. For example, small molecule inhibitors of RAF or MEK utilized in the treatment of K-RAS and B-RAF mutant tumors have resulted in such drug resistance. Similarly, drug resistance has been associated with other tumors driven by hyperactivation of the MAPK pathway (such as NF1 mutant tumors). Kinase selectivity was achieved through silencing the selective Cys in a combination of the interactions

between the covalent inhibitors of the invention and unique amino acids in the ATP binding pocket. Targeting the selective Cys provides for prolonged pharmacodynamics in silencing ERK activity, as well as potential lower doses in cancer treatment, compared to reversible inhibitors.

[0088] As described above, in some embodiments, Compound **1**, and pharmaceutically acceptable salts thereof, are inhibitors of one or both of ERK1 and ERK2 protein kinases, and ERK1 and ERK2 are downstream targets within the MAPK pathway. Without wishing to be bound by any particular theory, such compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder in which activation of the MAPK pathway at any level (Ras-Raf-Mek-ERK) is known or suspected to play a role. Such disease, condition, or disorder may be referred to herein as associated with the MAPK pathway or alternatively as associated with one or both of ERK1 and ERK2. Such diseases, conditions, or disorders may also be refererd to herein as an "ERK1- or ERK2-mediated disease, condition, or disorder."

[0089] In some embodiments, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation of the MAPK pathway (at any level in Ras-Raf-Mek-ERK), including one or both of ERK1 and ERK2 protein kinases, is implicated in said disease, condition, or disorder wherein said method comprises administering to a patient in need thereof Compound **1**, or a pharmaceutically acceptable salt thereof.

[0090] In certain embodiments, the present invention provides a method for overcoming drug resistance to Raf or Mek inhibitors, comprising the step of administering to a patient an inhibitor compound of one or both of ERK1 and ERK2 such as Compound **1**, or a pharmaceutically acceptable salt thereof. In certain embodiments, the mechanism of drug resistance is through mutation of a target protein or reactivation of the MAPK pathway.

[0091] As used herein, the term “resistance” may refer to changes in a wild-type nucleic acid sequence coding a target protein, and/or to the amino acid sequence of the target protein and/or to the amino acid sequence of another protein, which changes, decreases or abolishes the inhibitory effect of the inhibitor on the target protein. The term “resistance” may also refer to overexpression or silencing of a protein differing from a target protein that can reactivate the MAPK pathway or other survival pathways.

[0092] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one

or both of ERK1 and ERK2, the method comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof.

[0093] In some embodiments, treatment is administered after one or more symptoms have developed. In other embodiments, treatment is administered in the absence of symptoms. For example, treatment is administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment is also continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0094] General diseases, disorders, or conditions treated by Compound **1**, and pharmaceutically acceptable salts thereof include cancer, an autoimmune disorder, a neurodegenerative or neurological disorder, liver disease, a cardiac disorder, schizophrenia, or a bone-related disorder.

[0095] In some embodiments, the present invention relates to a method of treating or lessening the severity of a disease, condition, or disorder selected from cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases, wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof.

[0096] In some embodiments, the present invention relates to a method of treating a cancer. For instance, in some embodiments, the present invention provides a method for treating cancer in a patient comprising the step of administering to said patient a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof. In some embodiments, the cancer is recurring. In certain embodiments, the cancer is refractory. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is locally advanced.

[0097] In certain embodiments, the cancer is a RAF inhibitor-resistant cancer. In some such embodiments, the RAF inhibitor-resistant cancer is a BRAF inhibitor-resistant cancer.

[0098] In certain embodiments, the cancer is a MEK inhibitor-resistant cancer.

[0099] In certain embodiments, the cancer is a MAPK-mediated cancer.

[00100] In some embodiments, the cancer is a BRAF-mutated cancer. In certain embodiments, the BRAF-mutated cancer is a $BRAF^{V600}$-mutated cancer, such as $BRAF^{V600E}$ and $BRAF^{V600K}$, $BRAF^{V600R}$, and $BRAF^{V600D}$.

[00101] In some embodiments, the cancer is a RAS-mutated cancer. In certain embodiments, the RAS-mutated involves codons 12, 13, or 61. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$. In certain embodiments, the RAS-mutated cancer is an NRAS-mutated cancer, including, but not limited to, $NRAS^{Q61R}$, $NRAS^{Q61K}$, $NRAS^{Q61L}$, or $NRAS^{Q61H}$. In certain embodiments, the RAS-mutated cancer is an HRAS-mutated cancer, including, but not limited to, $HRAS^{G12V}$, $HRAS^{Q61R}$, and $HRAS^{G12S}$.

[00102] In some embodiments, the cancer is selected from multiple myeloma, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung, bone, colon, thyroid, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma (including uveal melanoma) sarcoma, bladder carcinoma, liver carcinoma (e.g., hepatocellular carcinoma (HCC)) and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colorectal carcinoma, large intestine, rectum, brain and central nervous system, endometrial, multiple myeloma (MM), prostate, AML, and leukemia.

[00103] In some embodiments, the cancer is selected from carcinoma, lymphoma, blastoma, sarcoma, and leukemia. In some embodiments, a sarcoma is a soft tissue sarcoma. In some embodiments, a lymphoma is non-hodgkins lymphoma. In some embodiments, a lymphoma is large cell immunoblastic lymphoma. In some embodiments, the cancer is selected from adenocarcinoma; adenoma; adrenocortical cancer; bladder cancer; bone cancer; brain cancer; breast cancer; cancer of the buccal cavity; cervical cancer; colon cancer; colorectal cancer; endometrial or uterine carcinoma; epidermoid carcinoma; esophageal cancer; eye cancer; follicular carcinoma; gallbladder cancer; prostate, AML, multiple myeloma (MM), gastrointestinal cancer, such as, for example, gastrointestinal stromal tumor; cancer of the genitourinary tract; glioblastoma; hairy cell carcinoma; various types of head and neck cancer; hepatic carcinoma; hepatocellular cancer; Hodgkin's disease; keratoacanthoma; kidney cancer;

large cell carcinoma; cancer of the large intestine; laryngeal cancer; liver cancer; lung cancer, such as, for example, adenocarcinoma of the lung, anaplastic carcinoma of the lung, papillary lung adenocarcinoma, small-cell lung cancer, squamous carcinoma of the lung, non-small cell lung cancer; melanoma and nonmelanoma skin cancer; lymphoid disorders; myeloproliferative disorders, such as, for example, polycythemia vera, essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), hypereosinophilic syndrome, systematic mast cell disease, atypical CML, AML, or juvenile myelomonocytic leukemia; plasmacytoma; multiple myeloma; neuroblastoma; ovarian cancer; papillary carcinoma; pancreatic cancer; cancer of the peritoneum; prostate cancer, including benign prostatic hyperplasia; rectal cancer; salivary gland carcinoma; sarcoma; seminoma; squamous cell cancer; small cell carcinoma; cancer of the small intestine; stomach cancer; testicular cancer; thyroid cancer; undifferentiated carcinoma; and vulval cancer.

[00104] In certain embodiments, the cancer is selected from melanoma, pancreatic cancer, thyroid cancer, colorectal cancer, lung cancer (e.g., non-small cell lung cancer), breast cancer, endometrial cancer, prostate cancer, ovarian cancer, hepatocellular carcinoma (HCC), multiple myeloma (MM), and leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia. In certain embodiments, a leukemia is acute lymphoblastic leukemia.

[00105] In some embodiments, the cancer is selected from melanoma, colorectal cancer, lung cancer, or pancreatic cancer.

[00106] In some embodiments, the cancer is melanoma. In certain embodiments, the melanoma is uveal melanoma. In some embodiments, the melanoma is a melanoma of the skin. In certain embodiments, the melanoma is locally advanced. In some embodiments, the melanoma is metastatic. In some embodiments, the melanoma is recurring. In some embodiments, the melanoma is refractory. In some embodiments, the melanoma is $BRAF^{v600}$-mutated melanoma. In certain embodiments, the melanoma is a RAS-mutated melanoma. In some embodiments, the melanoma is NRAS-mutated melanoma. In certain embodiments, the melanoma is wild type for KRAS, NRAS or BRAF. In certain embodiments, the melanoma is a BRAF inhibitor-resistant (e.g., Vemurfenib-resistant, dabrafenib-resistant, encorafenib-resistant,

etc.) melanoma. In certain embodiments, the cancer is a VemR (i.e., Vemurfenib-resistant) BRAF-mutated melanoma.

[00107] In some embodiments, the cancer is colorectal cancer. In certain embodiments, the colorectal cancer is locally advanced. In certain embodiments, the colorectal cancer is metastatic. In certain embodiments, the colorectal cancer is recurring. In certain embodiments, the colorectal cancer is refractory. In certain embodiments, the colorectal cancer is a BRAF-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a $BRAF^{v600}$-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a RAS-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a KRAS-mutated colorectal cancer. In certain embodiments, the colorectal cancer is a NRAS-mutated colorectal cancer.

[00108] In some embodiments, the cancer is pancreatic cancer. In certain embodiments, the pancreatic cancer is locally advanced. In certain embodiments, the pancreatic cancer is metastatic. In certain embodiments, the pancreatic cancer is locally recurring. In certain embodiments, the pancreatic cancer is refractory. In certain embodiments, the pancreatic cancer is a pancreatic ductal adenocarcinoma (PDAC). In certain embodiments, the pancreatic cancer is a RAS-mutated pancreatic cancer. In certain embodiments, the pancreatic cancer is a KRAS-mutated pancreatic cancer. In certain embodiments, the pancreatic cancer is KRAS-mutated pancreatic cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$.

[00109] In some embodiments, the cancer is a papillary thyroid cancer. In certain embodiments, the papillary thyroid cancer is locally advanced. In some embodiments, the papillary thyroid cancer is metastatic. In certain embodiments, the papillary thyroid cancer is refractory. In some embodiments, the papillary thyroid cancer is recurring. In some embodiments, the papillary thyroid cancer is BRAF-mutated papillary thyroid cancer. In some embodiments, the papillary thyroid cancer is $BRAF^{v600}$-mutated papillary thyroid cancer. In some embodiments, the papillary thyroid cancer includes undifferentiated or dedifferentiated histology.

[00110] In some embodiments, the cancer is lung cancer. In certain embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In certain embodiments, the lung cancer is locally advanced. In certain embodiments, the lung cancer is metastatic. In certain embodiments, the lung cancer is recurring. In certain embodiments, the lung cancer is refractory. In certain embodiments, the lung cancer is a RAS-mutated lung cancer. In certain embodiments,

the lung cancer is KRAS-mutated lung cancer. In certain embodiments, the lung cancer is a KRAS-mutated lung cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$.

[00111] In certain embodiments, the cancer is a leukemia. In some embodiments, a leukemia is a chronic leukemia. In certain embodiments, a leukemia is chronic myeloid leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia (AML). In certain embodiments, a leukemia is acute monocytic leukemia (AMoL, or AML-M5). In certain embodiments, a leukemia is acute lymphoblastic leukemia (ALL). In certain embodiments, a leukemia is acute T cell leukemia. In certain embodiments, a leukemia is myelomonoblastic leukemia. In certain embodiments, a leukemia is human B cell precursor leukemia. In certain embodiments, a leukemia has a Flt3 mutation or rearrangement.

[00112] In some embodiments, the cancer is a CNS cancer, for instance CNS tumors. In certain embodiments, a CNS tumor is a glioblastoma or glioblastoma multiforme (GBM). In some embodiments, the present invention relates to a method of treating stomach (gastric) and esophageal tumors and cancers.

[00113] In some embodiments, the cancer is multiple myeloma (MM). In certain embodiments, the multiple myeloma is locally advanced. In certain embodiments, the multiple myeloma is metastatic. In certain embodiments, the multiple myeloma is locally recurring. In certain embodiments, the multiple myeloma is refractory. In certain embodiments, the multiple myeloma is a RAS-mutated multiple myeloma. In certain embodiments, the multiple myeloma is KRAS-mutated multiple myeloma. In certain embodiments, the RAS-mutated multiple myeloma is a KRAS-mutated multiple myeloma, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$, or $KRAS^{Q61L/H/R}$.

[00114] In some embodiments, the cancer is hepatocellular carcinoma (HCC). In certain embodiments, the HCC is locally advanced. In certain embodiments, the HCC is metastatic. In certain embodiments, the HCC is locally recurring. In certain embodiments, the HCC is refractory. In certain embodiments, the cancer is a RAS-mutated HCC. In certain embodiments, the cancer is KRAS-mutated HCC. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$, or $KRAS^{Q61L/H/R}$.

[00115] In some embodiments, the cancer is selected from breast, colorectal, endometrial, hematological, leukemia (e.g., AML), liver, lung, melanoma, ovarian, pancreatic, prostate, or thyroid.

[00116] In some embodiments, the cancer is selected from breast, colorectal, endometrial, liver, lung, melanoma, ovarian, pancreatic, or thyroid.

[00117] In some embodiments, the cancer is selected from colorectal, lung, melanoma, or pancreatic.

[00118] In some embodiments, the cancer is selected from colorectal, melanoma, or pancreatic.

[00119] In certain embodiments, the cancer is a RAF inhibitor resistant cancer, for example the cancer is a BRAF inhibitor resistant cancer. In certain embodiments, the cancer is a MEK inhibitor resistant cancer.

Dosing

[00120] As described above, the present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or conditions associated with one or both of ERK1 and ERK2, wherein the method comprises administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof. It is understood that in instances where the methods described herein refer to administering Compound **1**, such methods are equally applicable to methods of administering a salt form of Compound **1**, e.g., a phosphate salt of Compound **1**. Accordingly, methods provided herein are to be understood to encompass either the administration of Compound **1** or a pharmaceutically acceptable salt thereof.

[00121] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 1% to about 60% of Compound **1**, or a pharmaceutically acceptable salt thereof, based upon total weight of the formulation.

[00122] In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising the phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 2% to about

18% or about 4% to about 12% or about 5% to about 10% or about 6% to about 9% or about 7% to about 8% of the phosphate salt of Compound **1** based upon total weight of the composition. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14% or about 15% of the phosphate salt of Compound **1**, based on total weight of the composition.

[00123] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 20% to about 60% or about 25% to about 55% or about 30% to about 50% or about 40% to about 50% or about 45% to 46% of the phosphate salt of Compound **1** based upon total weight of the formulation. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 25%, about 30%, about 35%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, or about 55% of the phosphate salt of Compound **1**, based on total weight of the composition.

[00124] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, or about 13% of the phosphate salt of Compound **1** based upon total weight of given composition or formulation. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 43%, about 44%, about 45%, about 46%, about 47%, or about 48% of the phosphate salt of Compound **1** based upon total weight of given composition or formulation.

[00125] In some embodiments, provided methods comprise administering a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, one, two, three, or four times a day.

[00126] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once daily ("QD").

[00127] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered twice daily. In some

embodiments, twice daily administration refers to a compound or composition that is administered "BID". A "BID" dose is a particular dose (e.g., a 150 mg dose) that is administered twice a day (i.e., two doses of 150 mg administered at two different times in one day). In some embodiments, twice daily administration refers to a compound or composition that is administered in two different doses, wherein the first administered dose differs from the second administered dose. For example, a 180 mg dose administered twice daily can be administered as two separate doses, one 150 mg dose and one 30 mg dose, wherein each dose is administered at a different time in one day. Alternatively, a 180 mg dose administered twice daily can be administered 90 mg BID (i.e., three 30 mg doses administered at different times in one day). By way of non-limiting example, a total daily dose of 180 mg of Compound **1**, or a pharmaceutically acceptable salt thereof, can be administered as a 150 mg dose administered at a given timepoint (for example, in the morning) and a 30 mg dose administered at a later timepoint (for example, in the evening).

[00128] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered three times a day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered "TID", or three equivalent doses administered at three different times in one day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in three different doses, wherein at least one of the administered doses differs from another administered dose.

[00129] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered four times a day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered "QID" , or four equivalent doses administered at four different times in one day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in four different doses, wherein at least one of the administered doses differs from another administered dose.

[00130] In some embodiments, provided methods comprise administering a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof,

once a day ("QD"). In some embodiments, provided methods comprise administering a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, twice a day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered once or twice daily for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 days. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered once daily for a period of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27 or 28 days.

[00131] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once or twice daily for an amount of time during a period of 28 days ("a 28-day cycle"). In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once or twice daily for at least one 28-day cycle. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once daily for 21 consecutive days of at least one 28-day cycle. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once or twice daily for at least two, at least three, at least four, at least five or at least six 28-day cycles. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once or twice daily for at least seven, at least eight, at least nine, at least ten, at least eleven or at least twelve 28-day cycles. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once or twice daily for at least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen, at least nineteen or at least twenty 28-day cycles. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered to a patient for the duration of the patient's life.

[00132] In some embodiments, two adjacent 28-day cycles may be separated by a rest period. Such a rest period may be one, two, three, four, five, six, seven or more days during which the patient is not administered a unit dose of Compound **1**, or a pharmaceutically acceptable salt thereof. In a preferred embodiment, two adjacent 28-day cycles are continuous.

[00133] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once or twice daily for at least two, at least three, at least four, at least five consecutive days every seven days. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once daily for at least five consecutive days every seven days. In some embodiments, Comound 1, or a pharmaceutically acceptable salt thereof, is administered every other day. In some embodiments, Comound 1, or a pharmaceutically acceptable salt thereof, is administered every third day.

Unit Dosage Forms

[00134] Provided formulations may be prepared as a unit dosage form. Indeed, a tablet or capsule is typically a unit dosage form. A person of ordinary skill will appreciate that the unit dosage forms described herein refer to an amount of the active pharmaceutical ingredient, i.e., free base form Compound **1**. A person skilled in the art will further appreciate that, when a pharmaceutical composition comprises a salt form of Compound **1**, for example a phosphate salt form, the amount of the salt form present in the composition is an amount that is equivalent to a unit dose of the free base Compound **1**. For example, a pharmaceutical composition comprising the phosphate salt of Compound **1** would contain 6.07 mg of the phosphate salt form necessary to deliver an equivalent 5 mg unit dose of the free base Compound **1**. In some embodiments, a unit dosage form contains 5 mg Compound **1**. In some embodiments, a unit dosage form contains 30 mg Compound **1**. In some embodiments, a unit dosage form contains 150 mg Compound **1**.

[00135] In some embodiments, the present invention provides a method for treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 in a patient in need thereof, comprising the step of administering to said patient one or more unit doses of a provided formulation. In some embodiments, the present invention provides a method for treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 in a patient in need thereof comprising the step of administering to said patient one or more unit doses of the present invention wherein said unit dose provides about 5 mg to about 1000 mg of Compound **1**. In certain embodiments, a formulation of the present invention

provides about 1 mg, 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, or about 1000 mg of Compound **1**.

[00136] In some embodiments, the present invention provides a method for treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 in a patient in need thereof, comprising the step of administering to said patient one or more unit doses of the present invention wherein a unit dose provides about 5 mg, 30 mg, or 150 mg of Compound **1**. In certain embodiments, a unit dose formulation of the present invention provides about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, or about 150 mg of Compound **1**.

[00137] In some embodiments, the present invention provides a method for treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 in a patient in need thereof, comprising the step of administering to said patient one or more unit doses comprising the phosphate salt of Compound **1**, wherein the phosphate salt of Compound **1** is in an amount equivalent to any of the above unit dosage amounts of Compound **1**.

[00138] In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 1 mg to about 10 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 2 mg to about 8 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 4 mg to about 6 mg. In some embodiments, provided methods

comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 5 mg.

[00139] In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 20 mg to about 40 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 25 mg to about 35 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 28 mg to about 32 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 30 mg.

[00140] In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 100 mg to about 200 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 125 mg to about 175 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 140 mg to about 160 mg. In some embodiments, provided methods comprise administering to a patient in need thereof a composition comprising a unit dose of Compound **1**, wherein the unit dose is about 150 mg.

[00141] In some embodiments, a unit dose of Compound **1** is administered once a day (QD). In some embodiments, a unit dose of Compound **1** is administered twice a day . In some embodiments, a unit dose of Compound **1** is administered BID.

[00142] In some embodiments, the unit dose of Compound **1** is about 25 mg to 750 mg, or about 25 mg to about 625 mg, or about 25 mg to about 500 mg, or about 25 mg to about 375 mg, or about 25 mg to about 250 mg, or about 25 mg to about 125 mg, or about 25 mg to about 75 mg, or about 75 mg to about 750 mg, or about 75 mg to about 625 mg, or about 75 mg to about 500 mg, or about 75 mg to about 375 mg, or about 75 mg to about 250 mg, or about 75 mg to about 125 mg, or about 125 mg to about 750 mg, or about 125 mg to about 625 mg, or about 125 mg to about 500 mg, or about 125 mg to about 375 mg, or about 125 mg to about 250 mg, or about 250 mg to about 750 mg, or about 250 mg to about 625 mg, or about 250 mg to about 500

mg, or about 250 mg to about 375 mg, or about 375 mg to about 750 mg, or about 375 mg to about 625 mg, or about 375 mg to about 500 mg, or about 500 mg to about 750 mg, or about 500 mg to about 625 mg, or about 625 mg to about 750 mg.

[00143] In some embodiments, the unit dose of Compound **1** is about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745mg or about 750 mg.

[00144] In some embodiments, Compound **1** is administered once a day. In certain embodiments, Compound **1** is administered once a day in the morning. In certain embodiments, Compound **1** is administered once a day at night. In certain embodiments, Compound **1** is

administered once a day under fasted conditions. In certain embodiments, Compound **1** is administered once a day in the morning under fasted conditions.

[00145] In some embodiments, Compound **1** is administered two, three or four times a day. In some embodiments, Compound **1** is administered two, three or four times a day, wherein each dose is identical. In some embodiments, Compound **1** is administered two, three or four times a day, wherein at least one dose is different from another dose. In some such embodiments, each dose may be independently selected from those doses or dose ranges in the two preceeding paragraphs.

[00146] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutical composition comprising one or more unit doses of Compound **1**. In some such embodiments, a unit dose is about 5mg, about 30 mg, or about 150 mg and is present in the form of the phosphate salt of Compound **1**.

[00147] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, the method comprising administering to a patient in need thereof a solid oral dosage form comprising a unit dose of Compound **1**, wherein the unit dose is about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, or about 250 mg.

[00148] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of Compound **1**, wherein the therapeutically effective amount is a total daily dose selected from about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about

275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2950 mg, or about 3000 mg.

[00149] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of Compound **1**, wherein the

therapeutically effective amount is a total daily dose is about 100 mg to about 3000 mg, or about 500 mg to about 3000 mg, or about 100 mg to about 2500 mg, or about 500 mg to about 2500 mg, or about 100 mg to about 2200 mg, or about 500 mg to about 2200 mg, or about 600 mg to about 2200 mg, or about 700 mg to about 2200 mg, or about 800 to about 2200 mg, or about 800 to about 2100 mg, or about 800 to about 2000 mg. In certain embodiments, the daily dose is about 800 mg to about 2000 mg.

[00150] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, the method comprising administering to a patient in need thereof a therapeutically effective amount of Compound **1**, wherein the therapeutically effective amount is a total daily dose is about 10 mg to about 500 mg, or about 10 mg to about 450 mg, or about 10 mg to about 425 mg, or about 10 mg to about 400 mg, or about 10 mg to about 375 mg, or about 10 mg to about 350 mg, or about 10 mg to about 325 mg, or about10 mg to about 300 mg, or about 10 mg to about 275 mg, or about 10 to about 250 mg, or about 10 to about 225 mg, or about 10 mg to about 200 mg, or about 10 mg to about 190 mg, or about 10 mg to about 180 mg, or about 10 mg to about 170 mg, or about 10 mg to about 160 mg, or about 10 mg to about 150 mg, or about 10 mg to about 140 mg, or about 10 mg to about 130 mg, or about 10 mg to about 120 mg, or about 10 mg to about 110 mg, or about 10 mg to about 100 mg, or about 10 mg to about 90 mg, or about 10 mg to about 80 mg, or about 10 mg to about 70 mg, or about 10 mg to about 60 mg, or about 10 mg to about 50 mg, or about 10 mg to about 40 mg, or about 10 mg to about 30 mg, or about 20 mg to about 40 mg, or about 20 mg to about 60 mg, or about 20 mg to about 80 mg, or about 40 mg to about 200 mg, or about 40 mg to about 160 mg, or about 80 mg to about 320 mg, or about 80 mg to about 160 mg.

[00151] In some embodiments, a total daily dose of Compound **1** is administered as a single dose.

[00152] In some embodiments, a total daily dose of Compound **1** is administered as two, three or four doses in one day, wherein each dose is identical.

[00153] In some embodiments, a total daily dose of Compound **1** is administered as two, three or four doses in one day, wherein at least one dose is different from another dose.

[00154] When more than one dose is administered in one day, the doses are independently selected from about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg,

about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about 680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, or about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg,

about 2600 mg, about 2650 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2950 mg, or about 3000 mg.

[00155] In some embodiments, a total daily dose of Compound **1** is administered once daily (QD), wherein the dose is selected from about 5 mg, about 10 mg, about 20 mg, about 40 mg, about 80 mg, about 120 mg, about 180 mg, about 330 mg, about 480 mg, or about 640 mg.

[00156] In some embodiments, a total daily dose of Compound **1** is administered once daily (QD), wherein the dose is selected from about 20 mg, about 40 mg, about 80 mg, or about 160 mg.

