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(54) Title: COMBINATIONS OF AN ERK INHIBITOR AND AN EGFR INHIBITOR AND RELATED METHODS

(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.

# COMBINATIONS OF AN ERK INHIBITOR AND AN EGFR INHIBITOR AND RELATED METHODS

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** The present application claims priority to U.S. provisional application number 62/037,070, filed August 13, 2014, the entirety of which is hereby incorporated herein 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 protein kinase.

## 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.).

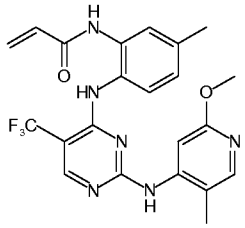
**[0005]** The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The MAPK or Raf-Mek-ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK occurs 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 colorectal, melanoma, breast, lung, and pancreatic tumors. High Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, activating mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased RAF, MEK, and ERK kinase activity. Tumors types with the most frequent mutations in BRAF include melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers.

**[0006]** Many diseases are associated with abnormal cellular responses, proliferation and evasion of programmed cell-death, 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]** In some 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 an inhibitor of one or both of ERK 1 and ERK2 in combination with an EGFR (epidermal growth factor receptor) inhibitor. In some aspects, the inhibitor of one or both of ERK1 and ERK2 is Compound **1** (*N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide*):



**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 WO 2014/124230 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]** Additional embodiments describing methods of utilizing a provided combination are described in detail herein, *infra*.

## DETAILED DESCRIPTION OF THE INVENTION

**[0010]** As described herein, in some 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 an inhibitor of one or both of ERK1 and ERK2 in combination with an EGFR inhibitor.

**[0011]** In some embodiments, an inhibitor of one or both of ERK1 and ERK2 is Compound **1**, or a pharmaceutically acceptable salt thereof, as described herein.

**[0012]** In some embodiments, an EGFR inhibitor is a compound as described herein, *infra*. In certain embodiments, an EGFR inhibitor is any EGFR inhibitor known to one of ordinary skill in the art. Such EGFR inhibitors are described herein, *infra*.

### *Definitions*

**[0013]** 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** in combination with an EGFR inhibitor.

**[0014]** 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 radiolabelled inhibitor, to show covalent modification of the enzyme, as well as other methods known to one of skill in the art.

**[0015]** 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.).

**[0016]** 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, condition, or disorder, to treat, diagnose, prevent, and/or delay the onset of the disease, condition, or disorder. 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, condition, or disorder 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, condition, or disorder. 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.

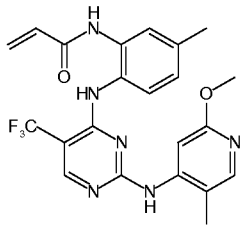
**[0017]** The terms "treat" or "treating," as used herein, refers to partially or completely alleviating, inhibiting, delaying onset of, preventing, ameliorating and/or relieving a disease or disorder, or one or more symptoms of the disease or disorder. As used herein, the terms "treatment," "treat," 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.

**[0018]** The expression "unit dosage form" as used herein refers to a physically discrete unit of therapeutic 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 and Pharmaceutically Acceptable Salts Thereof***

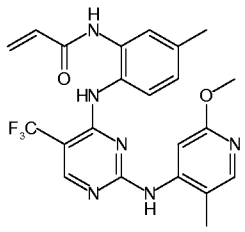
**[0019]** As described generally above, in some embodiments, the present invention provides methods of treating, stabilizing or lessening the severity or progression of one or more diseases or disorders associated with one or both of ERK1 and ERK2 comprising administering to a patient in need thereof an inhibitor of one or both of ERK 1 and ERK2 in combination with an EGFR inhibitor. In some aspects, the inhibitor of one or both of ERK1 and ERK2 is Compound **1** (*N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide*):



**1**

or a pharmaceutically acceptable salt thereof. For instance, in some embodiments, Compound **1** is in the form of a phosphate salt.

**[0020]** 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, comprising administering to a patient in need thereof a composition comprising Compound **1:**



**1**

or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor.

**[0021]** It is understood that although the methods described herein may refer to formulations, doses and dosing regimens/schedules of Compound **1**, such formulations, doses and/or dosing regimens/schedules are equally applicable to any pharmaceutically acceptable salt of Compound **1**. Accordingly, in some embodiments, a dose or dosing regimen for a pharmaceutically acceptable salt of Compound **1** is selected from any of the doses or dosing regimens for Compound **1** as described herein.

**[0022]** As described in the '230 publication, Compound **1** is a potent inhibitor of the kinase activities of ERK1 and ERK2. In some embodiments, Compound **1** inhibits one or both of ERK1 and ERK2 with an $IC_{50}$ of about 10 to about 20 nM. Compound **1** irreversibly inhibits ERK1 and ERK2 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.

