

ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, or heavy chain disease. In a further embodiment, the cancer is melanoma, non-small cell lung cancer, thyroid cancer, ovarian cancer, or colon cancer. The melanoma may be unresectable or metastatic melanoma.

[020] In another aspect, the present disclosure provides a method of treating a disorder mediated by EGFR kinase or EGFR mutants in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of the compounds described herein.

[021] In another aspect, the present disclosure provides a method of treating a disorder in a subject in need thereof, comprising: a) determining the presence or absence of a EGFR mutation in a biological sample isolated from the subject; and b) if a EGFR mutation is determined to be present in the subject, administering to the subject a therapeutically effective amount of a compound or pharmaceutically acceptable salt of any one of the compounds described herein.

[021a] In another aspect, the present disclosure provides the use of a compound or pharmaceutically acceptable salt as described herein, in the manufacture of a medicament for treating cancer in a subject.

[021b] In another aspect, the present disclosure provides the use of a compound or pharmaceutically acceptable salt as described herein, in the manufacture of a medicament for treating a disorder mediated by EGFR in a subject in need thereof.

[021c] In another aspect, the present disclosure provides the use of a compound or pharmaceutically acceptable salt as described herein, in the manufacture of a medicament for treating a disorder in a subject in need thereof, wherein the subject has a EGFR mutation or double mutation.

[022] Somatic activating mutations of the EGFR gene, increased gene copy number and certain clinical and pathological features have been found in certain types of cancer. The specific types of activating mutations may be Exon 19 deletion (del E746-A750) mutations, the single-point substitution mutation L858R in exon 21 and the point mutation T790M. A specific type of activating mutation may also be the double mutations of L858R and T790M. In some embodiments, determining the presence or absence of the EGFR mutation comprises

amplifying EGFR nucleic acid from a biological sample and sequencing the amplified nucleic acid. In some other embodiments, determining the presence or absence of the EGFR mutation comprises detecting a mutant EGFR polypeptide in a biological sample using a binding agent to a mutant EGFR polypeptide. The binding agent may be an antibody. The biological sample may be isolated from a tumor of the subject. In some embodiments, determining the presence or absence of the both L858R and T790M EGFR mutations comprises amplifying EGFR nucleic acid from the biological sample and sequencing the amplified nucleic acid, or detecting a double mutant EGFR polypeptide from the biological sample.

and N-(3-(2-((4-(4-(2-amino-2-oxoethyl)piperazin-1-yl)-3-fluorophenyl)amino)quinazolin-8-yl)phenyl)acrylamide.

76. A pharmaceutically acceptable salt of any of the compounds of claims 1-75.
77. The pharmaceutically acceptable salt of claim 76, wherein the salt is a chloride, carbonate, gluconate, benzoate, acetate, lactate, citrate, propionate, hydrogenphosphate, fumarate, succinate, or TRIS (hydroxymethyl-aminomethane), maleate, malonate, tartrate, oxalate, pamoate, or stearate salt.
78. The pharmaceutically acceptable salt of claim 77, wherein the salt is a chloride, fumarate, malonate, maleate, acetate, lactate, citrate, succinate, or tartrate salt.
79. The pharmaceutically acceptable salt of claim 78, wherein the salt is a chloride, fumarate, malonate, maleate, or tartrate salt.
80. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound or pharmaceutically acceptable salt of any one of claims 1 to 79.
81. A pharmaceutical composition of claim 80, wherein the composition is formulated in a form chosen from the group consisting of tablets, capsules, powders, liquids, suspensions, suppositories, and aerosols.
82. A packaged pharmaceutical composition comprising a pharmaceutical composition of claim 80 or 81 and instructions for using the composition to treat a subject suffering from cancer.
83. ~~A method of treating cancer in a subject which comprises administering to a subject in need thereof a therapeutically effective amount~~ Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 79, in the manufacture of a medicament for treating cancer in a subject.
84. ~~The method~~ use of claim ~~83~~83, wherein the cancer is colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, thyroid cancer, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung cancer, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma,

retinoblastoma, leukemia, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, or heavy chain disease.

85. The ~~method-use~~ of claim 8484, wherein the cancer is non-small cell lung cancer, breast cancer, colon cancer, thyroid cancer, or ovarian cancer.
86. ~~A method of treating a disorder mediated by EGFR in a subject in need thereof, comprising administering to the subject a therapeutically effective amount~~ Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 79, in the manufacture of a medicament for treating a disorder mediated by EGFR in a subject in need thereof.
87. ~~A method of treating a disorder in a subject in need thereof, comprising:~~
 - a) ~~determining the presence or absence of a EGFR mutation in a biological sample isolated from the subject; and~~
 - b) ~~if a EGFR mutation or double mutations are determined to be present in the subject, administering to the subject a therapeutically effective amount~~ Use of a compound or pharmaceutically acceptable salt of any one of claims 1 to 79, in the manufacture of a medicament for treating a disorder in a subject in need thereof, wherein the subject has a EGFR mutation or double mutation.
88. The ~~method-use~~ of claim 8787, wherein the EGFR mutation is in codon 790.
89. The ~~method-use~~ of claim 8787, wherein the EGFR mutation is del E746-A750, del E747-E749/A750P, del E747-S752/P753S, del E747-T751/Sins/A750P, del S752-I759, G719S, G719C, L861Q, L858R, T790M, or L858R/T790M.
90. The ~~method-use~~ of claim 8787, wherein determining the presence or absence of the EGFR mutation comprises amplifying EGFR nucleic acid from the biological sample and sequencing the amplified nucleic acid.
91. The ~~method-use~~ of claim 8787, wherein determining the presence or absence of the EGFR mutation comprises detecting a mutant EGFR polypeptide in the biological sample using a binding agent to a mutant EGFR polypeptide.
92. The ~~method-use~~ of claim 9194, wherein the binding agent is an antibody.
93. The ~~method-use~~ of claim 8787, wherein the biological sample is isolated from a tumor of the subject.
94. The ~~method-use~~ of any one of claims 8686-9393, wherein the disorder is cancer.
95. The ~~method-use~~ of claim 9494, wherein the cancer is colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, fibrosarcoma, myxosarcoma,

adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, non-small cell lung cancer, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemia, acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, or heavy chain disease.

- | 96. The ~~method-use~~ of claim 95, wherein the cancer is non-small cell lung cancer, colon cancer, thyroid cancer, or ovarian cancer.
- | 97. The ~~method-use~~ of any one of claims 83-96, further comprising administering an additional anti-cancer and/or cytotoxic agent.