[00157] In some embodiments, a total daily dose of Compound **1** is administered once daily (QD), wherein the therapeutically effective amount is a total daily dose selected from about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, about 120 mg, about 125 mg, about 130 mg, about 135 mg, about 140 mg, about 145 mg, about 150 mg, about 155 mg, about 160 mg, about 165 mg, about 170 mg, about 175 mg, about 180 mg, about 185 mg, about 190 mg, about 195 mg, about 200 mg, about 205 mg, about 210 mg, about 215 mg, about 220 mg, about 225 mg, about 230 mg, about 235 mg, about 240 mg, about 245 mg, about 250 mg, about 255 mg, about 260 mg, about 265 mg, about 270 mg, about 275 mg, about 280 mg, about 285 mg, about 290 mg, about 295 mg, about 300 mg, about 305 mg, about 310 mg, about 315 mg, about 320 mg, about 325 mg, about 330 mg, about 335 mg, about 340 mg, about 345 mg, about 350 mg, about 355 mg, about 360 mg, about 365 mg, about 370 mg, about 375 mg, about 380 mg, about 385 mg, about 390 mg, about 395 mg, about 400 mg, about 405 mg, about 410 mg, about 415 mg, about 420 mg, about 425 mg, about 430 mg, about 435 mg, about 440 mg, about 445 mg, about 450 mg, about 455 mg, about 460 mg, about 465 mg, about 470 mg, about 475 mg, about 480 mg, about 485 mg, about 490 mg, about 495 mg, about 500 mg, about 505 mg, about 510 mg, about 515 mg, about 520 mg, about 525 mg, about 530 mg, about 535 mg, about 540 mg, about 545 mg, about 550 mg, about 555 mg, about 560 mg, about 565 mg, about 570 mg, about 575 mg, about 580 mg, about 585 mg, about 590 mg, about 595 mg, about 600 mg, about 605 mg, about 610 mg, about 615 mg, about 620 mg, about 625 mg, about 630 mg, about 635 mg, about 640 mg, about 645 mg, about 650 mg, about 655 mg, about 660 mg, about 665 mg, about 670 mg, about 675 mg, about

680 mg, about 685 mg, about 690 mg, about 695 mg, about 700 mg, about 705 mg, about 710 mg, about 715 mg, about 720 mg, about 725 mg, about 730 mg, about 735 mg, about 740 mg, about 745 mg, about 750 mg, about 760 mg, about 770 mg, about 780 mg, about 790 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1125 mg, about 1150 mg, about 1175 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2950 mg, or about 3000 mg.

[00158] In some embodiments, a total daily dose of Compound **1** is administered once daily (QD), wherein the dose is selected from about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 35 mg, about 400 mg, about 450 mg, about 500 mg, about 550 mg, about 600 mg, about 650 mg, about 700 mg, about 750 mg, about 800 mg, about 850 mg, about 900 mg, about 950 mg, about 1000 mg, about 1050 mg, about 1100 mg, about 1150 mg, about 1200 mg, about 1250 mg, about 1300 mg, about 1350 mg, about 1400 mg, about 1450 mg, about 1500 mg, about 1550 mg, about 1600 mg, about 1650 mg, about 1700 mg, about 1750 mg, about 1800 mg, about 1850 mg, about 1900 mg, about 1950 mg, about 2000 mg, about 2050 mg, about 2100 mg, about 2150 mg, about 2200 mg, about 2250 mg, about 2300 mg, about 2350 mg, about 2400 mg, about 2450 mg, about 2500 mg, about 2550 mg, about 2600 mg, about 2650 mg, about 2700 mg, about 2750 mg, about 2800 mg, about 2850 mg, about 2900 mg, about 2950 mg, or about 3000 mg.

[00159] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered twice daily. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered "BID". In some embodiments, a

pharmaceutically acceptable composition comprising Compound **1** is administered in two different doses, wherein the first administered dose differs from the second administered dose.

[00160] In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered three times a day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered "TID". In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered in three different doses, wherein at least one of the administered doses differs from another administered dose. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered four times a day. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered "QID". In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered in four different doses, wherein at least one of the administered doses differs from another administered dose.

[00161] In some embodiments, a total daily dose of Compound **1** is administered to a patient once a day under fasted conditions. In some such embodiments, the total daily dose is any of those contemplated above and herein.

[00162] In some embodiments, a total daily dose of 100 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 200 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 300 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 400 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 500 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 600 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 700 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 800 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 900 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1000 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1100 mg of Compound **1** is administered

to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1200 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1300 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1400 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1500 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1600 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1700 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1800 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 1900 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of 2000 mg of Compound **1** is administered to a patient once a day, under fasted conditions. In some embodiments, a total daily dose of greater than 2000 mg of Compound **1** is administered to a patient once a day, under fasted conditions.

[00163] In some embodiments, a therapeutically effective amount of Compound **1** is administered over a period of 28 consecutive days ("a 28-day cycle").

[00164] In some embodiments, a therapeutically effective amount of Compound **1** is administered over a period of 28 consecutive days ("a 28-day cycle"), wherein dosing occurs daily for 21 consecutive days out of a 28 day cycle. In some such embodiments, dosing occurs once daily. In some such embodimemts, dosing occurs once daily under fasting conditions.

[00165] In some embodiments, a therapeutically effective amount of Compound **1** is administered for two, three, four, five or six 28-day cycles. In some embodiments, a therapeutically effective amount of Compound **1** is administered for seven, eight, nine, ten, eleven, twelve or more 28-day cycles. In some embodiments, a pharmaceutically acceptable composition comprising Compound **1** is administered for at least thirteen, at least fourteen, at least fifteen, at least sixteen, at least seventeen, at least eighteen, at least nineteen or at least twenty 28-day cycles. In some embodiments, a therapeutically effective amount of Compound **1** is administered to a patient for the duration of the patient's life.

Formulations Comprising Compound 1 or a Pharmaceutically Acceptable Salt Thereof

[00166] As described above, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof. In some embodiments, the pharmaceutically acceptable composition is an oral dosage form. In some embodiments, the pharmaceutically acceptable composition is formulated as a capsule. In some embodiments, the pharmaceutically acceptable composition is a blended powder.

[00167] In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, such as, for example, one or more solubilizers, surfactants/wetting agents, dispersing agents, fillers, disintegrants, glidants and lubricants. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising the phosphate salt of Compound **1**.

[00168] In certain embodiments, the present invention provides a composition comprising a pharmaceutically acceptable salt form of Compound **1** selected from the group consisting of phosphate salt forms, HCl salt forms, HBr salt forms, bis-phosphate salt forms, sulfate salt forms, bis-sulfate salt forms, tosylate salt forms, mesylate salt forms, besylate salt forms, maleate salt forms, and oxalate salt forms. In some embodiments, the present invention provides a composition comprising a pharmaceutically acceptable salt form of Compound **1** selected from the group consisting of phosphate salt forms.

[00169] One skilled in the art will readily appreciate that the category under which a particular component is listed is not intended to be limiting; in some cases a particular component might appropriately fit in more than one category. Also, as will be appreciated, the same component can sometimes perform different functions, or can perform more than one function, in the context of a particular formulation, for example depending upon the amount of the ingredient and/or the presence of other ingredients and/or active compound(s).

i. Solubilizers

[00170] In certain embodiments, provided formulations may comprise one or more solubilizers. Solubilizers include, by way of example and without limitation, cyclodextrins such

as alpha-cyclodextrin, beta-cyclodextrin, gamma-cyclodextrin, 2-hydroxypropyl-beta-cyclodextrin, hydroxymethyl cyclodextrin, hydroxyethyl cyclodextrin, and hydroxybutyl cyclodextrin, carboxymethyl cyclodextrin, carboxyethyl cyclodextrin, carboxypropyl cyclodextrin, carboxybutyl cyclodextrin, methylcarboxymethyl cyclodextrin; amino cyclodextrin, sulfobutyl-ether-β-cyclodextrin sodium salt ("SBECD", also referred to herein as betadex sulfobutyl ether sodium, sulfobutylether betacyclodextrin, or SBE betacyclodextrin), and the like, and combinations thereof. In certain embodiments, the solubilizer is sulfobutyl-ether-β-cyclodextrin sodium salt.

[00171] In some embodiments, provided compositions comprise from about 1% to about 50% solubilizer, based on the total weight of the composition. In some embodiments, provided compositions comprise from about 1% to about 45%, or about 1% to about 40%, or about 1% to about 35%, or about 1% to about 30%, or about 1% to about 25%, or about 1% to about 20% solubilizer based on the total weight of the composition.

[00172] In certain embodiments, provided compositions comprise about 1% to about 10% solubilizer, based on the total weight of composition. In certain embodiments, provided compositions comprise about 1% to about 9%, or about 1% to about 8%, or about 1% to about 7%, or about 1% to about 6%, or about 1% to about 5%, or about 2% to about 4% solubilizer based on the total weight of the composition. In some embodiments, provided compositions comprise a solubilizer in an amount of about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9%, about 3.0%, about 3.1%, about 3.2%, about 3.3%, about 3.4%, about 3.5%, about 3.6%, about 3.7%, about 3.8%, about 3.9%, or about 4.0%. In certain embodiments, provided compositions comprise a solubilizer in an amount of about 3.33%.

[00173] In certain embodiments, provided compositions comprise about 10% to about 30% solubilizer, based on the total weight of composition. In certain embodiments, provided compositions comprise about 10% to about 25%, or about 15% to about 25%, or about 17% to about 23%, or about 18% to about 22%, or about 19% to about 21% solubilizer based on the total weight of the composition. In some embodiments, provided compositions comprise a solubilizer in an amount of about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about

24%, about 25%, about 26%, about 27%, about 28%, about 29%, about 30%, about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, or about 40%. In certain embodiments, provided compositions comprise a solubilizer in an amount of about 20%.

[00174] In some embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt as a solubilizer in an amount of about 1% to about 45%, or about 1% to about 40%, or about 1% to about 35%, or about 1% to about 30%, or about 1% to about 25%, or about 1% to about 20% solubilizer based on the total weight of the composition.

[00175] In some embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt as a solubilizer in an amount of about 1% to about 10%. In some embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt as a solubilizer in an amount of about 1% to about 9%, or about 1% to about 8%, or about 1% to about 7%, or about 1% to about 6%, or about 1% to about 5%, or about 2% to about 4%. In certain embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt as a solubilizer in an amount of about 3.33%.

[00176] In some embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt as a solubilizer in an amount of about 10% to about 30%. In some embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt in an amount of about 10% to about 25%, or about 15% to about 25%, or about 17% to about 23%, or about 18% to about 22%, or about 19% to about 21%. In certain embodiments, provided compositions comprise sulfobutyl-ether- -cyclodextrin sodium salt as a solubilizer in an amount of about 20%.

ii. Surfactants/Wetting Agents

[00177] Surfactants/wetting agents are well known in the art and typically facilitate drug release and absorption by enhancing the solubility of poorly-soluble drugs. Representative surfactants/wetting agents include, but are not limited to, poloxamers, polyoxyethylene ethers (e.g., polyethylene glycol), polyoxyethylene sorbitan fatty acid esters, polyoxyethylene fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene hydrogenated castor oil, polyoxyethylene alkyl ether, polysorbates such as polysorbate 80, cetyl alcohol, glycerol fatty acid esters (e.g., triacetin, glycerol monostearate, and the like), polyoxymethylene stearate,

sodium lauryl sulfate, sorbitan fatty acid esters, sucrose fatty acid esters, benzalkonium chloride, polyethoxylated castor oil, docusate sodium, Vitamin E TPGS, copovidone, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), cellulose such as methylcellulose (MC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropylmethyl cellulose (HPMC), carboxymethylcellulose (CMC), hydroxyethylmethyl cellulose (HEMC), phospholipids (e.g., lecithin), hydrogenated phospholipids, Soluplus® (i.e., polyvinyl caprolactam/polyvinyl acetate/polyethylene glycol graft copolymer) and the like, and combinations thereof.

[00178] In some embodiments, provided compositions comprise from about 0.1% to about 10%, or from about 0.1% to about 9%, or from about 0.1% to about 8%, or from about 0.1% to about 7%, or from about 0.1% to about 6%, or from about 0.1% to about 5%, or from about 0.1% to about 4%, or from about 0.1% to about 3%, or from about 0.1% to about 2% surfactant/wetting agent, or from about 0.1% to about 1%, or from about 0.1% to about 0.5%, or from about 0.2% to about 0.4% surfactant/wetting agent based upon total weight of the formulation.

[00179] In some embodiments, provided compositions comprise from about 0.1% to about 10%, or from about 0.2% to about 8%, or from about 0.5% to about 5%, or from about 1% to about 5%, or from about 1% to about 4%, or from about 1% to about 3%, or from about 1.5% to about 2.5% surfactant/wetting agent based upon total weight of the formulation. In certain embodiments, a provide composition comprises about 2% surfactant/wetting agent.

[00180] In some embodiments, provided compositions comprise about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2.0%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9% or about 3.0% surfactant/wetting agent. In certain embodiments, a provide composition comprises about 0.33% surfactant/wetting agent.

[00181] In certain embodiments, a surfactant/wetting agent is a surfactant/wetting agent such as sodium lauryl sulfate (SLS). For instance, in certain embodiments, a surfactant/wetting agent is sodium lauryl sulfate in an amount of about 0.1% to about 10%, or from about 0.1% to about 9%, or from about 0.1% to about 8%, or from about 0.1% to about 7%, or from about 0.1% to about 6%, or from about 0.1% to about 5%, or from about 0.1% to about 4%, or from about 0.1%

to about 3%. In certain embodiments, a surfactant/wetting agent is sodium lauryl sulfate in an amount of about 2%.

[00182] In certain embodiments, a surfactant/wetting agent is sodium lauryl sulfate in an amount of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2.0%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9% or about 3.0%. In certain embodiments, a surfactant/wetting agent is sodium lauryl sulfate in an amount of about 0.33%.

iii. Dispersing Agents

[00183] In certain embodiments, provided formulations may comprise one or more dispersing agents. Dispersing agents are substances added to a formulation to prevent settling, clumping, or gelling. For instance, compound 2 in certain formulations has a tendency to gel in the presence of moisture. It has been found that the use of certain dispersing agents can minimize such gelling. Dispersing agents include, by way of example and without limitation, salts such as sodium carbonate, sodium bicarbonate, sodium phosphate tribasic, sodium phosphate dibasic, sodium phosphate monobasic, potassium chloride, potassium bicarbonate, potassium carbonate, potassium phosphate monobasic, and sodium chloride, sugars such as mannitol, fructose, sucrose, xylitol maleic acid, sorbitol, and dextrose, and acids such as D,L-malic acid, and the like, and combinations thereof.

[00184] In some embodiments, provided compositions comprise from about 0.1% to about 20% dispersing agent, based on the total weight of the composition. In some embodiments, provided compositions comprise from about 0.1% to about 15%, or about 0.1% to about 10%, or about 0.1% to about 8%, or about 0.1% to about 7%, or about 0.1% to about 6%, or about 0.1% to about 5%, or about 0.1% to about 4%, or about 0.1% to about 3%, or about 0.1% to about 2%, or about 0.1% to about 1%, or about 0.2% to about 0.8%, or about 0.2% to about 0.6%, or about 0.3% to about 0.5% dispersing agent.

[00185] In some embodiments, provided compositions comprise from about 0.5% to about 10%, or about 0.5% to about 5%, or about 1% to about 5%, or about 1% to about 4%, or about 1% to about 3.5%, or about 1.5% to about 3.5%, or about 2% to about 3% dispersing agent.

[00186] In certain embodiments, provided compositions comprise about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9% or about 3.0% dispersing agent.

[00187] In certain embodiments, provided compositions comprise about 0.4% dispersing agent. In certain embodiments, provided compositions comprise about 0.5% dispersing agent. In certain embodiments, provided compositions comprise about 0.42% dispersing agent.

[00188] In certain embodiments, provided compositions comprise about 2.0% dispersing agent. In certain embodiments, provided compositions comprise about 3.0% dispersing agent In certain embodiments, provided compositions comprise about 2.5% dispersing agent.

[00189] In some embodiments, a dispersing is a bicarbonate salt, such as sodium bicarbonate. In some embodiments, provided compositions comprise sodium bicarbonate as a dispersing agent in an amount of about 0.1% to about 15%, or about 0.1% to about 10%, or about 0.1% to about 8%, or about 0.1% to about 7%, or about 0.1% to about 6%, or about 0.1% to about 5%, or about 0.1% to about 4%, or about 0.1% to about 3%. In some embodiments, provided compositions comprise sodium bicarbonate as a dispersing agent in an amount of about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, about 2%, about 2.1%, about 2.2%, about 2.3%, about 2.4%, about 2.5%, about 2.6%, about 2.7%, about 2.8%, about 2.9% or about 3.0%.

[00190] In certain embodiments, provided compositions comprise about 0.4% sodium bicarbonate. In certain embodiments, provided compositions comprise about 0.5% sodium bicarbonate. In certain embodiments, provided compositions comprise about 0.42% sodium bicarbonate.

[00191] In certain embodiments, provided compositions comprise about 2.0% sodium bicarbonate. In certain embodiments, provided compositions comprise about 3.0% sodium bicarbonate. In certain embodiments, provided compositions comprise about 2.5% sodium bicarbonate.

iv. Fillers

[00192] Compositions for use in the present invention may comprise one or more fillers. Fillers are used in the formulation of solid oral dosage forms to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix.

[00193] Suitable fillers (also referred to as "diluents" and/or "binders") are known in the art. For example, suitable fillers include but are not limited to starch, PVP (polyvinyl pyrrolidone), celluloses such as low molecular weight HPC (hydroxypropyl cellulose), microcrystalline cellulose (e.g., Avicel®), silicified microcrystalline cellulose (Prosolv 50), low molecular weight HPMC (hydroxypropyl methylcellulose), low molecular weight carboxymethyl cellulose (e.g., sodium carboxymethyl cellulose) and ethylcellulose, pregelatinized starch, alginates, gelatin, polyethylene oxide, acacia, dextrin, sucrose, lactose (e.g., lactose monohydrate), mannitol, magnesium aluminum silicate, and polymethacrylates.

[00194] Fillers include agents selected from the group consisting of silicic acid, microcrystalline cellulose (e.g., Avicel®), starch, pregelatinized starch, sugars such as lactose, sucrose, glucose, dextrose, fructose, maltose, a suitable inorganic calcium salts such as dibasic calcium phosphate and calcium sulfate, polyols such as sorbitol, mannitol, lactitol, malitol and xylitol, or a combination thereof.

[00195] In certain embodiments, a filler is selected from the group consisting of microcrystalline cellulose, starch, pregelatinized starch, dextrose, sucrose, dibasic calcium phosphate, calcium sulfate, mannitol, or a combination thereof.

[00196] In some embodiments, provided compositions comprise from about 10% to about 90% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 15% to about 85% filler, based upon total weight of the formulation.

[00197] In some embodiments, provided compositions comprise from about 10% to about 50% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 10% to about 40% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 10% to about 30% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 15% to about 25% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 20% to about

25% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29% or about 30% filler.

[00198] In some embodiments, provided compositions comprise from about 40% to about 90% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 50% to about 90% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 60% to about 90% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 70% to about 90% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 75% to about 85% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 78% to about 82% filler, based upon total weight of the formulation. In some embodiments, provided compositions comprise about 70%, about 71%, about 73%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, or about 90% filler.

[00199] In some embodiments, the filler is microcrystalline cellulose. In some embodiments, provided compositions comprise from about 10% to about 90% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 15% to about 85% microcrystalline cellulose, based upon total weight of the formulation.

[00200] In some embodiments, provided compositions comprise from about 10% to about 50% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 10% to about 40% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 10% to about 30% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 15% to about 25% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 20% to about 25% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments,

provided compositions comprise about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, about 20%, about 21%, about 22%, about 23%, about 24%, about 25%, about 26%, about 27%, about 28%, about 29% or about 30% microcrystalline cellulose.

[00201] In some embodiments, provided compositions comprise from about 40% to about 90% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 50% to about 90% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 60% to about 90% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 70% to about 90% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 75% to about 85% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise from about 78% to about 82% microcrystalline cellulose, based upon total weight of the formulation. In some embodiments, provided compositions comprise about 70%, about 71%, about 73%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, or about 90% microcrystalline cellulose.

v. Disintegrants

[00202] Pharmaceutical compositions for use in the present invention may further comprise one or more disintegrants. Incorporation of suitable disintegrant(s) into provided compositions may facilitate breakdown of provided compositions. Thus, inclusion of disintegrants may be particularly desired in provided compositions that contain active compound(s). Suitable disintegrants are known in the art and include, but are not limited to, clays, agar, calcium carbonate, sodium carbonate, sodium bicarbonate, cross-linked sodium carboxymethyl cellulose (croscarmellose sodium), starch, sodium carboxymethyl starch (sodium starch glycolate), calcium carboxymethyl cellulose, pregelatinized starch, microcrystalline cellulose, cross-linked polyvinylpyrrolidone (e.g., crospovidone), potato or tapioca starch, alginic acid, certain silicates, microcrystalline starch, water insoluble starch, magnesium aluminum silicate (Veegum) or a combination thereof.

[00203] In some embodiments, a suitable disintegrants is selected from cross-linked polyvinylpyrrolidone, starch, pregelatinized starch, sodium starch glycolate, croscarmellose sodium, microcrystalline cellulose, clay, or a combination thereof.

[00204] In some embodiments, provided formulations comprise from about 1% to about 30% disintegrant, based upon total weight of the formulation. In some embodiments, provided formulations comprise from about 1% to about 25%, about 1% to about 20% disintegrant, about 1% to about 15% disintegrant, about 1% to about 10% disintegrant, about 2% to about 8% disintegrant, about 3% to about 7% disintegrant, or about 4% to about 6% disintegrant. In some embodiments, provided formulations comprise about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10% disintegrant, based upon total weight of the formulation. In certain embodiments, provided formulations comprise about 5% disintegrant, based upon total weight of the formulation.

[00205] In some embodiments, a disintegrant in a provided composition is a cross-linked polymer such as cross-linked polyvinylpyrrolidone. In some embodiments, a disintegrant is cross-linked polyvinylpyrrolidone. In certain embodiments, a disintegrant is cross-linked polyvinylpyrrolidone in an amount of about 1% to about 25%, about 1% to about 20% disintegrant, about 1% to about 15% disintegrant, about 1% to about 10% disintegrant, about 2% to about 8% disintegrant, about 3% to about 7% disintegrant, or about 4% to about 6%. In some embodiments, provided formulations comprise about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, or about 10% cross-linked polyvinylpyrrolidone, based upon total weight of the formulation.

vi. Glidants

[00206] Pharmaceutical compositions of the present invention may further comprise one or more glidants. A glidant is a substance that is added to a powder to improve its flowability. Such compounds include, without limitation, colloidal silica (also referred to as colloidal silicon dioxide), fumed silica, talc, starch, DL-leucine, metallic stearates such as sodium stearate, calcium stearate, zinc stearate and magnesium stearate, sodium lauryl sulfate, and the like, and combinations thereof.

[00207] In some embodiments, provided compositions comprise from about 0.1% to about 3% glidant, based on the total weight of the composition. In some embodiments, provided

compositions comprise from about 0.1% to about 2.5%, or about 0.1% to about 2.0%, or about 0.1% to about 1.5%, or about 0.5% to about 1.5%, or about 0.8% to about 1.2% glidant. In certain embodiments, provided compositions comprise about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about 1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, or about 2% glidant.

[00208] In some embodiments, a glidant is colloidal silica. In some embodiments, provided compositions comprise from about 0.1% to about 2.5%, or about 0.1% to about 2.0%, or about 0.1% to about 1.5%, or about 0.5% to about 1.5% colloidal silica, based on the total weight of the composition. In some embodiments, provided compositions comprise from about 0.5% to about 1.5% colloidal silica. In some embodiments, provided compositions comprise 1.0% colloidal silica.

vii. Lubricants

[00209] Pharmaceutical compositions of the present invention may further comprise one or more lubricants. Lubricants are agents added in small quantities to formulations to improve certain processing characteristics. For example, lubricants prevent the formulation mixture from sticking to the compression machinery and enhance product flow by reducing interparticulate friction. Such compounds include, by way of example and without limitation, sodium oleate, sodium stearate, calcium stearate, zinc stearate, magnesium stearate, polyethylene glycol, talc, boric acid, mineral oil, stearic acid, sodium benzoate, sodium acetate, sodium chloride, DL-leucine, glyceryl behenate, magnesium lauryl sulfate, sodium lauryl sulfate, hydrogenated vegetable oil, glyceryl distearate, sodium stearyl fumarate, sodium oleate, fatty acids (e.g., palmitic and stearic acids) and other materials known to one of ordinary skill in the art.

[00210] In some embodiments, provided compositions comprise from about 0.1% to about 3% lubricant, based on the total weight of the composition. In some embodiments, provided compositions comprise from about 0.1% to about 2.5%, or about 0.1% to about 2.0%, or about 0.1% to about 1.5%, or about 0.5% to about 1.5%, or about 0.8% to about 1.2% lubricant. In certain embodiments, provided compositions comprise about 0.1%, about 0.2%, about 0.3%, about 0.4%, about 0.5%, about 0.6%, about 0.7%, about 0.8%, about 0.9%, about 1.0%, about

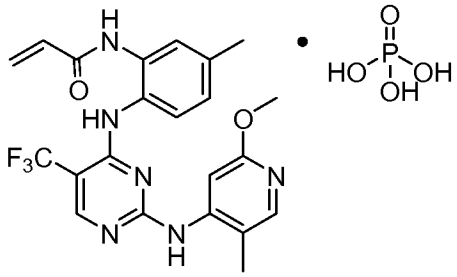
1.1%, about 1.2%, about 1.3%, about 1.4%, about 1.5%, about 1.6%, about 1.7%, about 1.8%, about 1.9%, or about 2% lubricant.

[00211] In certain embodiments, a lubricant is magnesium stearate. In some embodiments, provided compositions comprise from about 0.1% to about 2.5% magnesium stearate. In some embodiments, provided compositions comprise from about 0.1% to about 2.0% magnesium stearate. In some embodiments, provided compositions comprise from about 0.5% to about 1.5% magnesium stearate. In certain embodiments, provided compositions comprise about 1% magnesium stearate.

vi. Phosphate salt of Compound 1

[00212] As described above, the present invention provides a method of treating a cancer, the method comprising administering to a patient in need thereof a pharmaceutically acceptable composition comprising Compound **1** or a pharmaceutically acceptable salt thereof. Thus, in some embodiments, provided methods comprise administering to a patient in need thereof a phosphate salt of Compound **1**.