**[0023]** 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 particularly sensitive to Compound **1**. Notably, of 27 BRAF-mutant cancer cell lines tested, 25 (93%) demonstrated sensitivity to Compound **1** inhibition (GI50 <1μM). In the same cancer cell panel screening, 28 of 37 (76%) KRAS-mutant cancer cell lines were sensitive to Compound **1**. Compound **1** also exhibits inhibitory activity against, for instance, 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 human patients. Such patients whose tumors demonstrated resistance to BRAF inhibitors are often cross-resistant to MEK inhibitors. Without wishing to being bound by any particular theory, it is believed that inhibitors of one or both of ERK1 and ERK2, or a mutant

thereof, such as Compound **1**, or pharmaceutically acceptable salts thereof, provide effective salvage therapy.

***EGFR Inhibitors***

**[0024]** The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands. Epidermal growth factor receptor is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), HER 3 (ErbB-3) and HER 4 (ErbB-4). Mutations affecting EGFR expression or activity could result in cancer.

**[0025]** As described generally above, provided methods comprise combination therapies utilizing an inhibitor of one or both of ERK1 and ERK2 and an EGFR inhibitor.

**[0026]** 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, or a mutant thereof, comprising administering to a patient in need thereof Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor.

**[0027]** In some embodiments, Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in combination with an EGFR inhibitor selected from 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-y-l]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-y-l)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-

oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methansulfonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-y-l]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-

buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetyl-amino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methansulfonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yl-oxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-

[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulfonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-y-loxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-

phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]--piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, poziotinib, AP26113, necitumumab, D-69491 (SU11464), PKI-166, ZD6474 (Zactima®), PKC-412, sunitinib (SU-11248), vatalanib (ZK222584; Ptk787), SU5614 (5-Chloro-3-[(3,5-dimethylpyrrol-2-yl)methylene]-2-indolinone), CEP-701, MLN-518, XL999, VX-322, maztuzumab (EMD72000), XL-647, zalutumumab, nimotuzumab, vandetanib, BIBX1382, HM61713, Cetuximab, Mab ICR-62, Cetuximab, Panitumumab (ABX-EGF, Vectibix®), Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-

1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

**[0028]** In some embodiments, the EGFR inhibitor is a mutant-selective EGFR inhibitor. In some such embodiments, the mutant-selective EGFR inhibitor is selected from HM61713, AZD9291, Rociletinib (CO-1686), WZ3146, WZ4002, WZ8040 and CNX-2006.

**[0029]** In some embodiments, Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in combination with an EGFR inhibitor selected from Cetuximab, Panitumumab, Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

**[0030]** In some embodiments, Compound **1**, or a pharmaceutically acceptable salt thereof, is administered in combination with Cetuximab or Erlotinib (Tarceva®; OSI-744).

**[0031]** In some embodiments, an EGFR inhibitor is a compound disclosed in the publications listed below in **Table A**:

**Table A**

US Patent Publication Nos. 20140128409 and 2010/0009958; WO 2013/125709, WO 2013/017073, WO 2012/167415, WO 2011/162515, WO 2010/076764, WO 2010/083720, WO 2010/096289, WO 2010/002845, WO 2008/033748, WO 2008/033749, WO 96/30347, WO 97/02266, WO 99/35146, WO 00/31048, WO 00/78735, WO 01/34574, WO 01/61816, WO 01/77104, WO02/18351, WO 02/18372, WO 02/18373, WO 02/18376, WO 02/50043, WO 03/082290, Cancer Research 2004, 64:11 (3958-3965), Am J Health-Syst Pharm 2000, 57(15), 2063-2076, Clinical Therapeutics 1999, 21(2), 309-318, WO 98/50433, and WO 95/20045, each of which is incorporated by reference in its entirety.

**Methods of Treatment**

**[0032]** 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.

**[0033]** The activity of Compound **1**, and pharmaceutically acceptable salts thereof, as an inhibitor of one or both of an ERK1 and ERK2 kinase, or a mutant thereof, may be assayed in vitro, in vivo or in a cell line. In vitro assays include assays that determine inhibition of downstream phosphorylation, changes in gene expression, subsequent functional markers and consequences, and/or kinase activity of one or both of activated ERK1 and ERK2 kinase, or a mutant thereof. Alternate in vitro assays quantitate the ability of the test compound to bind to one or both of ERK1 and ERK2. Test compound binding may be measured by radiolabeling the test compound prior to binding, isolating one or both of the compound / ERK1 complex and the compound / ERK2 complex, and determining the amount of radiolabel bound. Alternatively, test compound binding may be determined by running a competition experiment where test compounds are incubated with one or both of ERK1 and ERK2 kinase bound to known

radioligands. Test compound binding may be determined by competition with an ERK covalent probe that is amenable to further functionalization with a detection probe, such as, for example, a fluorophore, biotin conjugate, radiolabel, or any other probe that facilitates its quantification. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of one or both of ERK1 and ERK2, or a mutant thereof, are also set forth below and/or in the Examples of the '230 publication.