[00213] As described above and herein, in some embodiments, the present invention provides a pharmaceutically acceptable salt of Compound **1**. For instance, in some embodiments the present invention provides a phosphate salt of Compound **1**, depicted below:



Phosphate Salt of Compound **1**

[00214] It will be appreciated by one of ordinary skill in the art that the phosphoric acid and compound **1** are ionically bonded to form a phosphate salt of Compound **1**. It is contemplated that a phosphate salt of Compound **1** can exist in a variety of physical forms. For example, a phosphate salt of Compound **1** can be in solution, suspension, or in solid form. In certain embodiments, a phosphate salt of Compound **1** is in solid form. When a phosphate salt of Compound **1** is in solid form, said compound may be amorphous, crystalline, or a mixture thereof. In some embodiments, a phosphate salt of Compound **1** is anhydrous. In some

embodiments, a phosphate salt of Compound **1** is a hydrate. In some embodiments, a phosphate salt of Compound **1** is a solvate. In some embodiments, a phosphate salt of Compound **1** is a dehydrate. In some embodiments, a phosphate salt of Compound **1** is a desolvate. Exemplary solid forms are described in more detail below.

[00215] In some embodiments, the present invention provides a phosphate salt of Compound 1 substantially free of impurities. As used herein, the term "substantially free of impurities" means that the compound contains no significant amount of extraneous matter. Such extraneous matter may include excess phosphoric acid, excess compound **1**, residual solvents, or any other impurities that may result from the preparation of, and/or isolation of, a phosphate salt of Compound **1**. In certain embodiments, at least about 95% by weight of a phosphate salt of Compound **1** is present. In still other embodiments of the invention, at least about 99% by weight of a phosphate salt of Compound **1** is present.

[00216] According to one embodiment, a phosphate salt of Compound **1** is present in an amount of at least about 97, 97.5, 98.0, 98.5, 99, 99.5, 99.8 weight percent where the percentages are based on the total weight of the composition. According to another embodiment, a phosphate salt of Compound **1** contains no more than about 3.0 area percent HPLC of total organic impurities and, in certain embodiments, no more than about 1.5 area percent HPLC total organic impurities relative to the total area of the HPLC chromatogram. In other embodiments, a phosphate salt of Compound **1** contains no more than about 1.0% are percent HPLC of any single impurity; no more than about 0.6 area percent HPLC of any single impurity, and, in certain embodiments, no more than about 0.5 area percent HPLC of any single impurity, relative to the total area of the HPLC chromatogram.

[00217] The structure depicted for a phosphate salt of Compound **1** is also meant to include all tautomeric forms of a phosphate salt of Compound **1**. Additionally, structures depicted here are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structure except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

[00218] It has been found that a phosphate salt of Compound **1** can exist in a variety of solid forms. Exemplary such forms include polymorphs such as those described herein.

[00219] In certain embodiments, a phosphate salt of Compound **1** is a crystalline solid. In other embodiments, a phosphate salt of Compound **1** is a crystalline solid substantially free of amorphous a phosphate salt of Compound **1**. As used herein, the term "substantially free of amorphous a phosphate salt of Compound **1**" means that the compound contains no significant amount of amorphous a phosphate salt of Compound **1**. In certain embodiments, at least about 95% by weight of crystalline a phosphate salt of Compound **1** is present. In still other embodiments of the invention, at least about 99% by weight of crystalline a phosphate salt of Compound **1** is present.

[00220] It has been found that a phosphate salt of Compound **1** can exist in at least four distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form A. In certain embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form B. In certain embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form C. In certain embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form D.

[00221] In some embodiments, a phosphate salt of Compound **1** is amorphous. In some embodiments, a phosphate salt of Compound **1** is amorphous, and is substantially free of crystalline phosphate salt of Compound **1**.

[00222] Polymorphs of a phosphate salt of Compound **1** include Forms A-D, described further below. Accordingly, It has been found that a phosphate salt of Compound **1** can exist in at least four distinct polymorphic forms. In some embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form A. In certain embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form B. In certain embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form C. In certain embodiments, the present invention provides a polymorphic form of a phosphate salt of Compound **1** referred to herein as Form D.

[00223] In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising a phosphate salt of Compound **1** of Form A.

[00224] In some embodiments, a phosphate salt of Compound **1** is of Form A and has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 1 below.

Table 1 – XRPD Peak Positions for Form A

Position (°2θ)	Position (°2θ)
5.9	21.3
6.3	22.2
6.8	23.0
9.8	23.3
10.1	23.6
11.1	24.0
13.8	24.7
14.4	25.5
15.4	26.0
16.0	26.8
16.6	27.4
17.3	27.9
17.9	28.4
18.9	29.2
19.2	30.5
19.7	31.3
20.3	31.8
20.8	

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00225] In some embodiments, Form A is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 6.8, 10.1, and 20.8. In some embodiments, Form A is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 6.8, 10.1, and 20.8. In some embodiments, Form A is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 6.8, 10.1, and 20.8.

[00226] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure 1.

[00227] In some embodiments, a phosphate salt of Compound **1** is of Form B and has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 2 below.

Table 2 – XRPD Peak Positions for Form B

Position (°2θ)	Position (°2θ)
3.6	22.9
7.3	23.4
8.6	24.1
9.5	24.9
10.7	25.3
12.0	25.7
13.5	26.3
14.6	26.9
15.0	27.8
15.7	28.7
16.6	29.5
18.2	30.2
19.2	31.8
19.9	34.2
20.3	36.1
21.6	37.1
22.0	38.8
22.5	39.3

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00228] In some embodiments, Form B is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 3.6, 7.3, and 15.0. In some embodiments, Form B is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 3.6, 7.3, and 15.0. In some embodiments, Form B is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 3.6, 7.3, and 15.0.

[00229] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure 2.

[00230] In some embodiments, a phosphate salt of Compound **1** is of Form C and has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 3 below.

Table 3 – XRPD Peak Positions for Form C

Position (°2θ)	Position (°2θ)
4.2	16.5
6.8	18.7
8.4	19.4
9.3	20.5
11.6	22.0
12.5	22.7
12.7	24.5
13.7	25.2
15.3	26.2
15.8	32.0

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00231] In some embodiments, Form C is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 8.4, 9.3, and 16.5. In some embodiments, Form C is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 8.4, 9.3, and 16.5. In some embodiments, Form C is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 8.4, 9.3, and 16.5.

[00232] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure 3.

[00233] In some embodiments, a phosphate salt of Compound **1** is of Form D and has at least 1, 2, 3, 4 or 5 spectral peak(s) selected from the peaks listed in Table 4 below.

Table 4 – XRPD Peak Positions for Form D

Position (°2θ)	Position (°2θ)
7.1	21.0
8.1	22.1
9.1	22.7
10.4	24.5
10.6	25.1
11.2	26.4
12.9	27.4
13.9	27.8
15.8	28.7
16.4	29.1
17.2	31.0
17.7	31.5
18.7	33.8
19.0	36.3
20.2	37.0
20.7	38.0

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00234] In some embodiments, Form D is characterized in that it has one or more peaks in its X-ray powder diffraction pattern selected from those at about 9.1, 10.4, and 25.1. In some embodiments, Form D is characterized in that it has two or more peaks in its X-ray powder diffraction pattern selected from those at about 9.1, 10.4, and 25.1. In some embodiments, Form D is characterized in that it has all three peaks in its X-ray powder diffraction pattern selected from those at about 9.1, 10.4, and 25.1.

[00235] In certain embodiments, the X-ray powder diffraction pattern is substantially similar to the XRPD provided in Figure 4.

[0001] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 1% to about 60% of a phosphate salt of Compound **1**, based upon total weight of given composition or formulation (wt %). In some embodiments, a provided composition, or formulation thereof, comprises from about 1 wt% to about 50 wt% of a phosphate salt of Compound **1**.

[0002] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 1 wt% to about 20 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise

administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 2 wt% to about 18 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 4 wt% to about 12 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 5 wt% to about 10 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 6 wt% to about 9 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 7 wt% to about 8 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising about 7.59 wt% of a phosphate salt of Compound **1**.

[0003] In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 20 wt% to about 60 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 25 wt% to about 55 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 30 wt% to about 50 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 35 wt% to about 50 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 40 wt% to about 50 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 41 wt% to about 49 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 42 wt% to about 48 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise

administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 43 wt% to about 47 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 44 wt% to about 46 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising from about 45 wt% to about 46 wt% of a phosphate salt of Compound **1**. In some embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutically acceptable composition comprising about 45.53 wt% of a phosphate salt of Compound **1**.

[0004] In some such embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutical composition comprising a unit dose of Compound **1**, wherein Compound **1** is in the form of a phosphate salt of any one of Forms A, B, C, or D, and wherein the unit dose is any of those described above and herein. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutical composition comprising a unit dose of Compound **1**, wherein Compound **1** is in the form of a phosphate salt of Form A, and wherein the unit dose is any of those described above and herein. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutical composition comprising a unit dose of Compound **1**, wherein Compound **1** is in the form of a phosphate salt of Form A, and wherein the unit dose is about 5 mg. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutical composition comprising a unit dose of Compound **1**, wherein Compound **1** is in the form of a phosphate salt of Form A, and wherein the unit dose is about 30 mg. In certain embodiments, provided methods comprise administering to a patient in need thereof a pharmaceutical composition comprising a unit dose of Compound **1**, wherein Compound **1** is in the form of a phosphate salt of Form A, and wherein the unit dose is about 150 mg.

[0005] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer described herein, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a phosphate salt of Compound **1** of Form A.

[00236] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a BRAF-mutated cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a phosphate salt of Compound **1** of Form A. In some such embodiments, the BRAF-mutated cancer is a $BRAF^{V600}$-mutated cancer, such as $BRAF^{V600E}$, $BRAF^{V600K}$, $BRAF^{V600R}$, and $BRAF^{V600D}$.

[00237] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a RAS-mutated cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a phosphate salt of Compound **1** of Form A. In certain embodiments, the RAS-mutation involves codons 12, 13, or 61. In certain embodiments, the RAS-mutated cancer is a KRAS-mutated cancer, including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$. In certain embodiments, the RAS-mutated cancer is an NRAS-mutated cancer, including, but not limited to, $NRAS^{Q61R}$, $NRAS^{Q61K}$, $NRAS^{Q61L}$, or $NRAS^{Q61H}$. In certain embodiments, the RAS-mutated cancer is an HRAS-mutated cancer, including, but not limited to, $HRAS^{G12V}$, $HRAS^{Q61R}$, and $HRAS^{G12S}$.

[00238] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a melanoma, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00239] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a colorectal cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00240] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a pancreatic cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00241] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a thyroid cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00242] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a lung cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00243] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a leukemia, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00244] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a CNS cancer, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00245] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a multiple myeloma, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00246] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of an HCC, wherein said method comprises administering to a patient in need thereof the phosphate salt of Compound **1,** or a pharmaceutically acceptable composition thereof. In certain embodiments, such methods comprise administering to a patient in need thereof a the phosphate salt of Compound **1** of Form A.

[00247] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, the method comprising administering to a patient in need thereof a pharmaceutical composition comprising the phosphate salt of Compound **1**, wherein the amount of phosphate salt is sufficient to deliver about 5 mg, about 10 mg, about 20 mg, about 40 mg, about 80 mg, about 100 mg, about 120 mg, about 180 mg, about 330 mg, about 480 mg, or about 640 mg of the free base of Compound **1**. In some such embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients selected from one or more solubilizers, surfactants/wetting agents, dispersing agents, fillers, disintegrants, glidants, lubricants, or combinations thereof. In some such embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients selected from betadex sulfobutylether sodium, sodium lauryl sulfate, sodium bicarbonate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate, wherein the amount of each component is based upon the total weight of the composition.

[00248] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, for example, a BRAF-mutated cancer, a RAF-mutated cancer, a melanoma, a colorectal cancer, a lung cancer, a leukemia, or a pancreatic cancer, the method comprising administering to a patient in need thereof a pharmaceutical composition comprising: (a) about 1% to about 60% phosphate salt of Compound **1**; (b) about

1% to about 50% solubilizer; (c) about 0.1% to about 10% surfactant/wetting agent; (d) about 0.1% to about 20% dispersing agent; (e) about 10% to about 90% filler; (f) about 1% to about 30% disintegrant; (g) about 0.1% to about 3% glidant; and (h) about 0.1% to about 3% lubricant; wherein the amount of each component is based upon the total weight of the composition.

[00249] In some embodiments, the present invention provides a method of treating, stabilizing or lessening the severity or progression of a cancer, for example, a RAS-mutated cancer, a RAF-mutated cancer, a melanoma, a colorectal cancer, a lung cancer, or a pancreatic cancer, the method comprising administering to a patient in need thereof a pharmaceutical composition comprising: (a) about 1% to about 60% phosphate salt of Compound **1**; (b) about 1% to about 50% betadex sulfobutylether sodium; (c) about 0.1% to about 10% sodium lauryl sulfate; (d) about 0.1% to about 20% sodium bicarbonate; (e) about 10% to about 90% microcrystalline cellulose; (f) about 1% to about 30% crospovidone; (g) about 0.1% to about 3% colloidal silicon dioxide; and (h) about 0.1% to about 3% magnesium stearate; wherein the amount of each component is based upon the total weight of the composition.

[00250] In some embodiments, the pharmaceutical composition is selected from those in Table 5:

Table 5. Pharmaceutical Formulations Comprising Compound 1

	Function	5 mg		30 mg		150 mg	
Component		%	Amt/cap (mg)	%	Amt/cap (mg)	%	Amt/cap (mg)
Compound 1 (as the phosphate salt)	Active ingredient	7.59%	6.07	45.53%	36.42	45.53%	182.10
Betadex sulfobutyl ether sodium	Solubilizer	3.33%	2.67	20.00%	16.00	20.00%	80.00
Sodium lauryl sulfate	Surfactant/ Wetting agent	0.33%	0.27	2.00%	1.60	2.00%	8.00
Sodium bicarbonate	Dispersing agent	0.42%	0.33	2.50%	2.00	2.50%	10.00
Microcrystalline cellulose	Filler	81.33%	65.06	22.98%	18.38	22.98%	91.90
Crospovidone	Disintegrant	5.00%	4.00	5.00%	4.00	5.00%	20.00
Colloidal silicon dioxide	Glidant	1.00%	0.80	1.00%	0.80	1.00%	4.00
Magnesium stearate	Lubricant	1.00%	0.80	1.00%	0.80	1.00%	4.00
Total			80		80		400

V. PROCESS FOR PREPARING PHARMACEUTICAL COMPOSITIONS

Dry Blend Process:

[00251] In certain embodiments, provided formulations are prepared by dry blending Compound **1**, or a pharmaceutically acceptable salt thereof, and excipients. Exemplary such methods are described below and in the Examples section.

[00252] In some embodiments, a provided formulation is prepared by a process comprising:

(a) blending a surfactant/wetting agent, a dispersing agent, a solubilizer, and a disintegrant to form a first blended powder;

(b) adding Compound **1**, or a pharmaceutically acceptable salt thereof, to the first blended powder and blending to form a second blended powder;

(c) screening the second blended powder;

(d) adding a portion of filler to the screened second blended powder and blending to form a third blended powder;

(e) screening the third blended powder;

(f) adding a glident and the remaining filler to the screened third blended powder and blending to form a fourth blended powder; and

(g) adding a lubricant to the fourth blended powder and blending to form a fifth blended powder.

[00253] In some embodiments, a provided formulation is prepared by a process comprising:

(a) blending sodium lauryl sulfate, sodium bicarbonate, betadex sulfobutyl ether sodium, and crospovidone to form a first blended powder;

(b) adding Compound **1**, or a pharmaceutically acceptable salt thereof, to the first blended powder and blending to form a second blended powder;

(c) screening the second blended powder;

(d) adding a portion of microcrystalline cellulose to the screened second blended powder and blending to form a third blended powder;

(e) screening the third blended powder;

(f) adding colloidal silicon dioxide and the remaining microcrystalline cellulose to the screened third blended powder and blending to form a fourth blended powder; and

(g) adding magnesium stearate to the fourth blended powder and blending to form a fifth blended powder.

[00254] In some embodiments, capsules are filled with the final blended powder.

[00255] In some embodiments, the above procedure is used to prepare a capsule containing Compound **1**, or a pharmaceutically acceptable salt thereof, in an amount of about 1 wt% to about 20 wt%, or from about 2 wt% to about 18 wt%, or from about 4 wt% to about 12 wt%, or from about 5 wt% to about 10 wt%, or from about 6 wt% to about 9 wt%, or from about 7 wt% to about 8 wt%. In certain embodiments, the above procedure is used to prepare a capsule

containing the phosphate salt of Compound **1** in an amount of about 7.59 wt%. In certain such embodiments, the phosphate salt of Compound **1** is of Form A.

[00256] In some embodiments, a provided formulation is prepared by a process comprising:

(a) blending a surfactant/wetting agent and a dispersing agent to form a first blended powder;

(b) screening the first blended powder;

(c) adding a disintegrant to the first blended powder and blending to form a second blended powder;

(d) screening the second blended powder;

(e) adding a solubilizer to the screened second blended powder and blending to form a third blended powder;

(f) screening the third blended powder;

(g) adding a glidant and a filler to the screened third blended powder and blending to form a fourth blended powder;

(h) screening the fourth blended powder;

(i) adding Compound **1**, or a pharmaceutically acceptable salt thereof, to the fourth blended powder and blending to form a fifth blended powder;

(j) screening the fifth blended powder;

(k) blending the screened fifth blended powder; and

(l) adding a lubricant to the screened fifth blended powder to form a sixth blended powder.

[00257] In some embodiments, a provided formulation is prepared by a process comprising:

(a) blending sodium lauryl sulfate and sodium bicarbonate to form a first blended powder;

(b) screening the first blended powder;

(c) adding crospovidone to the first blended powder and blending to form a second blended powder;

(d) screening the second blended powder;

(e) adding betadex sulfobutyl ether sodium to the screened second blended powder and blending to form a third blended powder;

(f) screening the third blended powder;

(g) adding colloidal silicon dioxide and microcrystalline cellulose to the screened third blended powder and blending to form a fourth blended powder;

(h) screening the fourth blended powder;

(i) adding Compound **1**, or a pharmaceutically acceptable salt thereof, to the fourth blended powder and blending to form a fifth blended powder;

(j) screening the fifth blended powder;

(k) blending the screened fifth blended powder; and

(l) adding magnesium stearate to the screened fifth blended powder to form a sixth blended powder.

[00258] In some embodiments, capsules are filled with the final blended powder.

[00259] In some embodiments, a provided formulation is prepared by a process comprising:

(a) blending sodium lauryl sulfate, sodium bicarbonate, and betadex sulfobutyl ether sodium to form a first blended powder;

(b) adding Compound **2**, crospovidone, microcrystalline cellulose, and colloidal silicon dioxide to the first blended powder and blending to form a second blended powder;

(c) screening the second blended powder;

(d) blending for a second time the screened second blended powder;

(f) adding magnesium stearate to the screened second blended powder to form a third powder; and

(g) blending the third powder.

[00260] In some embodiments, a provided formulation is prepared by a process comprising:

(a) blending sodium lauryl sulfate, sodium bicarbonate, and crospovidone to form a first blended powder;

(b) adding Compound **2**, betadex sulfobutyl ether sodium, microcrystalline cellulose, and colloidal silicon dioxide to the first blended powder and blending to form a second blended powder;

(c) screening the second blended powder;

(d) blending for a second time the screened second blended powder;

(e) screening for a second time the second blended powder;

(f) adding magnesium stearate to the screened second blended powder to form a third powder; and

(g) blending the third powder.

[00261] In some embodiments, the above procedure is used to prepare a capsule containing Compound **1**, or a pharmaceutically acceptable salt thereof, in an amount of about 20 wt% to about 60 wt%, or from about 25 wt% to about 55 wt%, or from about 30 wt% to about 50 wt%, or from about 35 wt% to about 50 wt%, or from about 40 wt% to about 50 wt%, or from about 41 wt% to about 49 wt%, or from about 42 wt% to 48 wt%, or from about 43 wt% to 47 wt%, or from about 44 wt% to about 46 wt%, or from about 45 wt% to about 46 wt%. In certain embodiments, the above procedure is used to prepare a capsule containing the phosphate salt of Compound **1** in an amount of about 45.53 wt%. In certain such embodiments, the phosphate salt of Compound **1** is of Form A.

[00262] All features of each of the aspects of the invention apply to all other aspects *mutatis mutandis*.

[00263] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

EXEMPLIFICATION

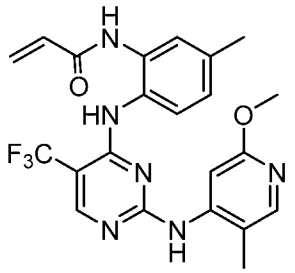
[00264] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

Example 1

General Preparation of Compound 1

[00265] As depicted in the Examples below, in certain exemplary embodiments, Compound **1** is prepared according to the following general procedure.

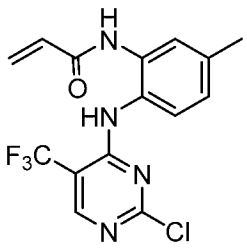
[00266] Proton Nuclear Magnetic Resonance (^{1}H NMR) spectra were obtained on a Bruker AVANCE-300 MHz NMR spectrometer. Deuterated DMSO was used as solvent.



Compound **1**

[00267] The title compound was prepared according to the steps and intermediates described below and in the '230 publication, the entirety of which is incorporated herein by reference.

Step 1: N-(2-(2-Chloro-5-(trifluoromethyl)pyrimidin-4-ylamino)5-methylphenyl)acrylamide (Intermediate 1)



[00268] To a stirred solution of N-(2-amino-5-methylphenyl)acrylamide (22.2 mmol) in dimethyl acetamide (25 mL) was added potassium carbonate (46.0 mmol) at rt, and the mixture was stirred for 15 minutes. To this reaction mixture, 2,4-dichloro-5-trifluoromethylpyrimidine (22.2 mmol) was added, and the stirring continued at 60 °C for 1 h. Upon completion, the reaction mixture was diluted with water (2x50 mL) and extracted with EtOAc (2x100 mL). The organic layer was dried over sodium sulfate and concentrated to get the crude product. This crude was purified by silica gel column chromatography and subsequently purified by prep-HPLC to get desired intermediate **1**.

Step 2: Acid catalyzed coupling method

[00269] To a solution of Intermediate **1** (2.923 mmol) in 0.04 M PTSA solution in 1,4-dioxane (20 mL) was added 2-methoxy-5-methylpyridin-4-amine (3.51 mmol), and the mixture was stirred at 95 °C for 16 h. Upon completion, the reaction mixture was directly absorbed on silica gel and purified by column chromatography. The resulting product was stirred in a mixture of DCM: EtOAc: diethyl ether (10 mL:10 mL:30 mL) for 10 min, then filtered and dried under vacuum to obtain the desired compound.

[00270] MS m/z 459.2 (ES+, M+H). ^{1}HNMR (DMSO-d6) δ 2.10 (s, 3H), 2.32 (s, 3H), 3.75 (s, 3H), 5.78 (dd, 1H, J = 2.0, 10.0 Hz), 6.28 (dd, 1H, J = 2.0, 16.8 Hz), 6.45 (dd, 1H, J = 10.6, 16.8 Hz), 7.09 (br t, 3 H, J = 8.0 Hz), 7.50 (d, 1H, J = 8.4 Hz), 7.79 (s, 1H), 8.36 (s, 2H), 8.72 (s, 1H), 10.25 (s, 1H).

Alternative Step 2: Pd-catalyzed coupling method:

[00271] Alternatively, Step 2 can be carried out by adding Intermediate **1** to a suitable coupling partner in the presence of Na_2CO_3, a degassed solvent (e.g., tert-amyl alcohol), a suitable palladium catalyst (e.g., tris-dibenzylamino dipalladium) and a suitable phosphine ligand (e.g., Dave Phos) under conditions suitable to effect coupling.

[00272] Compound **1** showed activity in various assays described at Examples 415-418 and in Table A (see Compound I-90 therein) of the '230 publication. Data disclosed therein for Compound **1** is reproduced below in Table 6.

Table 6

Assay	Activity
ERK1 Omnia WT ATP KM IC_{50} (nM)	A
ERK1/ERK2 PRSK MSD HT29 EC_{50} (nM)	A
ERK1 Mass Mod (%)	E
HT-29 GI_{50} (nM)	B
ERK1/ERK2 PRSK A375 EC_{50} (nM)	A
ERK1/ERK2 PRSK HCT116 EC_{50} (nM)	B
A375 GI_{50} (nM)	B
HCT116 GI_{50} (nM)	C

[00273] As described in the '230 publication, the designation of activity level "A" corresponds to an $EC_{50}/IC_{50}/GI_{50}$ ≤100 nM; the designation of "B" corresponds to an $EC_{50}/IC_{50}/GI_{50}$ of 101-500 nM; the designation of "C" corresponds to an $EC_{50}/IC_{50}/GI_{50}$ of 501-999 nM; the designation of "E" corresponds to a mass modification of ≥70%.

[00274] As described in detail in the '230 publication, Table 6 summarizes the activity of Compound **1** in each of the following assays:

ERK1 Omnia WT ATP KM IC_{50} (nM) – measuring the degree of inhibition of wildtype ("WT") ERK1 activity

ERK1/ERK2 PRSK MSD HT29 EC_{50} (nM) – measuring the degree of inhibition of the kinase activity of ERK1 and ERK2 to phosphorylate a substrate, p90RSK, in HT-29 cells (colorectal adenocarcinoma)

ERK1 Mass Mod (%) – measuring the percentage of covalently modified protein after one hour incubation of Compound **1** with ERK1

HT-29 GI_{50} (nM) – measuring the dose at which Compound **1** achieves 50% inhibition of HT-29 cell growth

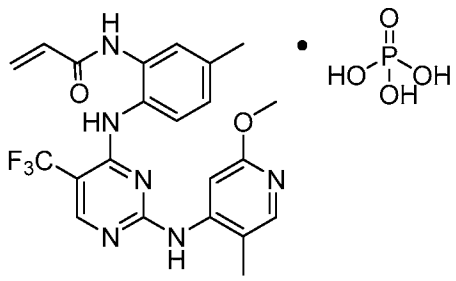
ERK1/ERK2 PRSK A375 EC_{50} (nM) - measuring the degree of inhibition of the kinase activity of ERK1 and ERK2 to phosphorylate a substrate, p90RSK, in A375 cells (malignant melanoma cell line)

ERK1/ERK2 PRSK HCT116 EC_{50} (nM) - measuring the degree of inhibition of the kinase activity of ERK1 and ERK2 to phosphorylate a substrate, p90RSK, in HCT116 cells (colorectal carcinoma cell line)

A375 GI_{50} (nM) - measuring the dose at which Compound **1** achieves 50% inhibition of A375 cell growth (malignant melanoma cell line)

Example 2

Synthesis of the phosphate salt of Compound 1



[00275] Form A of the phosphate salt of Compound **1** was prepared as follows.