**[0034]** The term "measurably inhibit", as used herein means a measurable change in one or both of ERK1 and ERK2 protein kinase activity between a sample comprising a provided composition, and one or both of an ERK1 and ERK2 protein kinase and an equivalent sample comprising one or both of ERK1 and ERK2 protein kinase in the absence of a provided composition. Such measurements of protein kinase activity are known to one of ordinary skill in the art and include those methods set forth herein below and/or in the Examples of the '230 publication.

**[0035]** As described above, in some embodiments, Compound **1**, and pharmaceutically acceptable salts thereof, either alone or in combination with another agent such as an EGFR inhibitor, 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 referred to herein as an "ERK1- or ERK2-mediated disease, condition, or disorder."

**[0036]** 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, in combination with an EGFR inhibitor.

**[0037]** In some embodiments, the present invention relates to a method of inhibiting one or both of ERK1 and ERK2 protein kinase activity in a patient comprising the step of administering to said patient a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, or a composition comprising any of the foregoing.

**[0038]** In other embodiments, the present invention provides a method for treating a disease, condition, or disorder mediated by one or both of ERK1 and ERK2 kinase, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient Compound **1**, or pharmaceutically acceptable salts thereof, in combination with an EGFR inhibitor, or a pharmaceutically acceptable composition comprising any of the foregoing. Such disorders are described in detail herein.

**[0039]** 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, either alone or in combination with an EGFR inhibitor. In certain embodiments, the mechanism of drug resistance is through mutation of a target protein or reactivation of the MAPK pathway.

**[0040]** 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.

**[0041]** 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, delay or lessen the severity of their recurrence.

**[0042]** In some embodiments, the present invention provides a system for treating, stabilizing or lessening the severity of one or more diseases or disorders associated with one or more of ERK1 and ERK2, the system comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor. In some such embodiments, the present invention contemplates a system comprising any of the above-described EGFR inhibitors.

**[0043]** In some embodiments, an EGFR inhibitor is selected from 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]- quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-

chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methansulfonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-o- xo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-

[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetyl-amino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methansulfonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulfonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-

amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4 [(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-

methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, poziotinib, AP26113, necitumumab, D-69491 (SU11464), PKI-166, ZD6474 (Zactima®), PKC-412, sunitinib (SU-11248), vatalanib (ZK222584; Ptk787), SU5614 (5-Chloro-3-[(3,5-dimethylpyrrol-2-yl)methylene]-2-indolinone), CEP-701, MLN-518, XL999, VX-322, maztuzumab (EMD72000), XL-647, zalutumumab, nimotuzumab, vandetanib, BIBX1382, HM61713, Cetuximab, Mab ICR-62, Cetuximab, Panitumumab (ABX-EGF, Vectibix®), Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

**[0044]** In some embodiments, an EGFR inhibitor is selected from Cetuximab, Panitumumab, Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

**[0045]** In some embodiments, an EGFR inhibitor is Cetuximab or Erlotinib (Tarceva®; OSI-744).

**[0046]** General diseases, conditions, or disorders treated by Compound **1**, and pharmaceutically acceptable salts thereof, in combination with an EGFR inhibitor include cancer, an autoimmune disorder, a neurodegenerative or neurological disorder, liver disease, a cardiac disorder, schizophrenia, or a bone-related disorder.

**[0047]** In some embodiments, the present invention provides a method for treating an ERK1- or ERK2-mediated disease, condition, or disorder comprising administering to a patient in need thereof Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor.

**[0048]** 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, in combination with an EGFR inhibitor.

**[0049]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor. 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.

**[0050]** 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.

**[0051]** In certain embodiments, the cancer is a MEK inhibitor-resistant cancer.

**[0052]** In certain embodiments, the cancer is a MAPK pathway-mediated cancer.

**[0053]** 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 $BRAF^{V600D}$.

**[0054]** 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 $HRAS^{G12S}$.

**[0055]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, 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 (e.g., hepatocellular carcinoma (HCC)) and biliary passage carcinoma), kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colorectal carcinoma (CRC) , large intestine, rectum, brain and central nervous system, endometrial, multiple myeloma (MM), prostate, 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.

**[0056]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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. 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.

**[0057]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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.

**[0058]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from melanoma, colorectal cancer, lung cancer, or pancreatic.

**[0059]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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, 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.

**[0060]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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 certain embodiments, the colorectal cancer is a NRAS-mutated colorectal cancer.

**[0061]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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 pancreatic cancer is KRAS-mutated pancreatic 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.

**[0062]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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.

**[0063]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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 lung cancer is a KRAS-mutated lung cancer,

including, but not limited to, $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$,or $KRAS^{Q61L/H/R}$. In some embodiments, the lung cancer is relapsed. In some embodiments, the lung cancer is refractory.