[00276] Procedure A: Compound **1** was dissolved in 15X tetrahydrofuran. One molar equivalent of 2 molar phosphoric acid in acetonitrile was charged. The batch was slurried at 20

°C for 1 to 2 hours. The solvent was removed under reduced pressure. The resulting solids were slurried in acetone for about 16 hours at 20 °C, filtered and dried.

[00277] Procedure B: Compound **1** was dissolved in THF. Equal molar equivalent of 1.08 M phosphoric acid in acetonitrile was charged. The sample was shaken at ambient temperature at 200 RPM for 1 hour. The solvent was removed under nitrogen purge. The resulting solids were slurried in acetone with a stirring bar at ambient temperature overnight, then filtered and dried in vacuum oven at 30 °C overnight.

[00278] Procedure C: Compound **1** was dissolved in THF (20X vol) at 20 °C. Seeds of Compound **2** Form A (5% wt) were charged. A 1 M solution of phosphoric acid (1 mol eq.) in ethanol was charged. The batch was left under vigorous agitation for two hours. Solvent exchange to isopropyl acetate was carried out with a constant volume distillation under reduced pressure, with temperature not exceeding 40 °C. The batch was cooled to 20 °C. The solvent was removed under nitrogen purge. The batch was filtered, washed two times with isopropyl acetate and dried in a vacuum oven at ~40 °C overnight, under vacuum with nitrogen bleed.

[00279] Procedure D: Compound **1** was dissolved in 9X vol THF/ H_2O (95:5 vol). A solution of H_3PO_4 (1.2 mol eq.) in ethanol was charged to a second flask, seeds of Form A (5%) were charged and vigorous agitation was started. The solution of Compound **1** was charged to the H_3PO_4 solution (reverse addition) over one hour. The slurry was aged for one hour. Solvent exchange to ethanol was started (constant volume vacuum distillation with continuous addition of ethanol, final THF NMT 0.5%). The batch was cooled to 20 °C, filtered and dried in a vacuum oven at ~40 °C overnight, under vacuum with nitrogen bleed.

[00280] Procedure E: Compound **1** was dissolved in 10X vol THF/H_2O (95:5 vol). Isopropyl alcohol (5X vol) was charged. Constant volume distillation, with continuous addition of isopropyl alcohol was started at atmospheric pressure. Solvent exchange was carried out until THF content was below 5%. Compound **1** recrystallized during the solvent exchange. The batch was cooled to 30 °C. A 1M solution of H_3PO_4 in IPA was charged over 2 hours. Seeds of Form A (1%) were then charged. The batch was stirred vigorously overnight. The batch was filtered and dried in a vacuum oven at ~40 °C overnight, under vacuum with nitrogen bleed.

[00281] Procedure F: Compound **1** was dissolved in 9X vol THF/H_2O (95:5 vol). After polish filtration, distillation to reduce volume from 9X to 5X was performed, followed by addition of 8X ethyl acetate to bring the total volume to 13X. Solvent exchange to ethyl acetate, with

constant volume distillation was carried out (final THF NMT 2%). The temperature was then reduced to 30 °C. Seeds of the phosphate salt of Compound **1** (1% wt) were charged. A solution of H_3PO_4 (1.2 eq.) in ethanol (5X) was then dosed in over 2 hours. The temperature was reduced to 20 °C, the batch was aged for 12 hours under vigorous stirring, then filtered, washed two times with ethyl acetate and dried in a vacuum oven at ~40 °C overnight, under vacuum with nitrogen bleed.

[00282] Procedure G: Compound **1** was charged to a reactor, then ethanol (4X vol) and ethyl acetate (6X), were charged. The batch was agitated at 30 °C. A solution of H_3PO_4 (1.2 mol eq.) in ethanol (2X vol) was charged over 2 hours. Seeds of Form A (1%) were charged. The batch was filtered, washed two times with ethyl acetate, dried overnight at ~40 °C, under vacuum with nitrogen bleed.

[00283] Characterization of the resulting material demonstrated a crystalline, anhydrous Form A of the phosphate salt of compound **1**. Up to 3.8% water uptake was observed for this form at 95% relative humidity.

[00284] **Table 1**, *supra*, is reproduced below and sets forth the X-ray diffraction peaks observed for Form A of the phosphate salt of compound **1**.

Table 1 – XRPD Peak Positions for Form A of the phosphate salt of Compound 1

Position (°2θ)	Position (°2θ)
5.9	21.3
6.3	22.2
6.8	23.0
9.8	23.3
10.1	23.6
11.1	24.0
13.8	24.7
14.4	25.5
15.4	26.0
16.0	26.8
16.6	27.4
17.3	27.9
17.9	28.4
18.9	29.2
19.2	30.5
19.7	31.3
20.3	31.8
20.8	

[1] In this and all subsequent tables, the position 2θ is within ± 0.2.

[00285] **Figure 1** depicts an XRPD pattern of Form A of the phosphate salt of compound **1**.

Example 3

Multiplexed Cytotoxicity Assay

[00286] This experiment describes the identification of certain tumor cell lines that are sensitive to treatment with Compound **1**, or a pharmaceutically acceptable salt thereof.

[00287] Cells were grown in RPMI1640, 10%FBS, 2 mM L-alanyl-L-Glutamine, 1mM Na Pyruvate or a special medium in a humidified atmosphere of 5% CO_2 at 37 °C. Cells were seeded into 384-well plates and incubated in a humidified atmosphere of 5% CO_2 at 37 °C. Compounds were serially diluted 3.16-fold and assayed over ten concentrations at a final assay concentration of 0.1% DMSO from the highest test concentrations specified in the sample information chapter. Compounds were added 24 hours post cell seeding. At the same time, a time zero untreated cell plate was generated.

[00288] After a 72 hour incubation period, cells were fixed and stained with fluorescently labeled antibodies and nuclear dye to allow visualization of nuclei, apoptotic cells and mitotic cells. Cell proliferation is measured by the signal intensity of the incorporated nuclear dye.

[00289] Automated fluorescence microscopy was carried out using a GE Healthcare IN Cell Analyzer 1000, and images were collected with a 4X objective.

[00290] Twelve bit tiff images were acquired using the InCell Analyzer 1000 3.2 and analyzed with Developer Toolbox 1.6 software. EC_{50} and IC_{50} values were calculated using nonlinear regression to fit data to a sigmoidal 4 point, 4 parameter One-Site dose response model, where: y (fit) = A + [(B – A)/(1 + ((C/x) ^ D))]. Curve-fitting, EC_{50} / IC_{50} calculations and report generation are performed using a custom data reduction engine MathIQ based software (AIM).

[00291] To determine the cell proliferation end point, the cell proliferation data output was transformed to percent of control (POC) using the following formula: POC = relative cell count (compound wells) / relative cell count (vehicle wells) x 100.

[00292] GI_{50} is the concentration needed to reduce the observed growth by half. This is the concentration that inhibits the growth midway between untreated cells and the number of cells seeded in the well (Time zero value). The tables below provide data on the sensitivity of the indicated tumor cell line to Compound **1**. Proliferation of the tumor cell lines provided below is inhibited by Compound **1**.

KRAS mutant cell lines

[00293] GI_{50} data for KRAS mutant cell lines shown below in Table 7.

Table 7

KRAS mutation (CCLE and COSMIC databases)	**Cell line**	**Tissue of Origin**	**GI_{50} (μM)**
G12C	UMUC3	Bladder	0.66
G12D	639V	Bladder	0.65
G12V	T24	Bladder	1.10
Q61H	SJSA1	Bone	1.69
G13D	MDAMB231	Breast	0.44

KRAS mutation (CCLE and COSMIC databases)	Cell line	Tissue of Origin	GI_{50} (μM)
G12D	AN3CA	Female GU (uterus)	0.17
G12D	HEC1A	Female GU (uterus)	1.52
G12V	A498	Kidney	1.19
G13D	SW1417	Large Intestine (colon)	0.07
Q61L	HT29	Large Intestine (colon)	0.23
G12C	SW837	Large Intestine (colon)	0.21
G13D	HCT116	Large Intestine (colon)	0.40
G12V	SW480	Large Intestine (colon)	0.39
G12V	SW403	Large Intestine (colon)	0.24
G12V	SW620	Large Intestine (colon)	0.78
G13D	NCIH747	Large Intestine (colon)	0.77
A146T	LS1034	Large Intestine (colon)	1.04
Q61L	SW948	Large Intestine (colon)	1.19
G12C	SW1463	Large Intestine (rectum)	1.56
G12D	COLO320HSR	Large Intestine (colon)	2.95
G13D	HCT15	Large Intestine (colon)	3.70
G12D	CCRFCEM	myelomonoblastic leukemia	2.87
G12D	HUCCT1	Liver	0.68
G12C	SW900	Lungb(Small cell)	0.06
G12S	A549	Lung	0.58
G12C	CALU1	Lung (squamous Cell)	0.61
G12V	CORL23	Lung	0.77
G12S	NCIH292	Lung	0.61
G12D	A427	Lung	0.69
Q61K	CALU6	Lung (anaplastic carcinoma)	0.75
Q61H	NCIH460	Lung	0.98
G12V	NCIH441	Lung (papillary lung adenocarcinoma)	0.88
G12V	SHP77	Lung	4.75
G12A	RPMI8226	Plasmacytoma; myeloma	0.66
Q61H	HS766T	Pancreas	0.18
G12D	ASPC1	Pancreas	0.49
G12D	HPAFII	Pancreas	0.47
G12C	MIAPACA2	Pancreas	0.44
G12V	CAPAN2	Pancreas	0.51
G12V	YAPC	Pancreas	0.84
G12D	HUPT4	Pancreas	1.35

KRAS mutation (CCLE and COSMIC databases)	Cell line	Tissue of Origin	GI_{50} (μM)
G12V	CAPAN1	Pancreas	1.51
G12V	CFPAC1	Pancreas	2.62
G12D	SU8686	Pancreas	3.08
G12V	DU145	Prostate	0.26
G12V	PC3	Prostate	2.12
G12D	LNCAP	Prostate	7.91
G12D	AGS	Stomach	0.15
G12D	SNU1	Stomach	0.26
G12R	CAL62	Thyroid	0.63

NRAS and HRAS mutant cell lines

[00294] GI_{50} data for NRAS mutant and HRAS mutant cell lines shown below in Table 8 and Table 9, respectively.

Table 8

NRAS mutation	Cell line	Tissue of Origin	GI_{50} (μM)
p.G12D	THP1	Acute monocytic leukemia	1.07
p.Q61R	HT1197	Bladder	0.13
p.Q61L	BFTC905	Bladder	0.60
p.H131R	639V	Bladder	0.65
p.Q61K	SJSA1	Bone (osteosarcoma)	1.69
p.Q61K	SW1353	Bone (sarcoma)	0.90
p.Q61K	CHP212	Central Nervous System	0.02
p.Q61K	SKNAS	Central Nervous System	0.76
p.Q61K	SW1088	Central Nervous System	1.44
p.R68T; p.D92N	CAL27	Head and Neck	0.42
p.A146T	NALM6	human B cell precursor leukemia	1.61
p.Q61L	HEPG2	Liver	0.10
p.?	22RV1	Prostate	0.92
p.Q61R	C32	Skin (Melanoma)	0.09
p.Q61K	HMCB	Skin (Melanoma)	0.28
p.Q61H	RD	Soft Tissue (sarcoma)	0.44
p.Q61K	HT1080	Soft Tissue (sarcoma)	1.13

Table 9

HRAS mutation	Cell line	Tissue of Origin	GI_{50} (μM)
p.G12V	T24	Bladder	1.10
p.G12D	HS578T	Breast	0.57
p.Q61H	RL952	Female GU (uterus)	0.02
p.F82L	AN3CA	Female GU (uterus)	0.17
p.L133R	SCC9	Head and Neck	1.02
p.G12V	SR	Large cell immunoblastic lymphoma	1.34
p.V14G	DU145	Prostate	0.26
p.R73C	SKUT1	Soft Tissue (sarcoma)	1.58

BRAF mutant cell lines

[00295] GI_{50} data for BRAF mutant cell lines shown below in Table 10.

Table 10

BRAF mutation	Cell line	Tissue of Origin	GI_{50} (μM)
A728V	JURKAT	Acute T cell Leukemia	4.21
G464V	MDAMB231	Breast	0.44
V600E	BT474	Breast	3.29
V600E	DBTRG05MG	Central Nervous System	0.14
R146Q	CCFSTTG1	Central Nervous System	1.45
A404fs*9	CMLT1	Chronic myeloid leukemia	2.94
A115V	C33A	Female GU (cervix)	1.50
V600E	ES2	Female GU (ovary)	0.64
P403fs	RL952	Female GU (uterus)	0.02
R682Q	HEC1A	Female GU (uterus)	1.52
V600E	DB	Large cell lymphoma	3.14
V600E	SW1417	Large Intestine	0.07
V600E	COLO205	Large Intestine (colon)	0.13
V600E	HT29	Large Intestine (colon)	0.23
V600E	COLO201	Large Intestine	0.30

BRAF mutation	Cell line	Tissue of Origin	GI_{50} (μM)
		(colon)	
V600E	RKO	Large Intestine (colon)	0.50
G596R	NCIH508	Large Intestine (colon)	0.93
K601N	U266B1	Myeloma	0.35
V487_P492>A	BXPC3	Pancreas	0.92
L597R	22RV1	Prostate	0.92
V600E	MALME3M	Skin (Melanoma)	0.02
V600E	SH4	Skin (Melanoma)	0.02
V600E	COLO829	Skin (Melanoma)	0.07
V600E	SKMEL3	Skin (Melanoma)	0.05
V600E	SKMEL28	Skin (Melanoma)	0.11
V600E	HS695T	Skin (Melanoma)	0.11
V600E	C32	Skin (Melanoma)	0.09
V600E	A375	Skin (Melanoma)	0.12
V600E	A101D	Skin (Melanoma)	0.17
V600E	RPMI7951	Skin (Melanoma)	0.26
V600E	SKMEL1	Skin (Melanoma)	0.41
V600E	SW872	Soft Tissue (sarcoma)	0.18
V600E	SW982	Soft Tissue (sarcoma)	0.11
V600E	A673	Soft Tissue (sarcoma)	0.66
A400V	SNU1	Stomach	0.26
V600E	BHT101	Thyroid	0.46

BRAF V600 E DATA

[00296] GI_{50} data for BRAF mutant cell lines shown below in Table 11.

Table 11

BRAF mutation	Cell line	Tissue of Origin	GI_{50} (μM)
V600E	BT474	Breast	3.29
V600E	DBTRG05MG	Central Nervous System	0.14
V600E	ES2	Female GU (ovary)	0.64
V600E	DB	Large cell lymphoma	3.14

BRAF mutation	Cell line	Tissue of Origin	GI_{50} (μM)
V600E	SW1417	Large Intestine	0.07
V600E	COLO205	Large Intestine (colon)	0.13
V600E	HT29	Large Intestine (colon)	0.23
V600E	COLO201	Large Intestine (colon)	0.30
V600E	RKO	Large Intestine (colon)	0.50
V600E	MALME3M	Skin (Melanoma)	0.02
V600E	SH4	Skin (Melanoma)	0.02
V600E	COLO829	Skin (Melanoma)	0.07
V600E	SKMEL3	Skin (Melanoma)	0.05
V600E	SKMEL28	Skin (Melanoma)	0.11
V600E	HS695T	Skin (Melanoma)	0.11
V600E	C32	Skin (Melanoma)	0.09
V600E	A375	Skin (Melanoma)	0.12
V600E	A101D	Skin (Melanoma)	0.17
V600E	RPMI7951	Skin (Melanoma)	0.26
V600E	SKMEL1	Skin (Melanoma)	0.41
V600E	SW872	Soft Tissue (sarcoma)	0.18
V600E	SW982	Soft Tissue (sarcoma)	0.11
V600E	A673	Soft Tissue (sarcoma)	0.66
V600E	BHT101	Thyroid	0.46

ADDITIONAL CELL LINES

[00297] GI_{50} data for additional cell lines shown below in Table 12.

Table 12

Cell line	Tissue of Origin	GI_{50} (μM)
C32TG	Skin (Amelanocytic melanoma)	0.04
MX1	Hematopoietic and lymphoid (acute promyelocytic leukemia)	0.11
PANC1	Pancreas	0.25
TE381T	Soft Tissue (Rhabdomyosarcoma)	0.15
WI38	Lung normal Fibroblast	0.29
WIDR	Large Intestine (colon)	0.18
SCABER	Bladder	0.30
CAMA1	Breast	0.37
EFM19	Breast	0.18

Cell line	Tissue of Origin	GI_{50}
MCF7	Breast	0.25
MDAMB468	Breast	0.34
T47D	Breast	0.24
SKNFI	Central Nervous System	0.10
SW48	Large Intestine (colon)	0.19
KATOIII	Colon GI (stomach)	0.22
CGTHW1	Thyroid	0.12
SW579	Thyroid	0.21
DOTC24510	Female GU (cervix)	0.27
OVCAR3	Female GU (ovary)	0.03
MV411	Hematopoietic and lymphoid (B myelomonocytic leukemia)	0.15
EM2	Hematopoietic and lymphoid (human chronic myeloid leukemia)	0.16
G401	Kidney	0.41
G402	Kidney	0.18
CORL105	Lung	0.11
MEWO	Skin (Melanoma)	0.22
A204	Soft Tissue (Rhabdomyosarcoma)	0.10
SJRH30	Soft Tissue (Rhabdomyosarcoma)	0.38

Example 4

Tumor Growth Inhibition and Target Occupancy Following Administration of Compound 1 to Mice Bearing HCT116 Colon Tumor Xenografts

[00298] The objectives of this study were to determine the tumor growth inhibition of Compound **1** (administered as free base) in HCT116 human colorectal cancer xenografts (a KRAS-mutated cancer ($KRAS^{G13D}$)) and to correlate efficacy to target occupancy. Occupancy Assay A (outlined below) was used for this Example.

[00299] Briefly, 8- to 12-week old female nu/nu mice were implanted with 5 x 10^6 HCT116 cells subcutaneously. Compound **1** was administered via oral gavage (PO) once per day (QD) at 50 or 100 mg/kg or twice per day (BID) at 12.5, 25, 50, or 75 mg/kg until Day 21 (D21). ERK occupancy by Compound **1** in tumor and plasma concentrations of Compound **1** was quantified following the last dose. Efficacy was determined by measurement of tumor growth inhibition

(TGI), which was defined as the percent difference between the D21 median tumor volumes of drug-treated and vehicle-treated groups. Compound **1** elicited dose and schedule dependent tumor growth inhibition in the HCT116 xenograft model (57% to 93% TGI), with a minimum efficacious dose (70% TGI) of 50 mg/kg/day, correlating to an area under the plasma concentration-time curve (AUC) of 1470 ng·hr/mL on the final day of dosing (See Figure 6) Occupancy of ERK (i.e., the proportion of ERK protein bound to Compound **1**), measured in tumor lysates collected on the last day of dosing with Compound **1** was comparable to tumor growth inhibition, and is summarized in **Table 13**.

Table 13: Tumor Growth Inhibition (TGI), ERK Occupancy, and Compound 1 Plasma Exposure in Female Nu/Nu Mice Implanted with HCT 116 Tumor Cells

Treatment	Dose[a] (mg/kg)	Schedule	TGI (%)	% Occupancy 2-8 hr[b] (mean ± SD)	AUC (ng·hr/mL)
Compound **1**	100	QD	77	76.1 ± 10	3900
	50	QD	70	59.3 ± 10.4	1470
	75	BID	ND[c]	ND[c]	ND[c]
	50	BID	93[d]	71.8 ± 12.3[d]	ND
	25	BID	65	44 ± 20.6	788
	12.5	BID	57	17 ± 29.9	270

AUC = area under the concentration-time curve; BID = twice daily; ND = not determined; QD = once daily; SD = standard deviation; TGI = tumor growth inhibition.
[a] Doses of Compound **1** refer to the free base.
[b] Occupancy in vehicle control tumor lysates was -23.6 ± 7.47 (SD) tumor lysates was -20.2 ± 31.4, respectively.
[c] Dosing terminated on Day 6 due to toxicity
[d] Determined on Day 18, due to toxicity and termination of dosing. Occupancy determined 4 hours post dose.

[00300] **Occupancy Assay A**: A standard curve of recombinant ERK1 (Millipore 14-439, lot 2052233) was prepared by first incubating human rERK1 with an excess of a probe compound that covalently binds to ERK, final concentration 0.6 μM in lysis buffer. The rERK1 standard was then diluted to concentrations of 0.34, 1.02, 3.06, 9.18, 27.54, 82.62, 250 ngs/60 μL and 60 μL was added to the sample plate. The following protocol was used for Erk occupancy in tumor homogenates.

[00301] To measure ERK occupancy in xenograft tumors, 22.5 μg of each tumor homogenate protein was incubated with the covalent probe compound (1 μL of 60 μM) for 1 hour at room

temperature. A biotin was clicked onto the covalent probe compound **I-362** (described in the '230 publication) by addition of 10 μL of 1 mM a copper chelating biotin-azide, 50 mM sodium ascorbate, 0.5 mM THPTA ligand, and $Cu(II)SO_4$. Samples were then incubated at 28 °C for 10 minutes. Each sample was transferred to a well of a 96-well Zeba desalting column (Thermo Scientific, Rockford, IL #89807, 7K MW cutoff), followed by a 10 μL water stacker. The plate was centrifuged at 1,000 x g for 2 minutes, sealed, and frozen at -80 °C until it was analyzed in the MSD assay.

[00302] The MSD assay was accomplished by first thawing the plate containing the rERK1 standard curve samples and tumor lysates at 4 °C on a plate shaker. An MSD ERK plate for detection of total ERK 1/2 (MesoScale Discovery, Cat# K15107A-3) was blocked with 3% BSA in TBST as per kit instructions. Blocking reagent was removed and the plate was washed 3 times with MSD washing buffer (1X TBST). All samples were mixed with an equal volume of MSD lysis buffer (containing 2X protease and phosphatase inhibitors) spiked with 0.5% SDS to a final SDS concentration of 0.25%. Equal volumes of the clicked samples were then added to two separate MSD wells, one for detection of biotin probe (for determination of free ERK) and one for detection of total ERK for normalization.

[00303] The plate was incubated for 2 hours at room temperature under constant shaking, washed 3 times with MSD washing buffer, tapped dry, then incubated with 25 μL/well of either ERK SULFO-TAG detection antibody (for total ERK detection, diluted 1:50 in 1% BSA in TBST) or SULFO-TAG streptavidin detection protein (MesoScale Discovery Cat#R32AD-1;for free ERK detection, diluted 1:500 in 1%BSA in TBST). Following incubation under constant shaking for 1 hour at room temperature, the plate was washed 3 more times with MSD washing buffer, tapped to dry, and 150 μL of 1X MSD read buffer added (per kit instructions). Plates were then read in an MSD plate reader. After subtracting the background MSD reading (BSA spot in the same well), the concentration of total ERK and free ERK is determined by referencing each sample to an ERK1 standard curve, one for tERK and a second for fERK. Those standard curves were each fit to a nonlinear regression yielding functions that relate MSD signal to nanograms of ERK1. The percent free ERK was, therefore, determined by dividing the concentration of free ERK by the concentration of total ERK multiplied by 100.

Example 5

Plasma Exposure and Target Occupancy Following Daily and Twice Daily Administration of Compound 1 to Mice Bearing A375 Human Melanoma Tumor Xenografts

[00304] This initial study was conducted to evaluate once and twice daily dosing of Compound **1** to A375 tumor bearing nude mice (a $BRAF^{V600E}$ mutated cancer). In addition to tumor growth inhibition, plasma exposure and ERK occupancy in tumor lystates were characterized in samples collected at the end of study. Occupancy Assay B (outlined below) was used for this Example.

[00305] Tumor growth inhibition (calculated in the same manner as in Example 4) following administration of Compound **1** in the A375 xenograft model at 100 mg/kg QD and 50 mg/kg BID was 84% and 87%, respectively (Table 14). Occupancy (i.e., the proportion of phosphorylated ERK protein bound to Compound 1) in tumor lysates 2 to 8 hours after the last dose was 48% to 54% in the 50 mg/kg BID treatment group and 82% to 86% in the 100 mg/kg QD treatment group (Table 14). Plasma exposure of Compound **1** in the 50 mg/kg BID group was 9280 ng·hr/mL (Table 14).

Table 14: Tumor Inhibition, Exposure, and Target Occupancy in Compound 1-treated Mice Bearing A375 Human Xenografts

Treatment	Dose[a] (mg/kg)	Schedule	TGI (%)	Occupancy[c]	$AUC_{0\text{-last}}$ (ng·hr/mL)
Compound **1**	100	QD	84	-73.7[d], 86.5, 81.6	NC[e]
	50	BID	87	53.5, 50.7, 47.6	9280

$AUC_{0\text{-last}}$ = area under the concentration-time curve to the last observable concentration at time t; BID = twice daily; NC = not calculable; QD = once daily; TGI = tumor growth inhibition.

[a] Doses of Compound **1** refer to the free base.

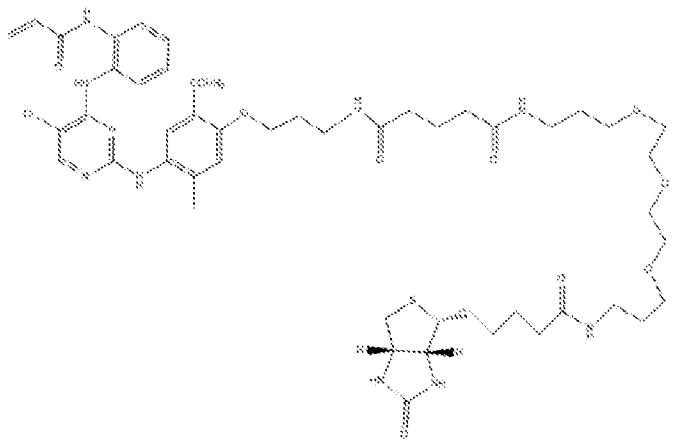
[c] Occupancy of phosphorylated ERK (pERK) with COMPOUND **1** at 2, 4, and 8 hours postdose, respectively, expressed as % of vehicle control signal in MSD assay.