**[0064]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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.

**[0065]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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.

**[0066]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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.

**[0067]** In some embodiments, the present invention relates to a method of treating a cancer, wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein 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 a RAS-mutated HCC. In certain embodiments, the HCC is KRAS-mutated HCC. In certain embodiments, the HCC is a KRAS-mutated HCC, 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.

**[0068]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from breast, colorectal, endometrial, hematological, leukemia (e.g., AML), liver, lung, melanoma, ovarian, pancreatic, prostate, or thyroid.

**[0069]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from breast, colorectal, endometrial, liver, lung, melanoma, ovarian, pancreatic, or thyroid.

**[0070]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from colorectal, lung, melanoma, or pancreatic.

**[0071]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition

comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from colorectal, melanoma, or pancreatic.

**[0072]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from colorectal, lung, or pancreatic.

**[0073]** In some embodiments, the present invention relates to a method of treating a cancer wherein the method comprises administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, wherein the cancer is selected from colorectal or pancreatic.

***Combination Dosing***

**[0074]** As described herein, provided methods comprise administration to a patient in need thereof Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor. As used herein, the term "in combination" with regard to administration of Compound **1** and an EGFR inhibitor means that each of Compound **1** and the EGFR inhibitor can be administered to the patient in any order (i.e., simultaneously or sequentially) or together in a single composition, formulation, or unit dosage form.

**[0075]** It will be appreciated that Compound **1**, or a pharmaceutically acceptable salt thereof, and the EGFR inhibitor can be administered on the same day or on different days and in any order as according to an appropriate dosing protocol.

***Dosing of Compound 1***

**[0076]** 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 comprising administering to a patient in need thereof an EGFR inhibitor in combination with a particular total daily dose of Compound **1**, wherein the total daily dose of Compound **1** is 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.

**[0077]** 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 comprising administering to a patient in need thereof an EGFR inhibitor in combination with a particular total daily dose of Compound **1**, wherein the total daily dose of Compound **1** is selected from about 100 mg, about 150 mg, about 200 mg, about 250 mg, about 300 mg, about 350 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.

**[0078]** 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 comprising administering to a patient in need thereof an EGFR inhibitor in combination with a particular total daily dose of Compound **1**, wherein the total daily dose of Compound **1** 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.

**[0079]** 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 comprising administering to a patient in need thereof an EGFR inhibitor in combination with a particular total daily dose of Compound **1**, wherein the total daily dose of Compound **1** 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.

**[0080]** 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.

**[0081]** 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.

***Dosing of an EGFR inhibitor***

**[0082]** In some embodiments, the present invention provides methods 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, comprising administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, wherein the EGFR inhibitor is administered in an amount of about 0.1 mg/day to about 1200 mg/day, about 1 mg/day to about 100 mg/day, about 10 mg/day to about 1200 mg/day, about 10 mg/day to about 100 mg/day, about 100 mg/day to about 1200 mg/day, about 400 mg/day to

about 1200 mg/day, about 600 mg/day to about 1200 mg/day, about 400 mg/day to about 800 mg/day or about 600 mg/day to about 800 mg/day. In some embodiments, methods disclosed herein comprise the administration of 0.1 mg/day, 0.5 mg/day, 1 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 30 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 60 mg/day, 75 mg/day, 100 mg/day, 125 mg/day, 150 mg/day, 200 mg/day, 250 mg/day, 300 mg/day, 400 mg/day, 600 mg/day or 800 mg/day of an EGFR inhibitor to a patient in need thereof.

**[0083]** In some embodiments, the present invention provides methods 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, comprising administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, wherein the total daily dose of an EGFR inhibitor is selected from about 5 mg, about 10 mg, about 20 mg, about 25 mg, about 30mg, 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 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 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.

*Unit Dosage Forms of Compound 1*

**[0084]** Compound **1**, or a pharmaceutically acceptable salt thereof, is preferably formulated in unit dosage form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of Compound **1**, or a pharmaceutically acceptable salt thereof, and compositions thereof, will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of Compound **1**; the duration of the treatment; drugs used in combination or coincidental with Compound **1**, and like factors well known in the medical arts. A person of ordinary skill will appreciate that the unit dosage forms described herein refer to an amount of Compound **1,** i.e. the free base form of the active pharmaceutical ingredient, which may be provided as the free base or as a pharmaceutically acceptable salt thereof.

**[0085]** In some embodiment, the present invention provides methods 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, comprising administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, wherein Compound **1** is administered in unit dosage formulations that comprise between about 5 mg to about 1000 mg of Compound **1**. In certain embodiments, a unit dosage 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**.

**[0086]** In some embodiments, the present invention provides methods 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, comprising administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, wherein Compound **1** is administered in unit dosage formulations that comprise about 5 mg, 30 mg, or 150 mg of Compound **1**. In certain embodiments, a capsule 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**.

**[0087]** In certain embodiments, Compound **1**, or a pharmaceutically acceptable salt thereof, is administered at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

***Unit Dosage Forms of an EGFR Inhibitor***

**[0088]** In some embodiment, the present invention provides methods 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, comprising administering to a patient in need thereof a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor, wherein the EGFR inhibitor is administered in unit dosage formulations that comprise between about 0.1 mg and about 2000 mg, about 1 mg and 200 mg, about 35 mg and about 1400 mg, about 125 mg and about 1000 mg, about 250 mg and about 1000 mg, or about 500 mg and about 1000 mg of an EGFR inhibitor.

**[0089]** In some embodiments, provided herein are unit dosage formulations comprising about 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 45 mg, 50 mg, 60 mg, 75 mg, 100 mg, 125 mg, 150 mg, 200 mg, 250 mg, 300 mg, 400 mg, 600 mg or 800 mg of an EGFR inhibitor.

**[0090]** In some embodiments, provided herein are unit dosage formulations that comprise 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg, 35 mg, 50 mg, 70 mg,

100 mg, 125 mg, 140 mg, 175 mg, 200 mg, 250 mg, 280 mg, 350 mg, 500 mg, 560 mg, 700 mg, 750 mg, 1000 mg or 1400 mg of an EGFR inhibitor. In a particular embodiment, provided herein are unit dosage formulations that comprise about 5 mg, about 15 mg, about 20 mg, about 30 mg, about 45 mg, and about 50 mg of an EGFR inhibitor.

*Administration of Compound 1*

**[0091]** Compound **1**, or a pharmaceutically acceptable salt thereof, and compositions thereof according to methods of the present invention, are administered using any amount and any route of administration effective for treating or lessening the severity of a disorder provided above. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like.

**[0092]** 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.

**[0093]** In some embodiments, a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is administered once daily ("QD").

**[0094]** 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", or two equivalent doses administered at two different times in one day.

**[0095]** 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.

**[0096]** 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.

**[0097]** In some embodiments, Compound **1** is administered to a patient under fasted conditions and the total daily dose is any of those contemplated above and herein.

**[0098]** In some embodiments, Compound **1** is administered to a patient under fed conditions and the total daily dose is any of those contemplated above and herein.

**[0099]** In some embodiments, Compound **1** is administered orally.

**[00100]** Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the disease or disorder being treated.

***Administration of an EGFR Inhibitor***

**[00101]** In some embodiments, provided methods comprise administering a pharmaceutically acceptable composition comprising an EGFR inhibitor one, two, three, or four times a day.

**[00102]** In some embodiments, a pharmaceutically acceptable composition comprising an EGFR inhibitor is administered once daily ("QD").

**[00103]** In some embodiments, a pharmaceutically acceptable composition comprising an EGFR inhibitor is administered twice daily. In some embodiments, twice daily administration refers to a compound or composition that is administered "BID", or two equivalent doses administered at two different times in one day.

**[00104]** In some embodiments, a pharmaceutically acceptable composition comprising an EGFR inhibitor is administered three times a day. In some embodiments, a pharmaceutically acceptable composition comprising an EGFR inhibitor is administered "TID", or three equivalent doses administered at three different times in one day.

**[00105]** In some embodiments, a pharmaceutically acceptable composition comprising an EGFR inhibitor is administered four times a day. In some embodiments, a pharmaceutically acceptable composition comprising an EGFR inhibitor is administered "QID", or four equivalent doses administered at four different times in one day.

**[00106]** In some embodiments, an EGFR inhibitor is administered to a patient under fasted conditions and the total daily dose is any of those contemplated above and herein.

**[00107]** In some embodiments, an EGFR inhibitor is administered to a patient under fed conditions and the total daily dose is any of those contemplated above and herein.

**[00108]** In some embodiments, an EGFR inhibitor is administered orally for reasons of convenience. In some embodiments, when administered orally, an EGFR inhibitor is administered with a meal and water. In another embodiment, the EGFR inhibitor is dispersed in water or juice (*e.g.*, apple juice or orange juice) and administered orally as a suspension. In some embodiments, when administered orally, an EGFR inhibitor is administered in a fasted state.

**[00109]** An EGFR inhibitor can also be administered intradermally, intramuscularly, intraperitoneally, percutaneously, intravenously, subcutaneously, intranasally, epidurally, sublingually, intracerebrally, intravaginally, transdermally, rectally, mucosally, by inhalation, or topically to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the health-care practitioner, and can depend in-part upon the site of the medical condition.

***Pharmaceutically Acceptable Compositions of Compound 1 and/or an EGFR inhibitor***

**[00110]** In some embodiments, the present invention provides a pharmaceutically acceptable composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof. In some embodiments, the present invention provides a pharmaceutically acceptable composition of an EGFR inhibitor. In some embodiments, a composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, is separate from a composition comprising an EGFR inhibitor. In some embodiments, Compound **1**, or a pharmaceutically acceptable salt thereof, and an EGFR inhibitor are present in the same composition.