[d] Plasma levels of Compound **1** in mice sacrificed at the 2 hour time point in the 100 mg/kg QD dose group were below the limit of quantitation (BLOQ). Occupancy was not observed in these mice likely due to a technical error in dosing of these mice.

[e] Plasma levels of Compound **1** in mice bled at the 15 minute and 2 hour time points in the 100 mg/kg QD dose group were below the limit of quantitation (BLOQ), likely due to technical error in the dosing of these mice.

[00306] **Occupancy Assay B:** For determination of pERK occupancy and total ERK levels, a tERK/pERK kit from Mesoscale Discovery was used (MSD K15107D-3, Rockville, MD). The kit contains a capture plate containing a tERK spot, a pERK spot and 2 BSA spots. Parallel plates were blocked with 3% bovine serum albumin (BSA) for 1 hour at room temperature. The

blocking buffer was discarded and 30 μL of lysate was added to each plate. The pERK covalent probe compound at 10 mM stock was diluted to 2 μM in lysis buffer. To each well 3.3 μLof probe compound was added so that the final concentration per well was 0.2 μM. After shaking at room temperature for 2 hours, plates were washed with 1X Tris wash buffer and 25 μL of SULFO-TAG streptavidin, diluted to 1 μg/mL in wash buffer, was added to one of the plates to determine ERK occupancy. Twenty five microliters of SULFO-TAG anti-ERK antibody, diluted according to manufacturer instructions, was added to the second plate to determine total ERK. Plates were then left on a shaker for 1 hour at room temperature, then washed with 1X Tris wash buffer before 150 μL of 1X Read buffer T (MSD R92TC-1, Rockville, MD) was added, and chemiluminescence signal detected using an MSD plate reader. To determine percent occupancy of pERK, signals were normalized by dividing the readings from the plate used to determine occupancy by the corresponding readings from the plate used to determine total ERK. The percentage occupancy of pERK in treated animals was calculated assuming the average of the vehicle control had 100% free ERK: 100 (% free ERK of vehicle) - % free ERK (treated animals) = % occupancy.



pERK Covalent Probe Compound

Example 6

Effect of Dose Schedule on Tumor Growth Inhibition and Target Occupancy Following Administration of Compound 1 to Mice Bearing A375 Human Melanoma Xenografts

[00307] The objectives of this study were to determine the effect of dose schedule of Compound **1** (administered as the free base) on tumor growth inhibition in A375 human

xenografts and to correlate efficacy with target occupancy. Occupancy Assay A (outlined above) was used for this Example.

[00308] Briefly, 8- to 12-week old female nu/nu mice were implanted with 1 mm^3 A375 fragments subcutaneously. Compound **1** was administered via oral gavage (PO) once per day (QD) at 25, 50, or 100 mg/kg, every other day (QOD) at 50, 100, or 200 mg/kg, or every third day (Q3D) at 100, 200, or 300 mg/kg, until vehicle-dosed control tumors reached an average size of 2000 mm^3 on Day 12. ERK occupancy was quantified in tumor lysates and plasma concentrations of Compound **1** were determined following the last dose. Administration of Compound **1** at all doses tested was well tolerated. There was one death in each of the groups dosed with 200 mg/kg QOD and 200 mg/kg Q3D, and 2 deaths in the group dosed with 25 mg/kg QD. These were noted to be non-treatment-related. ERK occupancy in tumors was determined by measuring total ERK and free ERK (ERK not bonded with Compound **1**) using a commercially available kit for detection of ERK1/2, and occupied ERK1/2 using a covalent probe compound. The ERK occupancy levels obtained with the dosing regimens evaluated are presented in Table 15. Plasma concentrations of Compound **1** following the final dose in each group were determined by LC/MS/MS and plasma exposures are summarized in Table 15.

Table 15: Tumor Growth Inhibition (TGI), ERK Occupancy, and Compound 1 Plasma Exposure in Female Nu/Nu Mice Implanted with A375 Tumor Cells

Treatment	Dose[a] (mg/kg)	Schedule	TGI (%)	Mean Occupancy (%) 2 to 8 hrs[c]	AUC (ng·hr/mL)[d]
Compound **1**	25	QD	53	39 ± 29	4960
	50	QD	69	59 ± 9	4350
	100	QD	82	62 ± 15	8700
	50	QOD	53	54 ± 15	7460
	100	QOD	68	65 ± 11	11500
	200	QOD	64	57 ± 19	17500
	100	Q3D	57[e]	65 ± 14	10400
	200	Q3D	32	74 ± 11	15100
	300	Q3D	67	66 ± 21	17100

AUC = area under the concentration-time curve; QD = once daily; QOD = every other day; Q3D = once every three days; TGI = tumor growth inhibition.

[a] Doses of Compound **1** refer to the free base.

[c] Occupancy in vehicle control tumor lysates was -34 ± 13 (mean ± standard deviation [SD]).

[d] Mice dosed on last day of study for exposure assessment regardless of dose regimen.

[e] Tumors in this group spontaneously regressed, which possibly inflated the TGI.

[00309] Compound **1** inhibited tumor growth in an A375 xenograft mouse model, with a minimum efficacious dose of 50 mg/kg/day, corresponding to an $AUC_{0\text{-}8\ hr}$ of 4350 ng·hr/mL and target occupancy of 59%. Comparable tumor growth inhibition was observed in mice dosed daily at 25 mg/kg or every other day at 50 mg/kg (53% for both groups), and similarly between mice that were dosed daily at 50 mg/kg and those dosed at 100 mg/kg every other day (68% and 69%, respectively). These data suggest that reduced dose frequency could inhibit tumor growth as effectively as daily administration.

Example 7

Effect of Compound 1 on tumor growth in the LOX-IVMI xenograft model

[00310] The antitumor activity of Compound **1** was evaluated in the LOX-IMVI human melanoma xenograft model (a $BRAF^{v600E}$-mutated cancer). Female severe combined immunodeficiency (SCID) mice were implanted with LOX-IMVI cells into the flank. Randomized groups of mice (n = 10/group) were treated with the phosphate salt of Compound **1**, orally once daily [PO, QD] for 7 days (Day 13 through Day 20 post-inoculation). Doses of the phosphate salt of Compound **1** evaluated in this study (30.25, 60.5 and 121 mg/kg) correspond to free base equivalent doses of 25, 50 and 100 mg/kg, respectively. Significant inhibition of LOX-IMVI human melanoma tumor growth was observed following treatment with the phosphate salt of Compound **1** (30.25, 60.5, and 121 mg/kg, resulted in 77.7%. 92.9%, 94.7% inhibition, respectively, compared to the vehicle control). Dose-dependent tumor inhibition was observed with the phosphate salt of Compound **1** at the 30.25 mg/kg and 60.5 mg/kg dose levels; however, there was no difference in tumor volume between the 60.5 mg/kg and the 121 mg/kg dose level. On Day 20, animals treated with the phosphate salt of Compound **1** at the 60.5 mg/kg and 121 mg/kg dose levels had average tumor volumes that were below the starting volumes on Day 13, indicating that the drug treatment caused regression of the established tumors (-54.7% -65.1% compared to the starting volume on Day 13 for 60.5 mg/kg and 121 mg/kg, respectively) (Figure 5). No significant change in body weight was observed in any of the treatment groups.

Example 8

BRAFi-Resistant and MEKi-Resistant Cells Are Sensitive to Compound 1

[00311] A375 cells (BRAF V600E mutant) were cultured in IMDM media in the presence of 10% FBS and were made resistant to a Raf inhibitor by continuous culture in the presence of increasing concentrations of Vemurafenib. These cells are referred to as A375-R. Similarly, HCT-116 cells (KRAS mutant) were made resistant to a MEK inhibitor by continuous culture in the presence of increasing concentrations of trametinib (referred here as HCT116R).

[00312] Inhibition of proliferation was assayed by measuring the difference in cell growth after 72 h between cells treated with Compund **1** and cells treated with DMSO (control). Cells were plated in 96-well plates in full media (10% FBS in DMEM for A375 and A375-R, or 10% FBS in RPMI for HCT-116 or HCT-116R) at 3000 cells per well. Compound **1** was serially diluted in 3-fold dilutions in DMSO, and added to the cells 6 hours after plating at a final concentration of 0.1% DMSO, 5% FBS. To determine the number of cells at the start of the experiment, an additional plate was prepared and read 6 hours after plating on day zero, which included a standard curve (starting at 50,000 cells in 8-point 2-fold serial dilution) and replicate wells of the plated cells on day 0. Cells were incubated for 72 h at 37 °C, 5% CO_2, and cell number was measured with cell titer glo (Promega). Luminescence was converted to cell number by linear regression to the standard curve. GI_{50} is defined as the 50% inhibition of the cell growth from day 0 to 72 h after treatment relative to DMSO treated control. Results of GI_{50} for Compound **1** in parental A375, BRAF inhibitor resistant A375 cells, HCT-116 parental, and Mek-inhibitor resistant HCT-116 is shown in Table 16 below. As shown in Tables 16 and 17, A375R and HCT116R cells are more sensitive to Compound **1** than a BRAF inhibitor (BRAFi) or a MEK inihibitor (MEKi), respectively.

Table 16

BRAF-Resistant A-375			
Compound	**Class**	**A-375 GI_{50} (nM)**	**A-375R GI_{50} (nM)**
Vemurafenib	BRAFi	10	3127
Trametinib	MEKi	2	>5000
Compound 1	ERKi	106	214

A-375 = $BRAF^{V600E}$ mutant melanoma line
A-375R = Vemurafenib-resistant A-375.
ERKi = ERK inhibitor
MEKi = MEK inhibitor
BRAFi = BRAF inhibitor

Table 17

MEKi-Resistant HCT-116			
Compound	**Class**	**HCT-116 GI_{50} (nM)**	**HCT-116R GI_{50} (nM)**
AZD 6244	MEKi	181	>5000
Trametinib	MEKi	24	1810
Compound 1	ERKi	201	190

HCT-116 = $KRAS^{G13D}$ colon cancer.
HCT-116R = trametinib-resistant HCT-116.
ERKi = ERK inhibitor
MEKi = MEK inhibitor

Example 9
In Vitro Assays

[00313] This Example describes experiments relating to the effect of Compound **1** (free base) on a Panc1 (a.k.a. PANC-1) pancreatic cancer cell line, a MIA PaCa-2 pancreatic cancer cell line, an HS294T melanoma cell line, an HCT-116 colorectal cancer cell line, a KRAS-mutant q61H NCI-H460 lung cancer cell line, a KRAS-unknown NCI-H522 lung cancer cell line, a p. G469A NCI-1755 lung cancer cell line, a KRAS-mutant p. G12V NCI-H727 lung cancer cell line, and a KRAS-mutant NCI-H522 lung cancer cell line.

[00314] For dose-response viability assays, cells were plated at a density of 3000 cells/well in 90 μL of growth media on 96 well clear bottom black-well plates (Corning Cat# 3904) and incubated overnight under standard cell culture growth conditions at 37 ^{0}C 5% CO_2. The outer most rows and columns of wells were filled with culture media, without cells, to avoid evaporation effects on subsequent readouts.

[00315] The following day, one plate for each cell line was used for "Day 0" cell growth control readout, and cell viability was measured with CellTiter Glo (Promega) reagent according to manufacturer specifications. Day 0 control plates were equilibrated to room temperature for 30 minutes in a tissue culture hood, followed by addition of 90 μL of CellTiter Glo reagent, a volume equal to cell media volume, to each well. The plates were covered with foil to protect from light and placed on a shaker at low speed for 5 minutes, followed by 10 minutes incubation without shaking. CellTiter Glo reagent signal was read on a spectramax L luminescence detector, and data were processed using Excel and Prism software.

[00316] At the same time (while Day 0 plate was equilibrating to room temperature), cells in the remaining plates were treated with Compound **1** or DMSO vehicle control, as specified for

each cell line. For cell treatment, compounds were diluted from starting concentration 10 mM stock in DMSO to 10 μM starting in-well concentration (3 dilution steps first serially in DMSO, then in cell growth media), such that resulting DMSO concentration in the growth media in wells containing cells was 0.1%. The cells were treated with a 9 point 3-fold dilutions of Compound **1**, and a DMSO control. Each treatment was contained in 10 μL treatment media added to the respective wells. Each concentration was tested in triplicate.

[00317] Thus, the final concentrations in treatment wells were: (in nM) 10000.00, 3333.33, 1111.11, 370.37, 123.46, 41.15, 13.72, 4.57, 1.52, 0.

[00318] Seventy two hours later "Day 3" cell viability was measured by adding 100 μL CellTiter Glo reagent to each of the treatment wells, equal to the volume of media and compound. Cell viability was assessed as described for "Day 0" control.

[00319] Results are depicted graphically in Figures 7 and 9-16. A curve crossing below the X-axis indicates that cell number has dropped below the starting point (i.e., the cells are dying).

[00320] Figure 9 depicts (a) a first in vitro assay of Compound **1** against HCT-116 colorectal cancer cells; and (b) a second in vitro assay of Compound **1** against HCT-116 colorectal cancer cells. As shown in Figure 9a, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1321.30 nM. As shown in Figure 9b, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1169.50 nM.

[00321] Figure 10 depicts an in vitro assay of Compound **1** against KRAS-mutant q61H NCI-H460 lung cancer cells. As shown in Figure 10, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 6839.12 nM.

[00322] Figure 11 depicts an in vitro assay of Compound **1** against KRAS-unknown NCI-H522 lung cancer cells. As shown in Figure 11, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 2338.84 nM.

[00323] Figure 12 depicts an in vitro assay of Compound **1** against p.G469A NCI-H1755 lung cancer cells. As shown in Figure 12, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 722.77 nM.

[00324] Figure 13 depicts an in vitro assay of Compound **1** against KRAS-mutant p.G12V NCI-H727 lung cancer cells. As shown in Figure 13, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 762.08 nM.

[00325] Figure 14 depicts an in vitro assay of Compound **1** against KRASunknown NCI-H522 lung cancer cells. As shown in Figure 14, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 3006.08 nM.

[00326] Figure 15 depicts (a) a second in vitro assay of Compound **1** against Mia PaCa-2 pancreatic cancer cells; and (b) a third in vitro assay of Compound **1** against Mia PaCa-2 pancreatic cancer cells. As shown in Figure 15a, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1238.80 nM. As shown in Figure 15b, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1534.62 nM

[00327] Figure 16 depicts a second in vitro assay of Compound **1** against HS294T melanoma cells. As shown in Figure 16, Compound **1** induces cell death (cytotoxic) effect (noted by the curve crossing the X-axis) at 1202.26 nM.

Example 10

Dosing and Administration Protocol

[00328] The following protocol describes a phase 1a multicenter, open-label safety and pharmacokinetics study of the phosphate salt of Compound **1** in subjects with locally-advanced or metastatic, relapsed, or refractory BRAF (e.g., $BRAF^{V600}$) or RAS-mutated malignancies. For ease of reading, the text of this Example sometimes refers to "Compound **1**" rather than the "phosphate salt of Compound **1**"; however it should be understood that the phosphate salt of Compound **1** is under study.

Objectives:

[00329] Primary Objective: The primary objectives of the study are to assess the safety, tolerability, and PK of the phosphate salt of Compound **1** when administered orally to subjects with locally-advanced or metastatic relapsed or refractory, BRAF-(e.g., $BRAF^{V600}$) or RAS-mutated solid tumors and to define its maximally tolerated dose (MTD).

[00330] Secondary Objective: The secondary objective of the study is to conduct a preliminary assessment of the anti-tumor activity of the phosphate salt of Compound **1**.

[00331] Exploratory Objectives: The exploratory objectives of the study are (1) explore the relationship between the Compound **1** exposure (AUC) and response (safety and efficacy); (2)

explore the influence of intrinsic and extrinsic factors that may influence Compound **1** exposures (e.g., age, gender, body weight, tumor type, measures of end-organ function, associated inter-individual and residual variability in Compound **1** recipients, etc.) (3) evaluate Compound **1** binding to ERK in peripheral blood mononuclear cells (PBMCs) and tumor biopsies, as well as inhibition of ERK signaling in tumor biopsies obtained prior to and during treatment with Compound **1** (4) characterize the principal metabolites of Compound **1** in plasma; and (5) explore changes to the levels of 4β-hydroxycholesterol (a marker of CYP3A activity) in plasma samples obtained prior to and during treatment with Compound **1**.

Study Endpoints:

[00332] The primary endpoints of this study are (1) safety as defined by the type, incidence and severity of adverse events, dose limiting toxicities, the MTD of Compound **1**, and changes from baseline in selected laboratory analytes, vital signs and ECG findings; and (2) PK endpoints: C_{max}, AUC, T_{max}, $t_{1/2}$, CL/F, Vz/F and accumulation index of Compound **1**.

[00333] The secondary endpoints of this study are anti-tumor activity as measured by response rate, duration of response, disease control rate, progression-free survival and overall survival.

[00334] Exploratory endpoints are (1) PK endpoints as assessed by non-mixed effect modeling (NMEM) compartment analysis; (2) clinically relevant intrinsic/extrinsic covariates of Compound **1** exposure from population PK analysis; (3) mechanism-based modeling of Compound **1** exposure and response relationships; (4) relationship between Compound **1** exposure (as measured by AUC) and binding to ERK in PBMCs and tumor biopsies obtained during vs. pre-treatment; (5) relationship between Compound **1** binding to ERK and inhibition of ERK signaling in tumor biopsies during vs. pre-treatment; and (6) relationship between biomarkers (ERK binding, inhibition of ERK signaling) in tumors and clinical outcomes; (7) profile of Compound **1** metabolites in plasma; and (8) plasma levels of 4β-hydroxycholesterol prior to and during Compound **1** administration.

Overall Study Design

[00335] This study is an open-label, multicenter, Phase 1a study in subjects with locally-advanced or metastatic, RAS or BRAF (e.g., $BRAF^{V600}$) -mutated solid tumors who are intolerant of, resistant to or have relapsed after at least one line of therapy and for whom no

standard therapy exists. The study will be conducted in two parts: Dose Escalation (Part 1) and Cohort Expansion (Part 2). For both parts, each 28-day cycle will consist of 21 consecutive days of Compound **1** treatment followed by a 7 day rest period. Subjects may continue Compound **1** until progression of their underlying malignancy, the occurrence of intolerable toxicity or physician/subject decision to discontinue Compound **1**. Subjects who discontinue study treatment for reasons other than progression will be requested to continue follow-up on study until progression, initiation of new anti-cancer therapy, or withdrawal of consent for further study participation.

[00336] Part 1: Cohorts of subjects with either BRAF (e.g., $BRAF^{V600}$)-mutated cancers (e.g. melanomas, colorectal cancer (CRC), papillary thyroid carcinomas) or RAS-mutated cancers (e.g. pancreatic ductal adenocarcinomas (PDAC), CRC, melanomas, non-small cell lung cancer (NSCLC)), or relapsed or refractory tumors will receive increasing doses of Compound **1** in order to assess its safety and tolerability, the MTD and PK profile. The initial cohort will receive 20 mg per day. Cycle 1, Days 1-28 will constitute the dose-limiting toxicity (DLT) assessment period for purposes of non-tolerated dose (NTD) and MTD determination. A modified accelerated titration design will be used to establish initial toxicity. During the accelerated phase, cohorts of one or more subjects each will be given Compound **1** at doses that will increase in 100% increments per cohort until the first occurrence of a Grade ≥2, study drug-related toxicity in Cycle 1. At this point, the accelerated phase will end and all subsequent cohorts (including the cohorts in question) will be expanded to 6-9 sequentially enrolled subjects. A dose escalation schedule with dose increments not to exceed 50% will concurrently be initiated in order to establish the NTD and MTD. Smaller dose increments and/or additional subjects within a dose cohort as well as modified dosing schedules (e.g., every other day dosing) may be evaluated, if necessary, based on toxicity, PK/PD or findings on tumor biopsies. Dose escalation decisions will be made at the discretion of the Study Review Committee (SRC), composed of representatives of the Sponsor (i.e. the medical monitor, drug safety physician and study manager) as well as the principal investigators from each of the participating institutions at which one or more study subjects was enrolled. See Figure 8.

[00337] A dose will be considered intolerable if >33% of evaluable subjects in a dose cohort experience DLT during Cycle 1. The putative MTD will be defined as the last dose below the NTD, at which ≤33% of evaluable subjects experienced DLT during Cycle 1. Investigation of an

intermediate dose between the NTD and the putative MTD may be required to determine the MTD with greater precision, as may alternate regimens if emerging PK results suggest they may be appropriate. A dose intermediate between the NTD and putative MTD may still be explored following initiation of Part 2 (see below).

[00338] Part 1 subjects will be evaluable for DLT if a.) they received the prescribed dose of Compound **1** on at least 80% of treatment days in Cycle 1 (i.e. 17 of 21 days), and have sufficient data for safety evaluation by the SRC, or b.) experienced a DLT. Non-DLT evaluable subjects within a given dose cohort will be replaced. Approximately 40 subjects in 10 dose cohorts are anticipated in Part 1 for initial assessment of safety, NTD/MTD, and PK (intensive blood sampling).

[00339] Intrasubject dose escalation will not be allowed during the DLT assessment period; however, in Cycle 2 and beyond, subjects without evidence of disease progression who are tolerating their assigned dose of Compound **1** may (at the investigator's discretion) escalate to the highest dose level shown to be adequately tolerated by at least one cohort of subjects in this study (i.e. ≤33% of evaluable subjects having experienced a DLT at that dose level).

[00340] Part 2: In Part 2, subjects will receive Compound **1** at or below the MTD until progression of disease, intolerable toxicity or physician/subject decision to discontinue Compound **1**. Approximately 42-60 subjects belonging to one of three tumor-specific cohorts will be evaluated for additional assessments of safety, PK (intensive sampling) and antitumor activity:

- Recurrent/progressed NRAS (G12, G13 or Q61) or $BRAF^{V600}$-mutant (e.g., V600E or V600K) melanoma (n=14-20)
- Recurrent/progressed KRAS (G12, G13 or Q61) or $BRAF^{V600}$-mutant, locally-advanced or metastatic CRC (n=14-20)
- Recurrent/progressed, locally-advanced or metastatic PDAC (n=14-20)

[00341] One or more of these tumor specific expansion cohorts may be modified (or additional cohorts may be added) that would allow an assessment of Compound **1** in other tumor types of interest.

[00342] Subjects in Part 2 will be required to undergo tumor biopsies in order to obtain tumor tissue for PD biomarkers at Screening (up to 28 days before Cycle 1, Day 1 of Compound **1**) and

during Cycle 1 (days 16 through 21). Enrollment into each tumor specific cohort will follow a two-stage design: if at least one objective response or 3 subjects with stable disease lasting ≥16 weeks (i.e., through the 2nd on-treatment, tumor assessment time point) is observed from among the first 14 efficacy-evaluable patients enrolled, the remainder of the cohort (the 2nd stage) will be completed in order to insure the availability of data from approximately 20 evaluable subjects. If necessary, accrual to the 2nd stage may be suspended until it can be determined with certainty that at least one of the aforementioned criteria for enrollment of the 2nd stage have been met. In the absence of either of the aforementioned criteria, enrollment into a given cohort will cease after 14 subjects. Decisions to expand or curtail enrollment into each tumor-specific cohort will be made in consultation with the Safety Review Committee.

[00343] The study design includes: (1) a screening period from day -28 to day -1; (2) a treatment and evaluation period, during which time Compound **1** is administered on Days 1-21of 28-day cycles until tumor progression, unacceptable toxicity or subject/physician decision to discontinue Compound **1** (Part 1: Dose-escalation; Part 2: Cohort expansion) ; and (3) an end of treatment and follow up period comprising end of treatment procedures and safety follow-up for 28 days after last dose of Compound **1** or until disease progression (in subjects who discontinue Compound **1** for reasons other than progression).

[00344] Study Design Rationale: This is a Phase 1a, multicenter, open-label study of orally administered Compound **1**. Compound **1** has a strong biological rationale for the treatment of subjects with locally-advanced or metastatic, relapsed or refractory cancers in which MAPK pathway dysregulation is pathogenetic. The safety, tolerability, PK/PD and preliminary efficacy of Compound **1** will be evaluated in this study. As noted, the study will be conducted in two parts: dose escalation (Part 1) and cohort expansion (Part 2). In both parts, eligibility will be confined to those subject whose tumors harbor specific activating mutations RAS or BRAF (e.g., $BRAF^{V600}$). Missense mutations involving codons 12, 13 and 61 are responsible for the vast majority of RAS-driven tumors. Similarly, glutamine and lysine substitutions at codon 600 of BRAF (V600E or V600K) comprise the vast majority of all BRAF mutations. Other substitutions at codon 600 of BRAF (e.g., V600R,V600D) as well as non-V600 activating mutations of BRAF (e.g., L597R S or Q, K601E) are uncommon. Tumors with non-V600 activating mutations in BRAF may be responsive to MEK inhibitor therapy and therefore, subjects whose tumors harbor these mutations may enroll in Part 1 of the study for determination of NTD/MTD.

[00345] In Part 1, use of a modified accelerated titration design is expected to be more efficient by limiting the number of subjects treated at lower, presumably sub-therapeutic doses and increasing the proportion of subjects treated at or near the MTD while reducing the duration of the study by dose doubling with each successive cohort until the first occurrence of a Grade 2 toxicity.

[00346] Part 2 will enroll approximately 42-60 subjects with pre-specified tumor types characterized by mutations in the classical MAPK pathway that are regarded as important to their continued growth and proliferation. Part 2 will further assess the safety and tolerability profile of Compound **1** at the dose and schedule established in Part 1 and provide a preliminary assessment of anti-tumor activity.

Study Population

Disease-specific inclusion criteria for Parts 1 and 2:

[00347] (1) Men and women, 18 years or older, with histological or cytological confirmation of advanced, unresectable or metastatic, BRAF (e.g., with activating mutations at V600 [E, K, D, or R], L597 [R, S, or Q] or K601E) or RAS-mutated (e.g., KRAS, NRAS, or HRAS, (with activating mutations at G12, G13 or Q61) mutant solid tumors, who are resistant or intolerant to or have progressed after at least one line of therapy and for whom no standard therapy exists. Subjects with PDAC only do not require documentation for the presence of *KRAS* mutation, given the known, very high prevalence of this mutation in this tumor type.