**[00111]** Exemplary such pharmaceutically acceptable compositions are described further below and herein.

**[00112]** Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, the liquid dosage forms may contain inert diluents commonly used in the art

such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

**[00113]** Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

**[00114]** Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

**[00115]** In order to prolong the effect of Compound **1**, and/or an EGFR inhibitor, it is often desirable to slow absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of parenterally administered Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the

nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

**[00116]** Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

**[00117]** Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

**[00118]** Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

**[00119]** Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

**[00120]** Dosage forms for topical or transdermal administration of Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

**[00121]** According to one embodiment, the invention relates to a method of inhibiting protein kinase activity in a biological sample comprising the step of contacting said biological sample with Compound **1**, or a pharmaceutically acceptable salt thereof, and/or an EGFR inhibitor, or a composition comprising said compound.

**[00122]** According to another embodiment, the invention relates to a method of inhibiting one or both of ERK 1 and ERK2 kinase, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, or a composition comprising any of the foregoing. In certain embodiments, the invention relates to a method of irreversibly inhibiting one or both of ERK1 and ERK2 kinase, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, or a composition comprising any of the foregoing.

**[00123]** The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

**[00124]** Inhibition of one or both of ERK1 and ERK2, or a mutant thereof, activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

**[00125]** Another embodiment of the present invention relates to a method of inhibiting protein kinase activity in a patient comprising the step of administering to said patient Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, or a composition comprising any of the foregoing.

**[00126]** According to certain embodiments, the invention relates to a method of irreversibly inhibiting one or both of ERK1 and ERK2 kinase, or a mutant thereof, activity in a patient comprising the step of administering to said patient Compound **1**, or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor, or a composition comprising any of the foregoing.

**[00127]** In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 166 of ERK2. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1 and Cys 166 of ERK2.

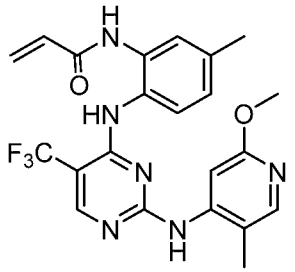
## EXEMPLIFICATION

### Example 1

### General Preparation of Compound 1

**[00128]** As depicted in the Examples below, in certain exemplary embodiments, Compound **1** is prepared according to the following general procedure.

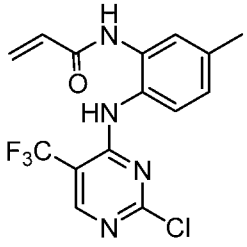
**[00129]** Proton Nuclear Magnetic Resonance ($^1$H NMR) spectra were obtained on a Bruker AVANCE-300 MHz NMR spectrometer. Deuterated DMSO was used as solvent.



Compound **1**

**[00130]** 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)**



Intermediate **1**

**[00131]** 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**

**[00132]** 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 (3.5076 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.

**[00133]** MS m/z 459.2 (ES+, M+H). $^1$HNMR (DMSO-$d_6$) 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).

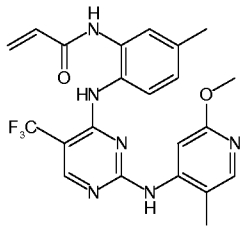
**Alternative Step 2: Pd-catalyzed coupling method:**

**[00134]** 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.

## 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 composition comprising Compound **1**:



**1**

or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor.

2. The method according to claim 1, wherein the EGFR inhibitor is selected from 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline- , 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morph- olin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-

ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-chinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methansulfonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-

(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperid- in-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-ylox- y)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetyl-amino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methan sulfonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yl-oxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulfonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-

phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4 [(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)- carbonyl]-piperidin-4-yloxy}-7-methoxy-

quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy- -quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, poziotinib, AP26113, necitumumab, D-69491 (SU11464), PKI-166, ZD6474 (Zactima®), PKC-412, sunitinib (SU-11248), vatalanib (ZK222584; Ptk787), SU5614 (5-Chloroo-3-[(3,5-dimethylpyrrol-2-yl)methylene]-2-indolinone), CEP-701, MLN-518, XL999, VX-322, maztuzumab (EMD72000), XL-647, zalutumumab, nimotuzumab, vandetanib, BIBX1382, HM61713, Cetuximab, Mab ICR-62, Cetuximab, Panitumumab (ABX-EGF; Vectibix®), Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

3. The method according to claim 2, wherein the EGFR inhibitor is selected from Cetuximab, Panitumumab, Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

4. The method according to claim 1, wherein the EGFR inhibitor is selected from those described in the publications listed in **Table A**.