[00348] (2) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1

[00349] (3) At least one measurable lesion as defined per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

[00350] Disease-specific inclusion criteria - Part I only: Histologic or cytologic confirmation of unresectable or metastatic BRAF (with activating mutations at V600 [E, K, D or R], L597 [R, S or Q] or K601E) - or K, N or HRAS (with activating mutations at G12, G13, or Q61) mutant solid tumors that are resistant to or have progressed after at least one line of therapy (or where the subject is intolerant of therapy) and for which no standard therapy exists. Intolerance to the prior line of therapy is defined as the occurrence of unacceptable toxicity in association with a minimum of 2 cycles of standard therapy.

[00351] Disease-specific inclusion criteria - Part II only: As paired tumor samples are required in Part 2 (at Screening and in Cycle 1), subjects with access to tumor tissue capable of being biopsied using non-significant risk biopsy procedures (including, but not limited to, liver, skin/subcutaneous or superficial lymph node biopsy) will be considered for study participation.

[00352] Histologically or cytologically confirmed tumors of the following types that are resistant to or have progressed after at least one line of therapy (or where the subject is intolerant of therapy, as defined above) and for which no standard therapy exists:

[00353] Melanomas: recurrent/progressed, locally advanced, unresectable or metastatic NRAS-mutant (G12, G13, or Q61) melanoma; locally advanced, unresectable or metastatic, $BRAF^{V600}$-mutant melanoma (e.g., V600E, V600K, etc.) progressed on BRAF inhibitor (e.g., vemurafenib, dabrafenib), MEK inhibitor (eg, trametinib, cobimetinib [formerly GDC-0973] or selumetinib) or combination BRAF/MEK inhibitor therapy. Subjects with a history of anti-CTLA 4 (ipilimumab; Yervoy®) or other immune checkpoint blockade inhibitors (e.g., pembrolizumab; nivolumab) as their last therapy prior to enrolling in this trial are eligible as long as they have radiographic evidence of disease progression as defined by Immune-Related Response Criteria.

[00354] Colorectal cancer (CRC): recurrent/progressed, locally advanced, unresectable or metastatic BRAF- (e.g., $BRAF^{V600}$) or RAS- (e.g., KRAS- (G12, G13 or Q61)) mutant CRC recurrent or progressed after at least one fluoropyrimidine-based regimen.

[00355] Pancreatic ductal adenocarcinoma (PDAC): recurrent/progressed, locally advanced, unresectable or metastatic PDAC recurrent or progressed after at least one gemcitabine- or fluropyrimidine-based regimen.

[00356] General inclusion criteria for Parts 1 and 2 (unless otherwise specified) include, but are not limited to subjects exhibiting the following laboratory values:

- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
- Hemoglobin (Hgb) ≥ 9 g/dl
- Platelet count (plt) $\geq 75 \times 10^9$/L
- Serum potassium concentration within normal range, or correctable with supplements
- Serum AST/SGOT and ALT/SGPT ≤ 3.0 x Upper Limit of Normal (ULN) or ≤ 5.0 x ULN if liver metastases are present
- Serum total bilirubin ≤ 1.5 x ULN or ≤ 2 x ULN if liver metastases are present

- Serum creatinine ≤ 1.5 x ULN, or 24-hr measured creatinine clearance ≥ 50 mL/min
- Negative serum or urine pregnancy test within 72 hrs before starting study treatment in females of childbearing potential (see below)
- Adequate left ventricular function (LVEF >50% as measured on MUGA or ECHO)

Description of Study Treatments

[00357] Formulation: Compound **1** will be supplied as capsules in three strengths, 5, 30 and 150-mg for oral administration. The 5, 30, and 150-mg Compound **1** capsules are equivalent to 6.07, 36.42, and 182.10 mg Compound **1** phosphate salt respectively. The 5, 30, and 150 mg strength dose are encapsulated in size 4 reddish brown, size 4 reddish brown /white opaque, and size 0 reddish brown capsule shells, respectively (See Table 5, supra).

[00358] The capsules contain the following excipients: betadex sulfobutyl ether sodium, sodium lauryl sulfate, sodium bicarbonate, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, and magnesium stearate.

Treatment Administration and Schedule

[00359] Compound **1** will be administered once daily in the morning on an empty stomach (i.e. 1 hour before breakfast) with at least 200 mL of water after an overnight fast lasting at least 6 hours in both Parts 1 and 2. Subjects will administer Compound **1** on Days 1 through 21 of each 28 day treatment cycle. On study days that require PK assessments, Compound **1** will be administered in the clinic in the fasted state after any predose assessments are completed. On all other days, subjects will self-administered their assigned doses at home. Subjects may continue study treatment for as long as they continue to derive clinical benefit or until the occurrence of documented disease progression, intolerable toxicity or subject/investigator decision to discontinue study treatment for other reasons.

[00360] In Part 1, subjects will be assigned sequentially to each successive dose cohort using an interactive voice response scheme (IVRS). Progression from one dose level to the next higher dose level will follow satisfactory review of relevant safety and available PK/PD data from lower dose cohorts (see below). There will be a minimum of 28 days after the first dose has been administered to the last subject enrolled to a given cohort between dose escalations. Within each dose cohort, enrollment will be staggered so that there is a minimum of 24 hours between the

Cycle 1, Day 1 dose for each subject, in order to evaluate acute toxicity. In Part 2, subjects will be treated at or below the MTD within cohorts defined by specified tumor types.

Definition of Dose-Limiting Toxicity

[00361] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4 will be used to grade the severity of all adverse events (AEs). Dose-limiting toxicities (DLTs) are defined as the occurrence of one or more of the following AEs.

[00362] Any Grade 4, non-hematologic toxicity of any duration during Cycle 1 that is suspected to be related to study drug.

[00363] A clinically relevant, Grade $\geq$ 3 clinical AE that is suspected to be related to Compound **1** and commences within 28 days of first dose except for:

- Alopecia
- Grade 3 rash of the acneiform, pustular or maculopapular type, which resolves to Grade $\leq$2 within 4 days of study drug interruption and does not recur at the same level with resumption of Compound **1** at the same dose in the setting of optimal medical management
- Grade 3 diarrhea, nausea or vomiting lasting < 72 hours with optimal medical management
- Grade 3 fatigue, which resolves to Grade $\leq$2 within 4 days of study drug interruption and does not recur at the same severity with resumption of study drug at the same dose.
- Any non-hematologic Grade 3 laboratory abnormality that is asymptomatic and rapidly reversible (i.e. returns to $\leq$Grade 1 within 4 days of treatment interruption). Treatment must be held in the face of such a Grade 3 abnormality until it is clear that its causality is not related to Compound **1**.

[00364] Hematologic AEs that are suspected of being relate to Compound **1** and occur within 28 days of commencing treatment as follows:

- Grade 3 febrile neutropenia
- Grade 4 neutropenia lasting > 7 days
- Grade 4 thrombocytopenia lasting > 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

- Grade 3 hemolytic anemia

[00365] Any AE necessitating Compound **1** dose reduction in Cycle 1 or interruption for longer than 4 days.

[00366] Note**:** The occurrence of a second primary skin neoplasm in any melanoma subject treated with a BRAF inhibitor (with or without concomitant MEK inhibitor therapy) within 6 months of Cycle 1, Day 1, will not be considered a dose-limiting toxicity for purposes of dose-escalation decision making. The 6 month latency period proposed is consistent with prescribing information for the BRAF inhibitors, vemurafenib (ZELBORAF® package insert) and dabrafenib (TAFINLAR® package insert), which indicates the importance of surveillance for second primary skin neoplasms for up to 6 months after BRAF inhibitor treatment discontinuation.

[00367] Isolated laboratory changes without associated clinical signs or symptoms may not be included in the definition of DLT. These findings will be discussed and reviewed by the Safety Review Committee.

Criteria for Dose Escalation in Part 1

[00368] Upon completion of the accelerated phase (i.e. single subject cohorts), cohorts will consist of 6-9 subjects. The algorithm for dose escalation is as follows:

[00369] Dose reduction for AEs that occur in Cycle 1 during Part 1 will constitute a DLT. Nevertheless, dose reductions are permitted in any cycle (including Cycle 1) in both Parts 1 and 2 and subjects will be allowed to continue on IP at the reduced dose.

Unless otherwise specified, up to 2 dose reductions will be allowed for AEs. Dose reduction guidelines for non-hematologic and hematologic toxicities are provided in Table 15 and **Error! Reference source not found.** 16, respectively.

[00370] Once the dose of Compound **1** has been reduced, it may be re-escalated at the discretion of the investigator but only after:

- the AE leading to the dose reduction has decreased in severity to ≤ Grade 1, and
- after consultation with the study's medical monitor.

[00371] Subjects should continue to adhere to the protocol-specified schedule of study visits/assessments during periods of Compound **1** interruption. Repeat PK/PD evaluations may be conducted following continuation/resumption of Compound **1** treatment at a lower dose.

[00372] Subjects who require interruption of dosing for more than 28 days beyond Cycle 1 for treatment related toxicity will permanently discontinue Compound **1** treatment. On rare occasion, such subjects may derive benefit from resumption of Compound **1** treatment. Investigators should notify the sponsor's medical monitor for any permanent discontinuation of study treatment as a result of TEAEs.

Table 15: Compound **1** Dose Reduction Guidelines – Non-Hematologic Adverse Events

Adverse Event:	**1st Occurrence:**	**2nd Occurrence:**	**3rd Occurrence:**
Intolerable Grade 2 or Grade 3/4 diarrhea despite maximal supportive care measures	Interrupt Compound **1** dosing until resolution to ≤ Grade 1; if resolution within 28 days, restart at 75% of original dose; if not, permanently discontinue	Interrupt Compound **1** dosing until resolution to ≤ Grade 1; if resolution within 28 days, restart at 50% of original dose; if not, permanently discontinue	Permanently discontinue
Intolerable Grade 2 or Grade 3/4 nausea/vomiting despite maximal supportive care measures	Interrupt Compound **1** dosing until resolution to ≤ Grade 1; if resolution within 28 days, restart at 75% of original dose; if not, permanently discontinue	Interrupt Compound **1** dosing until resolution to ≤ Grade 1; if resolution within 28 days, restart at 50% of original dose; if not, permanently discontinue	Permanently discontinue
Rash/desquamation ≥ Grade 3	Interrupt Compound **1** dosing; initiate supportive care measures per institutional standards or as outlined in Lynch (2007). If resolved to ≤ Grade 1 within 28 days, restart at 75% of original dose; if not, permanently discontinue	Interrupt Compound **1** dosing; if resolved to ≤ Grade 1 within 28 days (and in conjunction with supportive care measures), re-institute dosing at 50% of original dose; if not, permanently discontinue	Permanently discontinue
Ocular toxicity ≥ Grade 2 (ie, any changes in visual acuity or other ocular symptoms)	Interrupt Compound **1** dosing pending complete ophthalmologic examination including visual acuity testing, tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy and spectral domain optical coherence tomography; **if RVO is diagnosed**, permanently discontinue dosing and institute standard of care treatment. **If RVO is not present**, but there is evidence of central serous retinopathy on optical coherence tomography, resume Compound **1** dosing at 75% of original dose once visual symptoms improve	**If RVO is not present** on repeat ophthalmologic examination, but there is evidence of recurrent or persistent central serous retinopathy on optical coherence tomography, resume Compound **1** dosing at 50% of original dose once visual symptoms improve to ≤ Grade 1.	Permanently discontinue

Adverse Event:	1st Occurrence:	2nd Occurrence:	3rd Occurrence:
	to ≤ Grade 1. **If neither RVO nor central serous retinopathy is present AND visual symptoms have resolved to ≤ Grade 1within 28 days,** resume Compound **1** at the original dose (at the investigator's discretion)		
≥ Grade 3 QTc interval prolongation	Interrupt Compound **1** dosing; check ECGs twice per week; re-institute dosing at 75% of the original dose once QTc has returned to ≤ Grade 1 (if within 28 days)	Interrupt Compound **1** dosing; check ECGs twice per week; re-institute dosing at 50% of the original dose once QTc has returned to ≤ Grade 1 (if within 28 days)	Permanently discontinue

Table 16. Compound **1** Dose Reduction Guidelines – Hematologic Adverse Events

Adverse Event:	1st Occurrence:	2nd Occurrence:	3rd Occurrence:
≥ Grade 3 febrile neutropenia defined as an ANC 1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour	Interrupt Compound **1** dosing; institute supportive care measures including treatment with myeloid growth factor (eg, G-CSF) until subject is afebrile and ANC is ≥2.0 x 10^3/μL; may re-institute dosing (at investigator's discretion) at 75% of original dose upon resolution of fever and recovery of ANC (if within 28 days)	Permanently discontinue	NA
≥ Grade 3 neutropenia in the absence of fever	Interrupt Compound **1** dosing; check blood counts twice per week and institute supportive measures per institutional standards of care until ANC is ≥ 1.5 x 10^3/μL (≤ Grade 1); re-institute dosing at 75% of original dose upon recovery of ANC (if within 28 days)	Interrupt Compound **1** dosing; check blood counts twice per week and institute supportive measures per institutional standards of care until ANC is ≥ 1.5 x 10^3/μL (≤ Grade 1); re-institute dosing at 50% of original dose	Permanently discontinue
Grade 3 thrombocytopenia lasting longer than 7 days	Interrupt Compound **1** dosing; check blood counts twice per week until platelet count is ≥75 x 10^3/μL (≤ Grade 1); re-institute dosing at 75% of original dose upon recovery of platelet count (if within 28 days)	Interrupt Compound **1** dosing; check blood counts twice per week until platelet count is ≥ 75 x 10^3/μL (≤ Grade 1); re-institute dosing at 50% of original dose upon recovery of platelet count (if within 28 days)	Permanently discontinue
Grade 4 thrombocytopenia of any duration	Interrupt Compound **1** dosing; check blood counts twice per week until recovery of platelet count to ≥ 75 x 10^3/μL (≤ Grade	Interrupt Compound **1** dosing; check blood counts twice per week until recovery of platelet	Permanently discontinue

Adverse Event:	1st Occurrence:	2nd Occurrence:	3rd Occurrence:
	1); re-institute dosing at 75% of original dose upon recovery of platelet count (if within 28 days)	count to ≥75 x 10^3/μL (≤ Grade 1); re-institute dosing at 50% of original dose upon recovery of platelet count (if within 28 days)	
≥ Grade 2 hemolysis	Interrupt Compound **1** dosing; request Hematology consultation and initiate work-up for etiology including investigations listed in Table of Events. Do not re-institute treatment with Compound **1** until the outcome of hemolysis work-up is known and only after consultation with the Medical Monitor. Permanently discontinue Compound **1** if hemolytic episode persists for > 28 days.	Permanently discontinue	NA

Tumor Assessments

[00373] Subjects in Part 1 and Part 2 will undergo FDG-PET imaging at Screening and at between Day 16 to 21 in Cycle 1 (the latter only in subjects with FDG update by tumor at Screening), in order to assess the predictive value of early metabolic response to Compound **1** administration.

Phase 1 Trial Data Results

[00374] A total of 7 subjects have been treated with the phosphate salt of Compound **1** at doses varying from 20 to 160 mg/day administered on 21 consecutive days, followed by a 7 day treatment-free interval each 28 day cycle. These subjects were treated for a variety of relapsed/refractory solid tumors including pancreatic cancer, non-small cell lung cancer (NSCLC; n=2), colorectal cancer (CRC), jejunal adenocarcinoma, endometrial cancer and high grade neuroendocrine tumor. All subjects had tumors harboring KRAS mutations (including the subject with pancreatic cancer presumptively). Treatment durations have varied from approximately 4 to 9 weeks. To date, the toxicity profile has been shown to be acceptable with mostly Grade 1 and Grade 2 (mild or moderate) toxicities reported. No maximally tolerated dose has yet been identified.

Cohorts

[00375] Cohort #1 was a single subject cohort, treated with 20mg/day for pancreatic cancer (tumor not tested for RAS mutation, per protocol); duration of Rx: 2 cycles (off study for progressive disease after cycle 2).

[00376] Cohort #2 was a single subject cohort, treated with 40 mg/day for adenocarcinoma of the jejunum (KRAS G12C mutation); duration of Rx: 2 cycles (off study for progressive disease after cycle 2).

[00377] Cohort #3 was a single subject cohort, treated with 80 mg/day for high grade neuroendocrine tumor (KRAS G12 mutation); duration of Rx: 1 cycle (off study for progressive disease after cycle 1).

[00378] Cohort #4 represents the first four-subject cohort.

[00379] Cohert #4, Subject 1 was treated with 160 mg/day for NSCLC (KRAS G12C mutation); duration of Rx: 2.5 cycles (continuing on study at 50% dose, 80 mg/day – response to date: stable disease).

[00380] Cohort #4, Subject 2 was treated with 160 mg/day for NSCLC (KRAS G12C mutation); duration of Rx: 0.75 cycles (continuing on study; no response assessment to date).

[00381] Cohort #4, Subject 3 was treated with 160 mg/day for endometrial cancer (KRAS G12D mutation); duration of Rx: 0.75 cycles (continuing on study; no response assessment to date).

[00382] Cohort #4, Subject 4 was treated with 160 mg/day for CRC (KRAS G12V mutation); duration of Rx: 0.5 cycles (continuing on study; no response assessment to date).

Example 11

Additional Cell Viability Assays

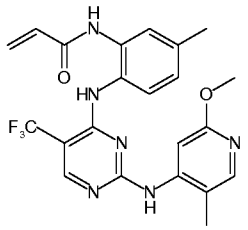
[00383] To assess the effects of Compound **1** (free base) on cell proliferation, Vemurafenib-resistant melanoma cell lines having either N-RAS or B-RAF mutations were seeded into 96 well plates 24-48 hours prior to the addition of eight-ten half-$\log_{10}$ doses of Compound **1** or dimethylsulfoxide (DMSO) as vehicle control. Cell number was assessed using either the IncuCyte live cell imaging system (Essen Instruments) or using a standard sulforhodamine B (*SRB*) assay (Monks, et al., J. Natl. Cancer Inst., 83:757-766, 1991; Skehan, et. al., J. Natl Cancer Inst., 82:1107-1112, 1990). In all experiments cells were plated so that the cell confluency at the end of incubation was less than 90% in control (DMSO treated) wells. The

GI50 was defined as the concentration of Compound **1** that induced a 50% decrease in cell number and was determined using GraphPad Prism (GraphPad Software). As shown in **Figure 17A**, Compound **1** inhibits growth of both NRAS and BRAF mutant vemurafenib-resistant melanoma cell lines with an average GI50 of 290 nM. **Figure 17B** Compound **1** induced cell death in all NRAS and BRAF mutant vemurafenib-resistant melanoma cell lines except in line 4 (in which the effect was cytostatic) at 10 μM.

CLAIMS

We claim:

1. A method of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutically acceptable composition comprising Compound **1**:



1,

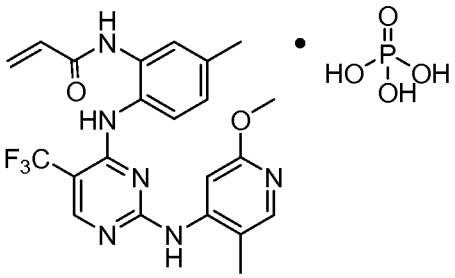
or a pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein the therapeutically effective amount is a total daily dose of about 100 mg to about 2000 mg.

3. The method according to claim 2, wherein the total daily dose is administered QD.

4. The method according to claim 2, wherein the total daily dose is administered under fasted conditions.

5. The method according to any of claims 1-4, wherein Compound **1**, or a pharmaceutically acceptable salt thereof, is administered as the phosphate salt of Compound **1**:



6. The method according to any of claims 1-5, wherein the one or more diseases or disorders associated with one or both of ERK1 and ERK2 is cancer.

7. The method according to claim 6, wherein the cancer is a MAPK-mediated cancer.

8. The method according to claim 6, wherein the cancer is a BRAF-mutated cancer.

9. The method according to claim 8, wherein the BRAF-mutated cancer is $BRAF^{V600}$-mutated cancer.

10. The method according to claim 9, wherein the $BRAF^{V600}$-mutated cancer is $BRAF^{V600E}$, $BRAF^{V600K}$, $BRAF^{V600R}$, or $BRAF^{V600D}$.

11. The method according to claim 6, wherein the cancer is a RAS-mutated cancer.

12. The method of claim 11, wherein the RAS-mutated cancer is a KRAS-mutated cancer.

13. The method according to claim 12, wherein the KRAS-mutated cancer is $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$, or $KRAS^{Q61L/H/R}$.

14. The method according to claim 11, wherein the RAS-mutated cancer is an NRAS-mutated cancer.

15. The method according to claim 14, wherein the NRAS-mutated cancer is $NRAS^{Q61R}$, $NRAS^{Q61K}$, $NRAS^{Q61L}$, or $NRAS^{Q61H}$.

16. The method according to claim 11, wherein the RAS-mutated cancer is an HRAS-mutated cancer.

17. The method according to claim 16, wherein the HRAS-mutated cancer is $HRAS^{G12V}$, $HRAS^{Q61R}$, or $HRAS^{G12S}$.

18. The method according to claim 6, wherein the cancer is selected from multiple myeloma, breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung, bone, colon, thyroid, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma (including uveal melanoma)sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colorectal carcinoma, large intestine, rectum, brain and central nervous system, and leukemia.

19. The method according to claim 6, wherein the cancer is selected from carcinoma, lymphoma, blastoma, sarcoma, and leukemia.

20. The method according to claim 6, wherein the cancer is selected from adenocarcinoma; adenoma; adrenocortical cancer; bladder cancer; bone cancer; brain cancer; breast cancer; cancer of the buccal cavity; cervical cancer; colon cancer; colorectal cancer; endometrial or uterine carcinoma; epidermoid carcinoma; esophogeal cancer; eye cancer; follicular carcinoma; gallbladder cancer; gastrointestinal cancer, such as, for example, gastrointestinal stromal tumor; cancer of the genitourinary tract; glioblastoma; hairy cell carcinoma; various types of head and neck cancer; hepatic carcinoma; hepatocellular cancer; Hodgkin's disease; keratoacanthoma; kidney cancer; large cell carcinoma; cancer of the large intestine; laryngeal cancer; liver cancer; lung cancer, such as, for example, adenocarcinoma of the lung, anaplastic carcinoma of the lung, papillary lung adenocarcinoma, small-cell lung cancer, squamous carcinoma of the lung, non-small cell lung cancer; melanoma and nonmelanoma skin cancer; lymphoid disorders; myeloproliferative disorders, such as, for example, polycythemia vera, essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), hypereosinophilic syndrome, systematic mast cell disease, atypical CML, or juvenile myelomonocytic leukemia; plasmacytoma; multiple myeloma; neuroblastoma; ovarian cancer; papillary carcinoma; pancreatic cancer; cancer of the

peritoneum; prostate cancer, including benign prostatic hyperplasia; rectal cancer; salivary gland carcinoma; sarcoma; seminoma; squamous cell cancer; small cell carcinoma; cancer of the small intestine; stomach cancer; testicular cancer; thyroid cancer; undifferentiated carcinoma; and vulval cancer.

21. The method according to claim 6, wherein the cancer is selected from melanoma, pancreatic cancer, thyroid cancer, colorectal cancer, lung cancer, breast cancer, ovarian cancer, and leukemia.

22. The method according to claim 6, wherein the cancer is selected from melanoma, colorectal cancer, or pancreatic cancer.

23. The method according to claim 6, wherein the cancer is a melanoma.

24. The method according to claim 23, wherein the melanoma is uveal melanoma.

25. The method according to claim 23, wherein the melanoma is locally advanced.

26. The method according to claim 23, wherein the melanoma is metastatic.

27. The method according to claim 23, wherein the melanoma is recurring.

28. The method according to claim 23, wherein the melanoma is a BRAF inhibitor-resistant melanoma.

29. The method according to claim 23, wherein the melanoma is $BRAF^{v600}$-mutated melanoma.

30. The method according to claim 23, wherein the melanoma is NRAS-mutated melanoma.

31. The method according to claim 6, wherein the cancer is colorectal cancer.

32. The method according to claim 31, wherein the colorectal cancer is locally advanced.

33. The method according to claim 31, wherein the colorectal cancer is metastatic.

34. The method according to claim 31, wherein the colorectal cancer is a $BRAF^{v600}$-mutated colorectal cancer.

35. The method according to claim 31, wherein the colorectal cancer is a RAS-mutated colorectal cancer.

36. The method according to claim 30, wherein the colorectal cancer is a KRAS-mutated colorectal cancer.

37. The method according to claim 6, wherein the cancer is pancreatic cancer.

38. The method according to claim 37, wherein the pancreatic is locally advanced.

39. The method according to claim 37, wherein the pancreatic is metastatic.

40. The method according to claim 37, wherein the pancreatic cancer is a pancreatic ductal adenocarcinoma (PDAC).

41. The method according to claim 37, wherein the pancreatic cancer is a RAS-mutated pancreatic cancer.

42. The method according to claim 37, wherein the pancreatic cancer is a KRAS-mutated pancreatic cancer.

43. The method according to claim 6, wherein the cancer is a papillary thyroid cancer.

44. The method according to claim 43, wherein the papillary thyroid cancer is locally advanced.

45. The method according to claim 43, wherein the papillary thyroid cancer is metastatic.

46. The method according to claim 43, wherein the papillary thyroid cancer is recurring.

47. The method according to claim 43, wherein the papillary thyroid cancer is a $BRAF^{v600}$-mutated papillary thyroid cancer.