5. The method according to claim 3, wherein the EGFR inhibitor is Cetuximab or Erlotinib (Tarceva®; OSI-744).

6. The method according to claim 1, wherein Compound **1** and the EGFR inhibitor are administered simultaneously.

7. The method according to claim 1, wherein Compound **1** and the EGFR inhibitor are administered sequentially.

8. The method according to any of claims 1-7, wherein the disease or disorder is a cancer.

9. The method according to claim 8, wherein the disease or disorder is a MAPK pathway-mediated cancer.

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

11. The method according to claim 10, wherein the BRAF-mutated cancer is a $BRAF^{V600}$ mutated cancer.

12. The method according to claim 11, wherein the $BRAF^{V600}$ mutated cancer is selected from $BRAF^{V600E}$, $BRAF^{V600K}$, $BRAF^{V600R}$, and $BRAF^{V600D}$.

13. The method according to claim 8, wherein the cancer is a RAS-mutated cancer.

14. The method according to claim 13, wherein the RAS-mutated cancer is a KRAS-mutated cancer.

15. The method according to claim 14, wherein the KRAS-mutated cancer is selected from $KRAS^{G12C/D/V}$, $KRAS^{G13C/D}$, or $KRAS^{Q61L/H/R}$

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

17. The method according to claim 16, wherein the NRAS-mutated cancer is selected from $NRAS^{Q61R}$, $NRAS^{Q61K}$, $NRAS^{Q61L}$, or $NRAS^{Q61H}$.

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

19. The method according to claim 18, wherein the HRAS-mutated cancer is selected from $HRAS^{G12V}$, $HRAS^{Q61R}$, and $HRAS^{G12S}$.

20. The method according to claim 8, wherein the cancer is selected from breast, colorectal, endometrial, hematological, leukemia (e.g., AML), liver, lung, melanoma, ovarian, pancreatic, prostate, or thyroid.

21. The method according to claim 20, wherein the cancer is selected from colorectal, lung, or pancreatic.

22. The method according to claim 21, wherein the cancer is selected from colorectal or pancreatic.

23. The method according to claim 22, wherein the cancer is colorectal cancer.

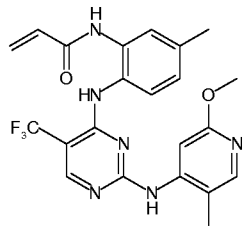
24. The method according to claim 23, wherein the colorectal cancer is BRAF-mutated colorectal cancer.

25. The method according to claim 23, wherein the colorectal cancer is KRAS-mutated colorectal cancer.

26. The method according to claim 22, wherein the cancer is pancreatic cancer.

27. The method according to claim 26, wherein the cancer is KRAS-mutated pancreatic cancer.

28. A system for treating, stabilizing or lessening the severity of one or more diseases or disorders associated with one or more of ERK1 and ERK2, the system comprising Compound **1:**



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or a pharmaceutically acceptable salt thereof, in combination with an EGFR inhibitor.

29. The system according to claim 28, wherein the EGFR inhibitor is selected from 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-

cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl- )-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-

fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vin- ylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-chinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methansulfonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulfonylamino]-cyclohexan-1-

yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulfonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetyl-amino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methan- sulfonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yl-oxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulfonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulfonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(tert-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbo- nyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperid- in-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-

phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethinyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2.2.1]-hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy- quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methansulfonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methansulfonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, poziotinib, AP26113,

necitumumab, D-69491 (SU11464), PKI-166, ZD6474 (Zactima®), PKC-412, sunitinib (SU-11248), vatalanib (ZK222584; Ptk787), SU5614 (5-Chloro-3-[(3,5-dimethylpyrrol-2-yl)methylene]-2-indolinone), CEP-701, MLN-518, XL999, VX-322, maztuzumab (EMD72000), XL-647, zalutumumab, nimotuzumab, vandetanib, BIBX1382, HM61713, Cetuximab, Mab ICR-62, Cetuximab, Panitumumab (ABX-EGF, Vectibix®), Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

34. The system according to claim 33, wherein the EGFR inhibitor is selected from Cetuximab, Panitumumab, Erlotinib (Tarceva®; OSI-744), Gefitinib (Iressa®; ZD1839), Lapatinib (GW572016), Afatinib (BIBW2992), Neratinib (HKI-272), AZD9291, Rociletinib (CO-1686, AVL-301), Canertinib (CI-1033), AG18, Butein, PD168393, CNX-2006, AC480 (BMS599626), PD153035, AG490 (TyrphostinB42), CP-724714, WZ3146, WZ4002,WZ8040, CUDC-101, Genistein, pelitinib (EKB-569), AEE788 (NVP-AEE788), AZD8931 (Sapitinib), Chrysophanic acid (chrysophanol), Dacomitinib (PF299804, PF299), AG-1478 (Tyrphostin AG-1478), ARRY334543 (Varlitinib), AST-1306 , TAK-285, Desmethyl Erlotinib (CP-473420,OSI-420), WHI-P154, Tyrphostin 9, and Icotinib.