48. The method according to claim 6, wherein the cancer is a lung cancer.

49. The method according to claim 48, wherein the lung cancer is locally advanced.

50. The method according to claim 48, wherein the lung cancer is metastatic.

51. The method according to claim 48, wherein the lung cancer is non-small cell lung cancer (NSCLC).

52. The method according to claim 48, wherein the lung cancer is a RAS-mutated lung cancer.

53. The method according to claim 48, wherein the lung cancer is a KRAS-mutated lung cancer.

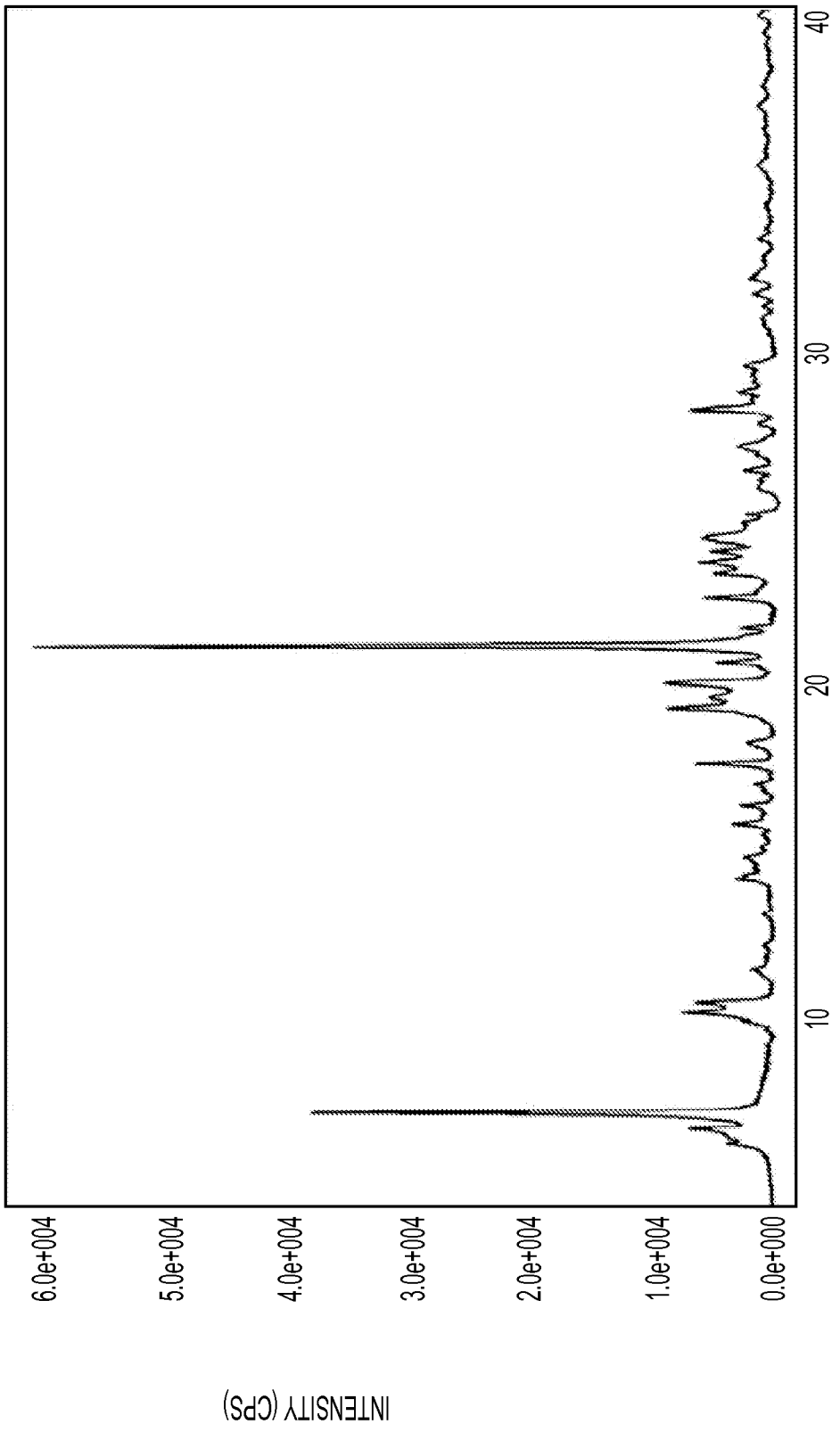

6.0e+004
5.0e+004
4.0e+004
3.0e+004
2.0e+004
1.0e+004
0.0e+000
INTENSITY (CPS)
10
20
30
40
2-THETA (DEG)

FIG. 1

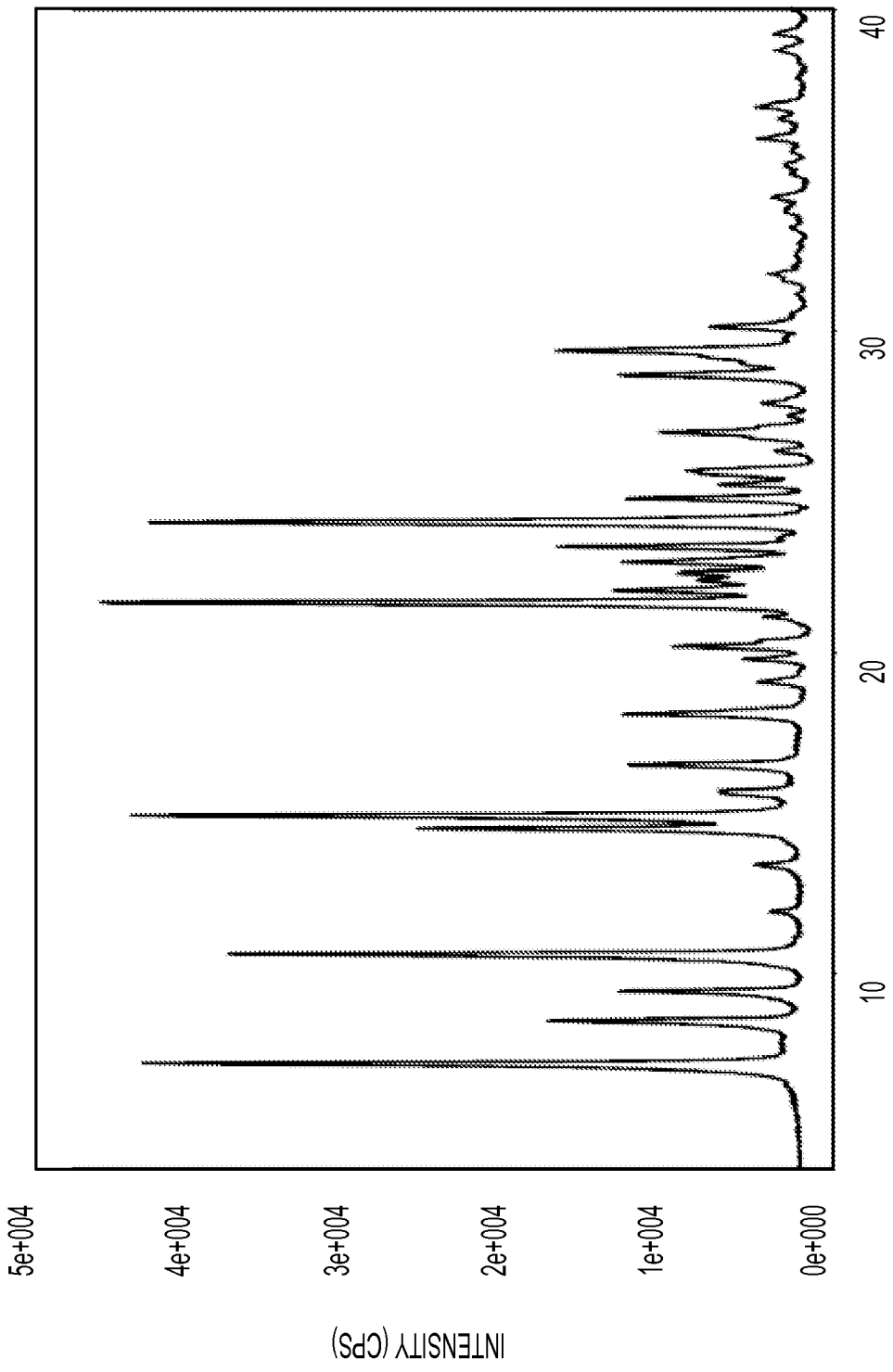

INTENSITY (CPS)
5e+004
4e+004
3e+004
2e+004
1e+004
0e+000
10
20
30
40
2-THETA (DEG)

FIG. 2

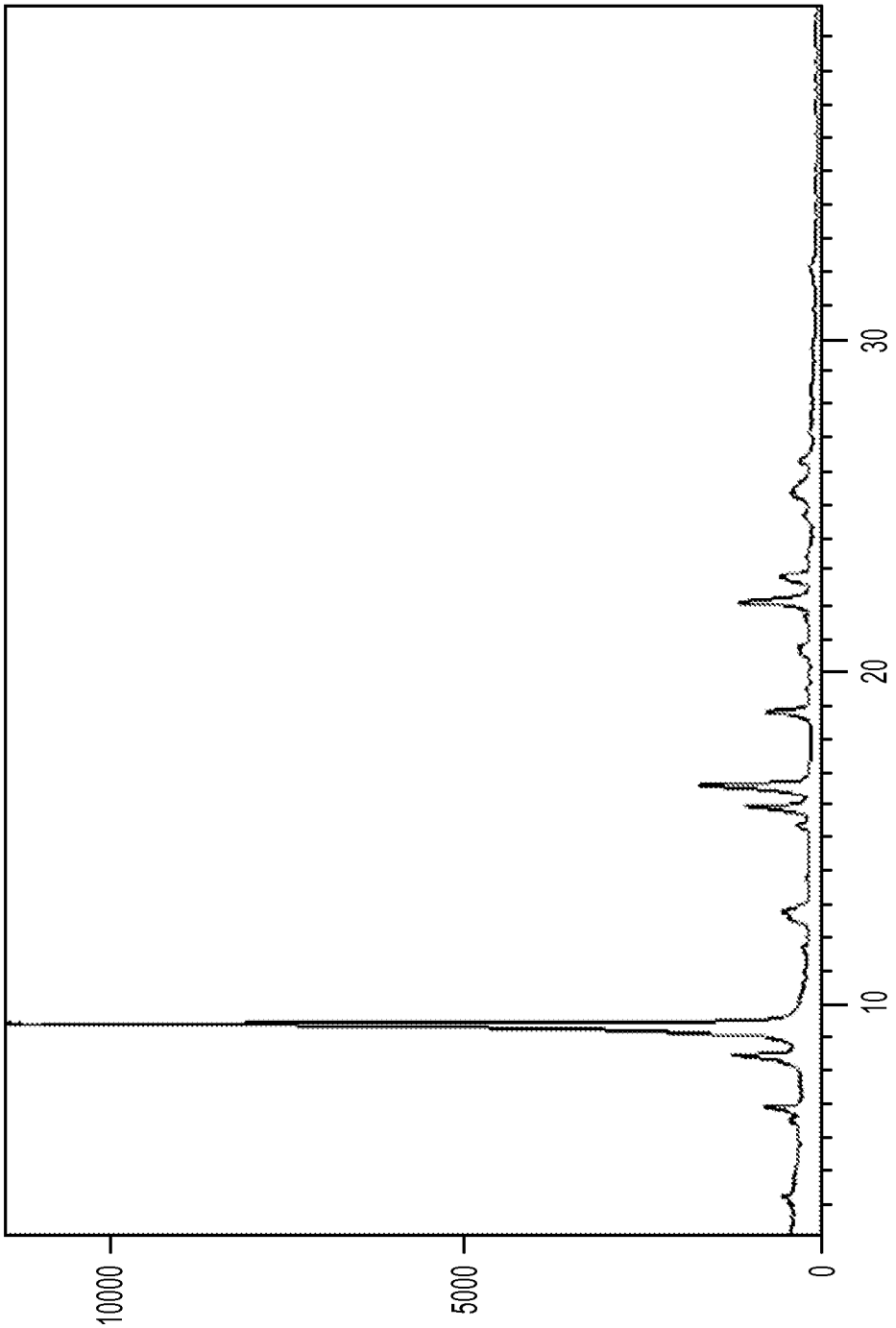


FIG. 3

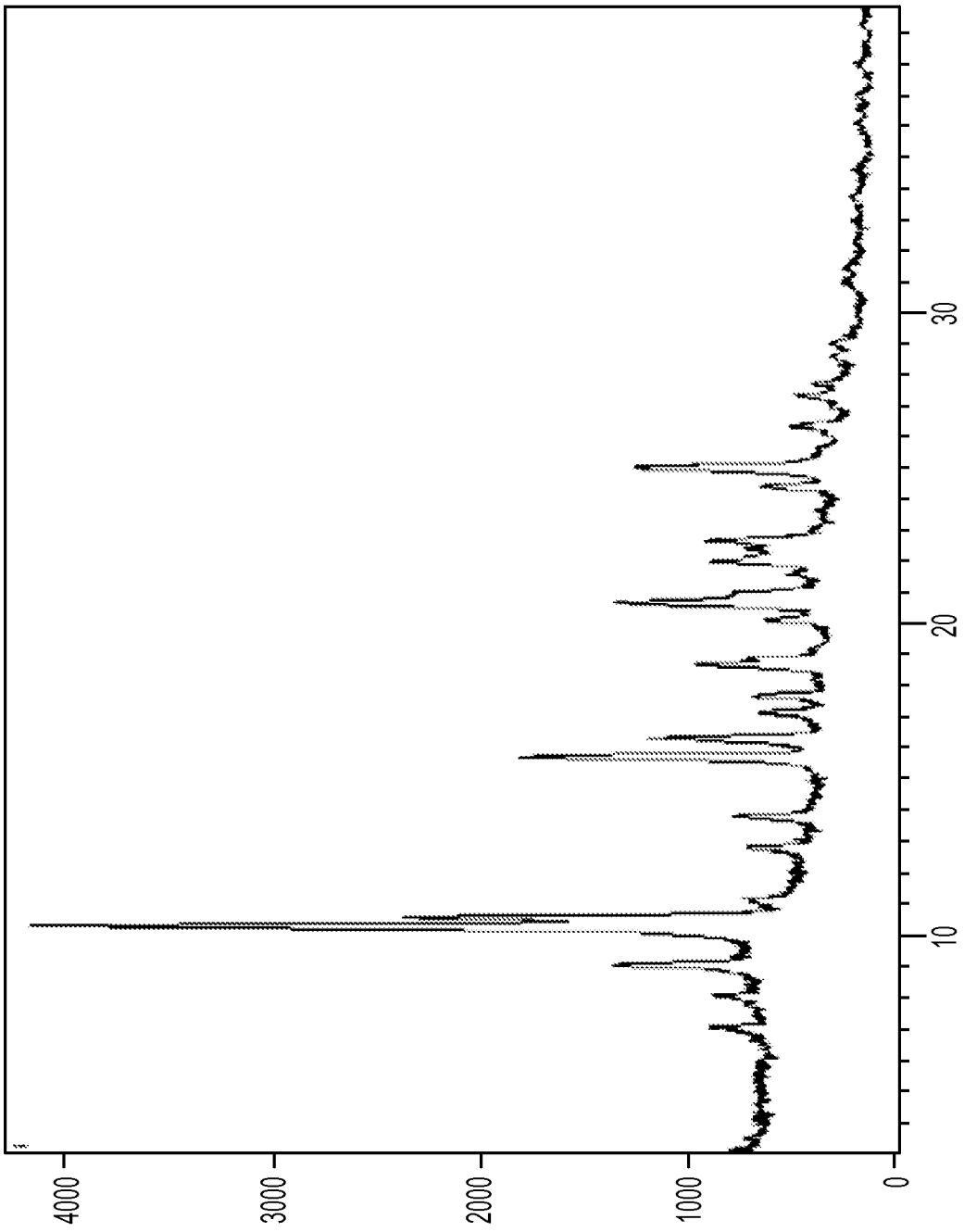


FIG. 4

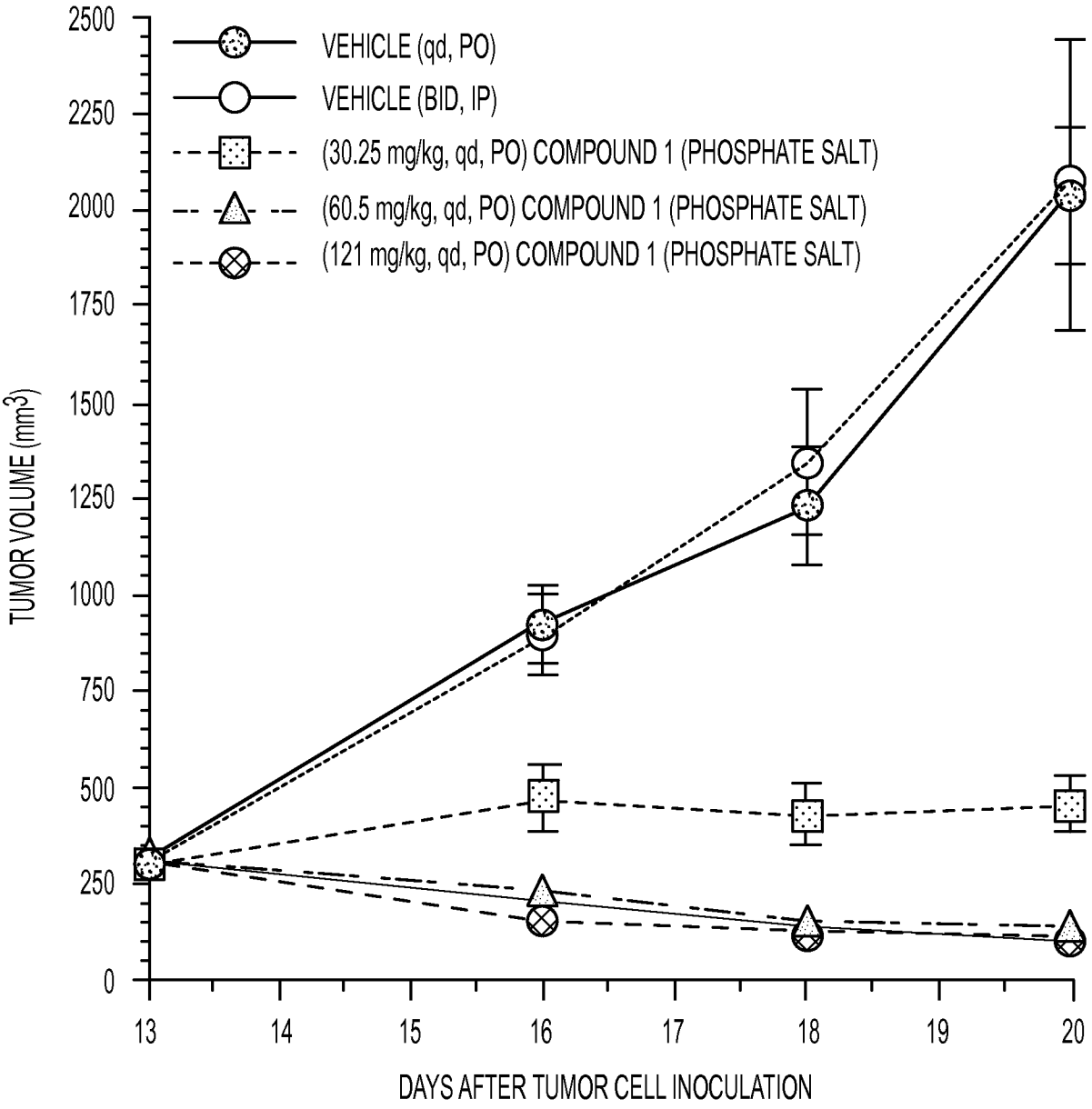

VEHICLE (qd, PO)
VEHICLE (BID, IP)
(30.25 mg/kg, qd, PO) COMPOUND 1 (PHOSPHATE SALT)
(60.5 mg/kg, qd, PO) COMPOUND 1 (PHOSPHATE SALT)
(121 mg/kg, qd, PO) COMPOUND 1 (PHOSPHATE SALT)
TUMOR VOLUME (mm3)
2500
2250
2000
1750
1500
1250
1000
750
500
250
0
13
14
15
16
17
18
19
20
DAYS AFTER TUMOR CELL INOCULATION

FIG. 5

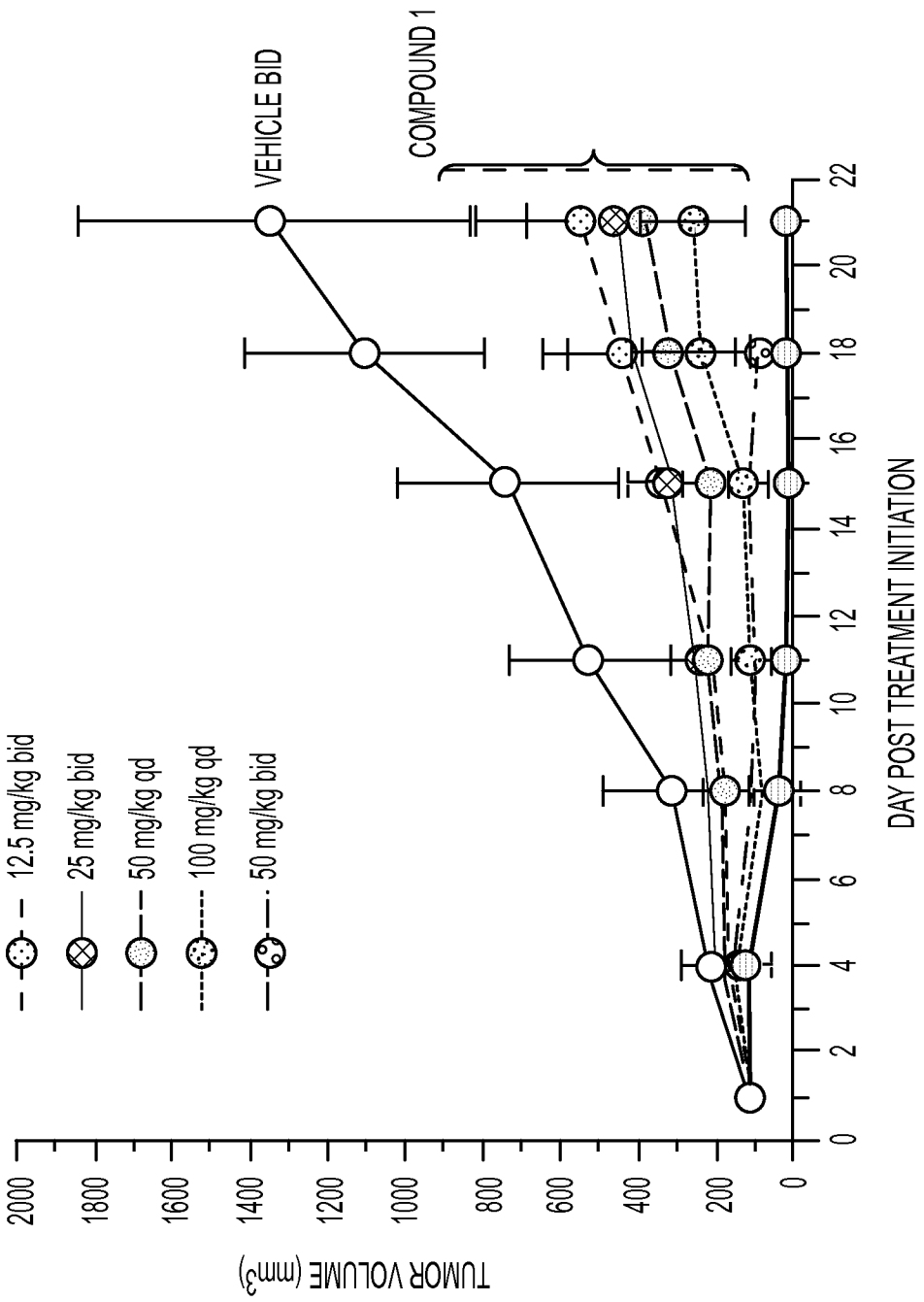

VEHICLE BID
COMPOUND 1
12.5 mg/kg bid
25 mg/kg bid
50 mg/kg qd
100 mg/kg qd
50 mg/kg bid
TUMOR VOLUME (mm3)
DAY POST TREATMENT INITIATION
0
200
400
600
800
1000
1200
1400
1600
1800
2000
0
2
4
6
8
10
12
14
16
18
20
22