35. The system according to claim 34, wherein the EGFR inhibitor is Cetuximab or Erlotinib (Tarceva®; OSI-744).

36. A composition comprising Compound **1**, or a pharmaceutically acceptable salt thereof, an EGFR inhibitor, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/44919

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 239/48, 401/12, 495/04 (2015.01)
CPC - C07D 239/48, 401/12, 495/04
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): C07D 239/48, 401/12, 495/04 (2015.01)
CPC: C07D 239/48, 401/12, 495/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); ProQuest; Scifinder; Google/Google Scholar; KEYWORDS: treat, cancer, ERK1, ERK2, EGFR, inhibitor, Erlotinib; Cetuximab, MAPK, BRAF, NRAS, KRAS, HRAS, pancreatic

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2005/0014753 A1 (DING, Q et al.) 20 January 2005; paragraphs [0006]-[0014], [0017], [0027], [0095], [0109] | 1-7, 8/1-7, 9/8/1-7, 10/8/1-7, 11/10/8/1-7, 12/11/10/8/1-7, 13/8/1-7, 14/13/8/1-7, 15/14/13/8/1-7, 16/14/13/8/1-7, 17/16/14/13/8/1-7, 18/16/14/13/8/1-7, 19/18/16/14/13/8/1-7, 20/8/1-7, 21/20/8/1-7, 22/21/20/8/1-7, 23/22/21/20/8/1-7, 24/23/22/21/20/8/1-7, 25/23/22/21/20/8/1-7, 26/22/21/20/8/1-7, 27/26/22/21/20/8/1-7, 28-32 |

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 30 September 2015 (30.09.2015) | 13 NOV 2015 |
| Name and mailing address of the ISA/<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Shane Thomas<br>PCT Helpdesk: 571-272-4300<br>PCT OSP: 571-272-7774 |

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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US15/44919

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | US 2013/0225620 A1 (ALIAGAS-MARTIN, I et al.) 29 August 2013; paragraphs [0068], [0095], [0127]-[0129] | 1-7, 8/1-7, 9/8/1-7, 10/8/1-7, 11/10/8/1-7, 12/11/10/8/1-7, 13/8/1-7, 14/13/8/1-7, 15/14/13/8/1-7, 16/14/13/8/1-7, 17/16/14/13/8/1-7, 18/16/14/13/8/1-7, 19/18/16/14/13/8/1-7, 20/8/1-7, 21/20/8/1-7, 22/21/20/8/1-7, 23/22/21/20/8/1-7, 24/23/22/21/20/8/1-7, 25/23/22/21/20/8/1-7, 26/22/21/20/8/1-7, 27/26/22/21/20/8/1-7, 28-32 |
| Y | WO 2013/109142 A1 (STICHTING HET NEDERLANDS KANKER INSTITUUT) 25 July 2013; page 23, lines 24-28; claims 1-5 | 9/8/1-7, 10/8/1-7, 11/10/8/1-7, 12/11/10/8/1-7 |
| Y | WO 2013/169858 A1 (THE BROAD INSTITUTE, INC.) 14 November 2013; page 3, lines 4-10; page 5, lines 1-5; page 9, lines 31-34; page 12, lines 1-5; page 13, lines 11-20; page 30, lines 30-34; page 31, line 28; page 73, lines 1-10 | 13/8/1-7, 14/13/8/1-7, 15/14/13/8/1-7, 16/14/13/8/1-7, 17/16/14/13/8/1-7, 18/16/14/13/8/1-7, 19/18/16/14/13/8/1-7, 24/23/22/21/20/8/1-7, 25/23/22/21/20/8/1-7, 26/22/21/20/8/1-7, 27/26/22/21/20/8/1-7 |
| Y | US 2014/0178339 A1 (UNIVERSITY OF MASSACHUSETTS) 26 June 2014; paragraphs [0005]-[0006], [0112], [0194] | 16/14/13/8/1-7, 17/16/14/13/8/1-7, 18/16/14/13/8/1-7, 19/18/16/14/13/8/1-7 |
| A | WO 2013/169401 A1 (ARIAD PHARMACEUTICALS, INC.) 14 November 2013; entire document | 1-7, 8/1-7, 9/8/1-7, 10/8/1-7, 11/10/8/1-7, 12/11/10/8/1-7, 13/8/1-7, 14/13/8/1-7, 15/14/13/8/1-7, 16/14/13/8/1-7, 17/16/14/13/8/1-7, 18/16/14/13/8/1-7, 19/18/16/14/13/8/1-7, 20/8/1-7, 21/20/8/1-7, 22/21/20/8/1-7, 23/22/21/20/8/1-7, 24/23/22/21/20/8/1-7, 25/23/22/21/20/8/1-7, 26/22/21/20/8/1-7, 27/26/22/21/20/8/1-7, 28-32 |