FIG. 6

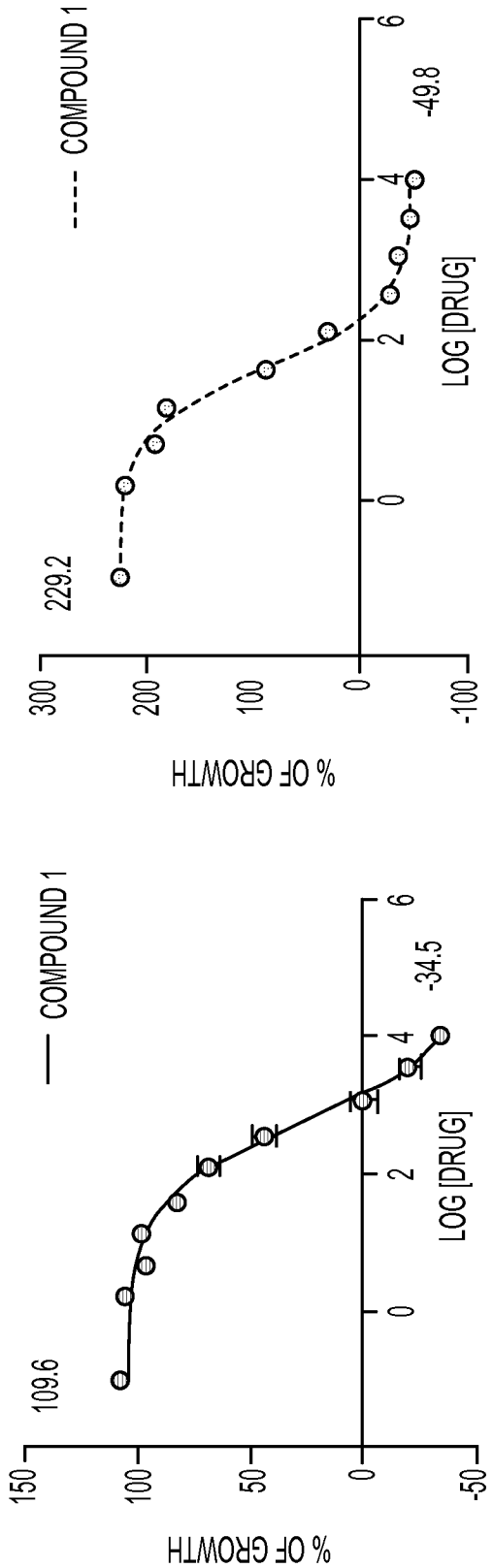


FIG. 7A

FIG. 7B

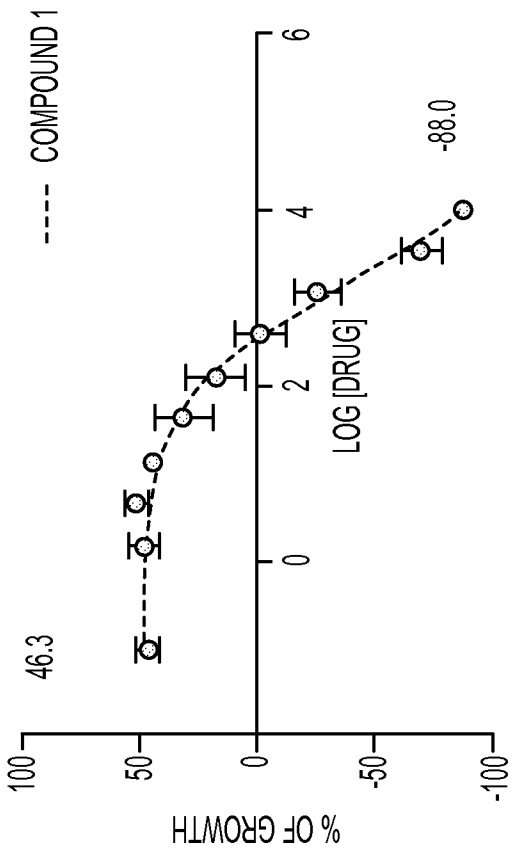


FIG. 7C

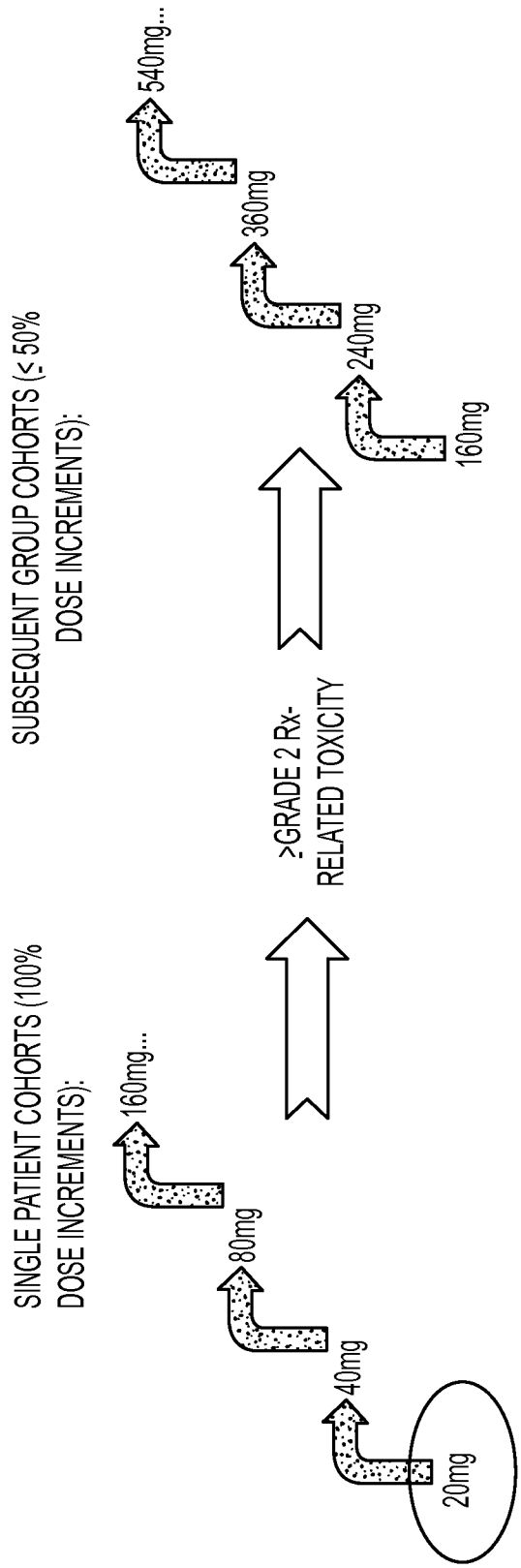

SINGLE PATIENT COHORTS (100% DOSE INCREMENTS):
20mg
40mg
80mg
160mg...
≥GRADE 2 Rx-RELATED TOXICITY
SUBSEQUENT GROUP COHORTS (< 50% DOSE INCREMENTS):
160mg
240mg
360mg
540mg...

FIG. 8

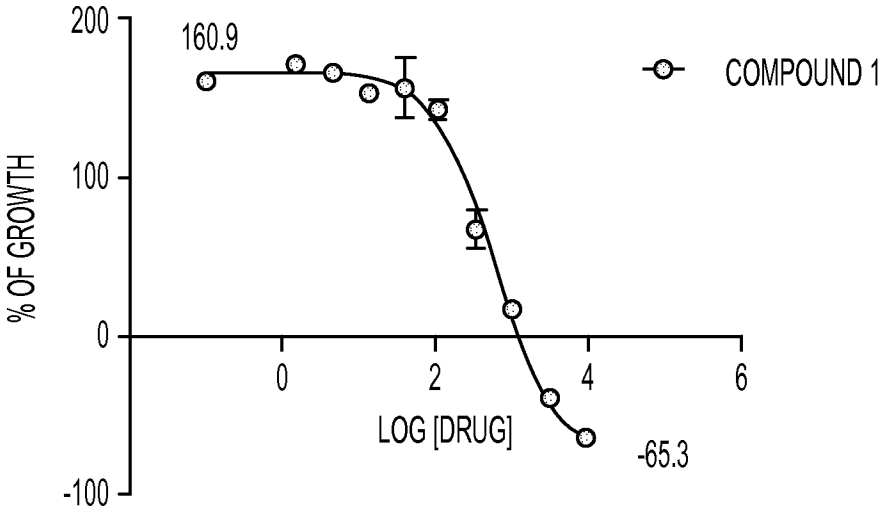

200
160.9
100
0
-100
% OF GROWTH
0
2
4
6
LOG [DRUG]
-65.3
COMPOUND 1

FIG. 9A

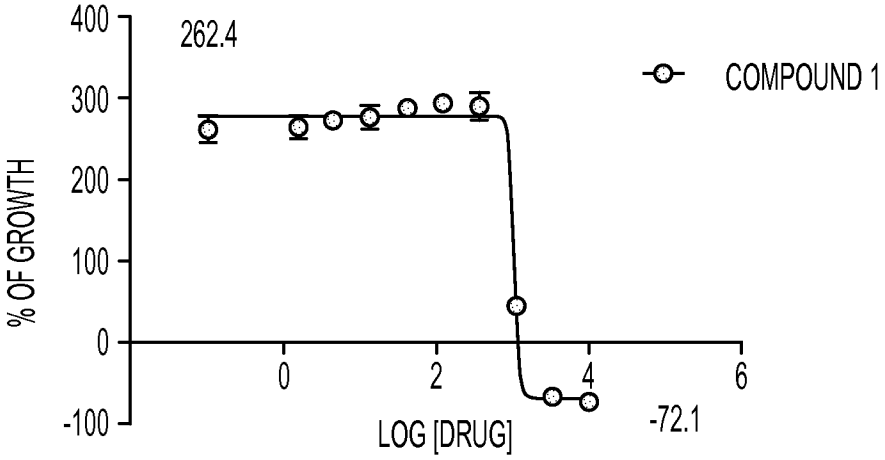

400
262.4
300
200
100
0
-100
% OF GROWTH
0
2
4
6
LOG [DRUG]
-72.1
COMPOUND 1

FIG. 9B

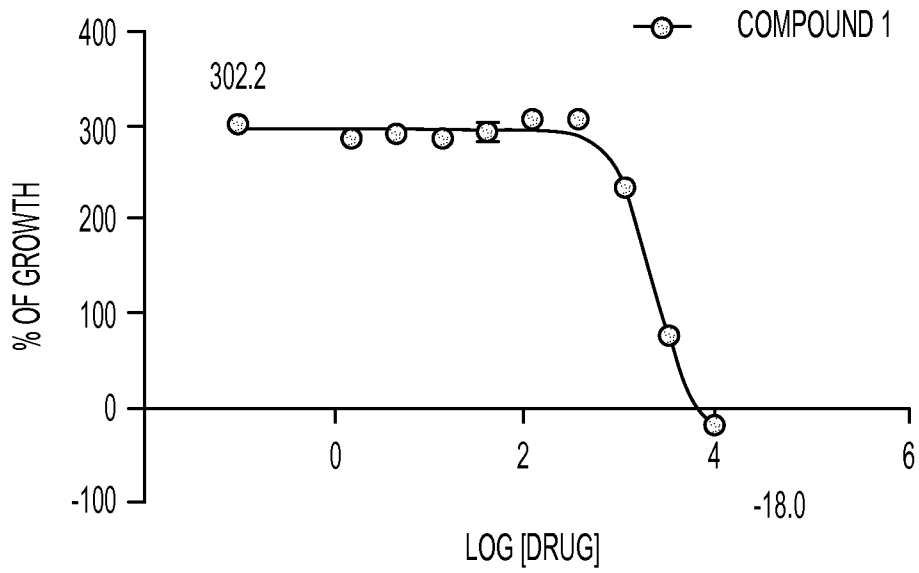

COMPOUND 1
302.2
400
300
200
100
0
-100
% OF GROWTH
0
2
4
6
-18.0
LOG [DRUG]

FIG. 10

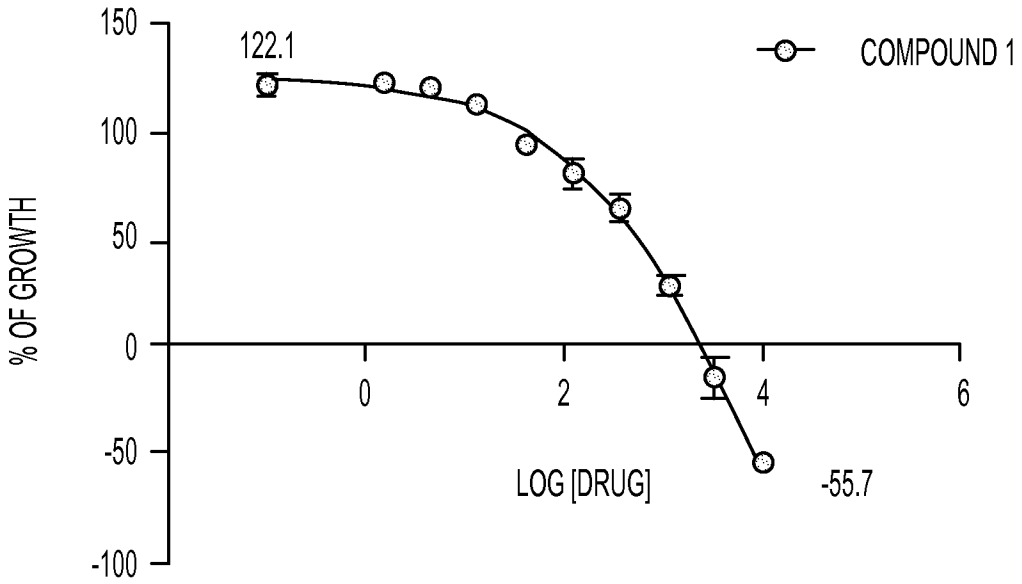


FIG. 11

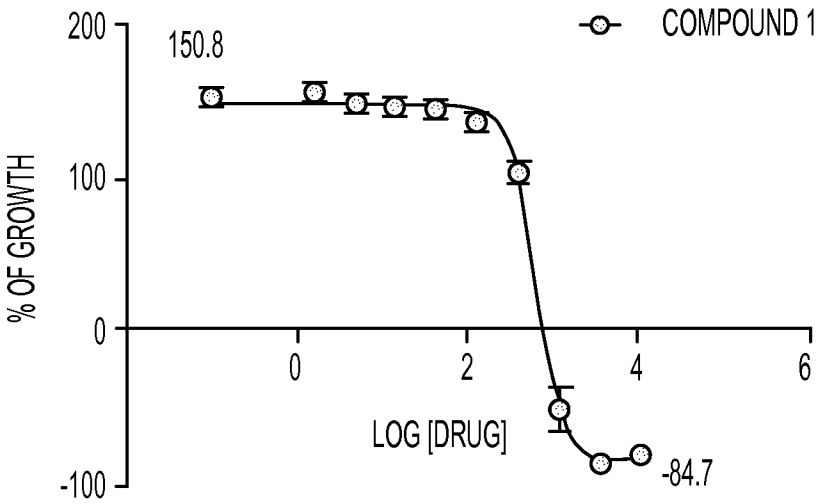


FIG. 12

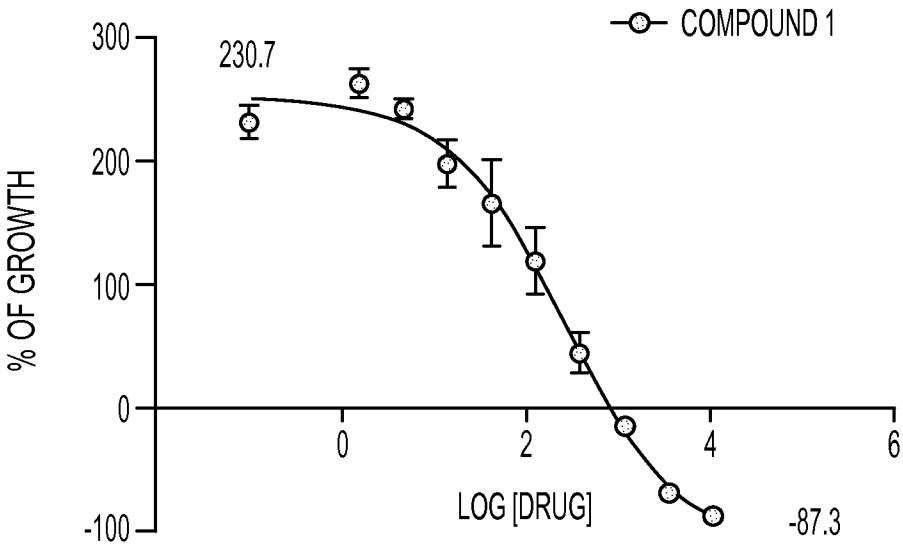


FIG. 13

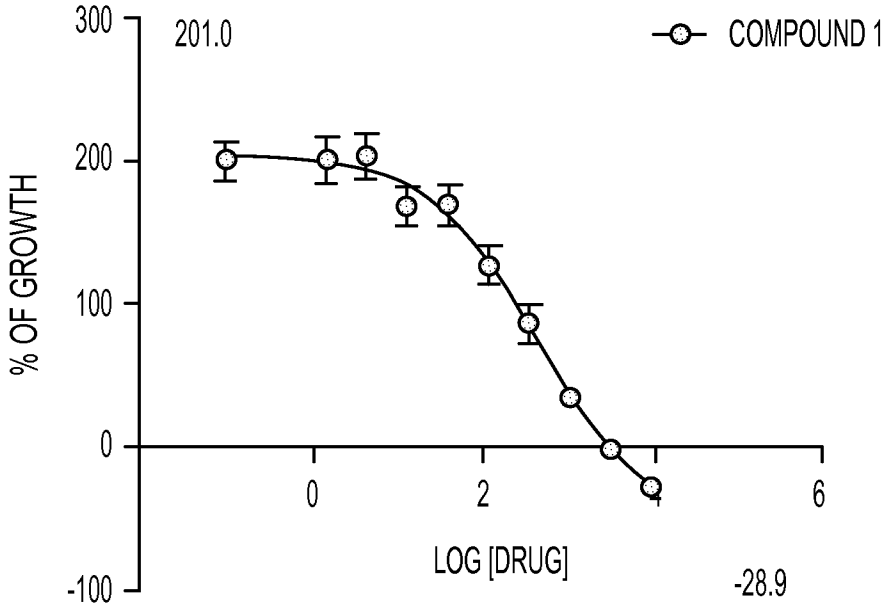


FIG. 14

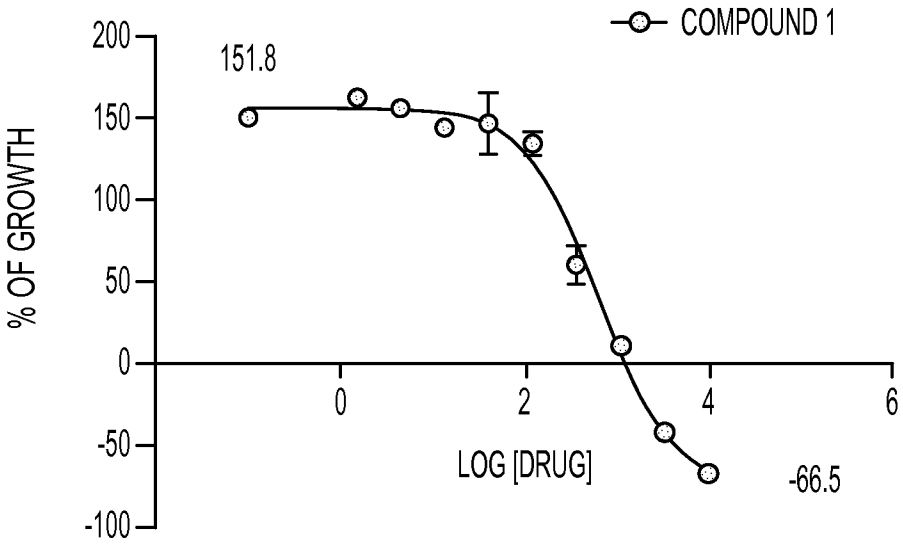


FIG. 15A

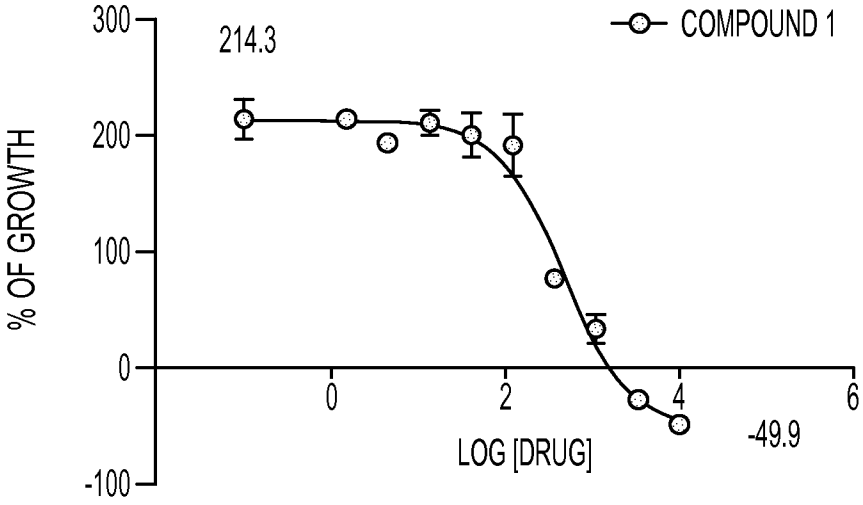


FIG. 15B

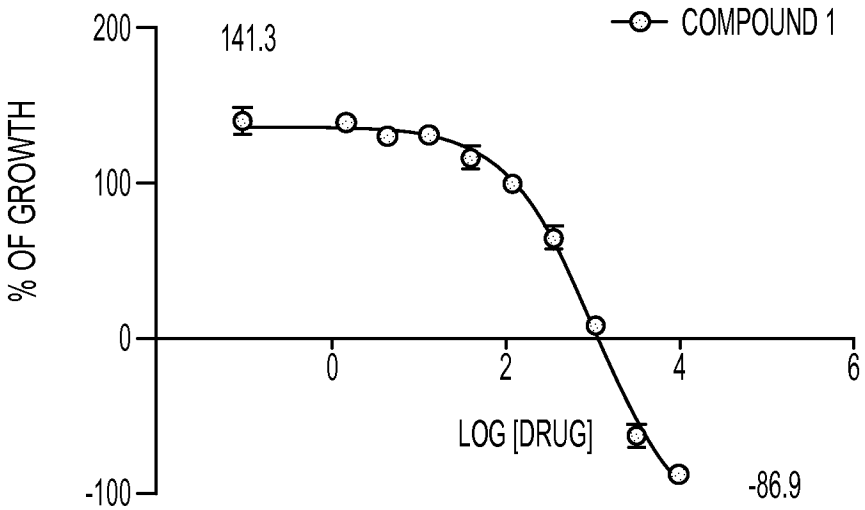


FIG. 16

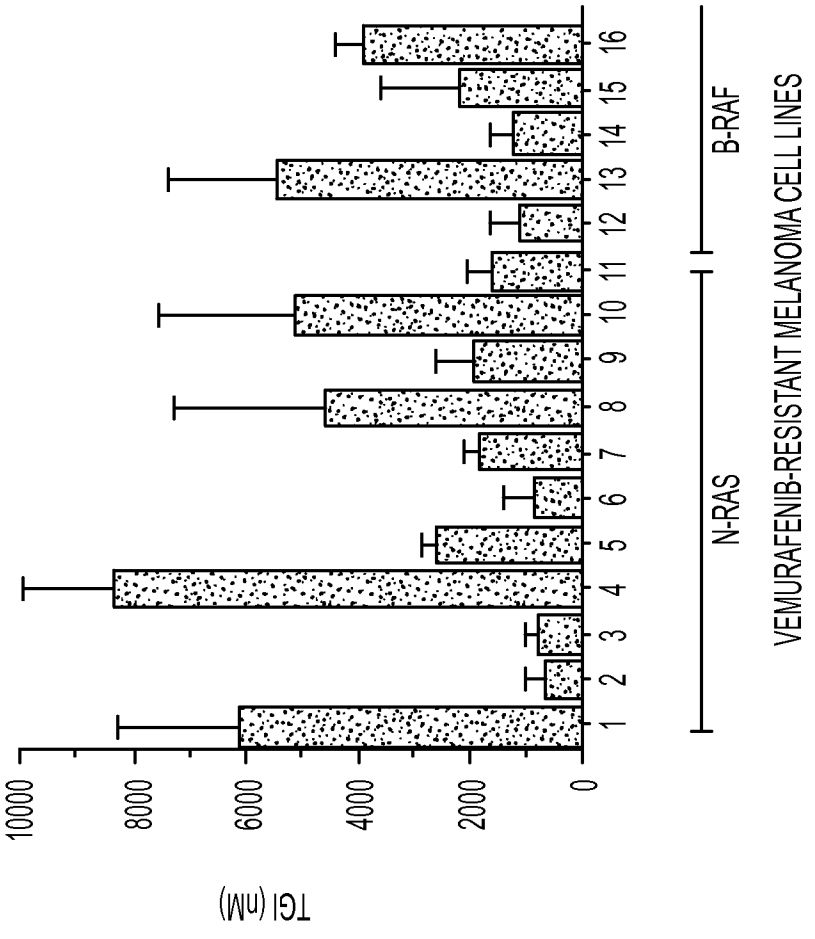


FIG. 17A

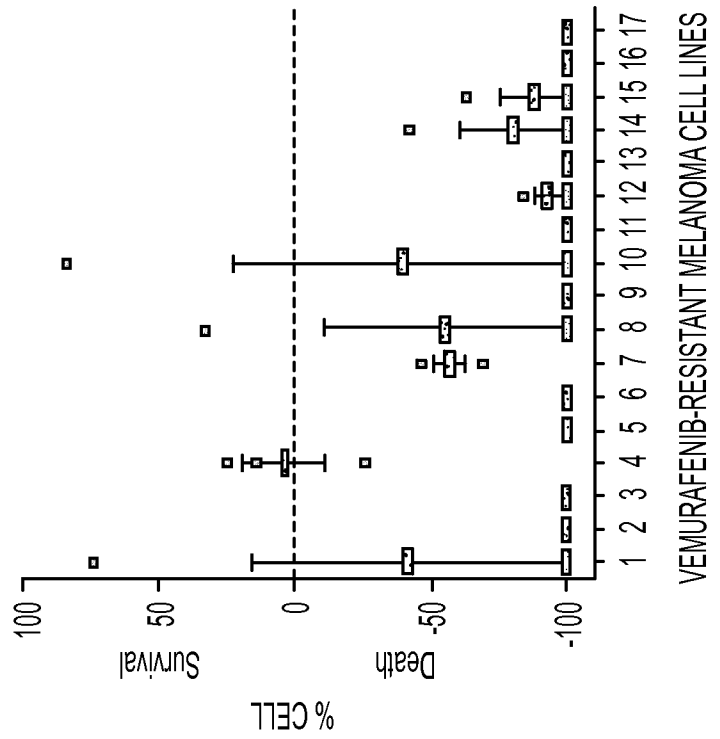


FIG. 17B

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/44890

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 43/90 (2015.01)
CPC - C07D 471/04; C07D 487/04; A61K 31/519
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A01N 43/90 (2015.01)
CPC: C07D 471/04; C07D 487/04; A61K 31/519

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/264.1, 514/269

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; Keyword limited: Inhibitors, ERK, kinases, irreversible inhibitor, acrylamide kinase, diaminopyridine, 2,4-diaminopyridine, administer

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2010/0029610 A1 (SINGH, J et al.) 4 February 2010 (04.02.2010), entire document, especially: para [0286]; para [0379]; Table 5, pg 83, Formula I-258.	1-5
A	WALTER, AO et al. "Discovery of a Mutant-Selective Covalent Inhibitor of EGFR that Overcomes T790M Mediated Resistance in NSCLC", Cancer Discovery. 2013. Vol. 3(12), pp 1405-1415, entire document, especially: Figure 1A, CO-1686.	1-5
A	ZHOU, W et al. "Novel mutant-selective EGFR kinase inhibitors against EGFR T790M", Nature. 2009. Vol. 462(7276), pp 1070-1074, entire document, especially: Figure 1A, WZ-4002.	1-5
A	LIU, Q et al. "Developing Irreversible Inhibitors of the Protein Kinase Cysteinome", Chemistry & Biology. 2013. Vol. 20, 146-159, entire document, especially: Figure 2.	1-5
A	WO 2012/170976 A2 (Hodous et al.) 13 December 2012 (13.12.2012) entire document	1-5

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 October 2015 (03.10.2015)	04 NOV 2015

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 15/44890

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-53
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.