METHOD OF TREATING CANCERS WITH ALKYNE SUBSTITUTED QUINAZOLINE DERIVATIVES

RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 63/244,540, filed September 15, 2021, U.S. Provisional Application No. 63/237,782, filed August 27, 2021, U.S. Provisional Application No. 63/218,717, filed July 6, 2021, U.S. Provisional Application No. 63/190,067, filed May 18, 2021, U.S. Provisional Application No. 63/166,045, filed March 25, 2021, and U.S. Provisional Application No. 63/108,645, filed November 2, 2020, the entire contents of each of which are incorporated herein by reference.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on November 2, 2021, is named "ASET-023_001WO_SeqList.txt" and is about 57,901 bytes in size.

BACKGROUND

[0003] Mutations affecting either the intracellular catalytic domain or extracellular ligand binding domain of an ErbB receptor can generate oncogenic activity (the ErbB protein family consists of 4 members including ErbB-1, also named epidermal growth factor receptor (EGFR) and Erb-2, also named HER2 in humans). ErbB inhibitors are a known treatment for a number of cancers. However, not every patient responds satisfactorily to this treatment. Thus, there is a long-felt need in the art for new therapies that are able to address the variable responsiveness of cancer patients to known therapies. The present disclosure provides compositions and methods for preventing or treating cancer in patients with these oncogenic mutations without the variable responsiveness observed when patients having these ErbB mutants are treated using the existing standard of care.

SUMMARY

[0004] In some aspects, the present disclosure provides a method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective

amount of Compound No. 1 or a pharmaceutically acceptable salt thereof.

[0005] In some aspects, the present disclosure provides Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof for treating or preventing cancer in a subject in need thereof.

[0006] In some aspects, the present disclosure provides use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

[0007] In some aspects, the present disclosure provides a pharmaceutical composition for treating or preventing cancer, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[0008] In some aspects, the present disclosure provides a pharmaceutical kit for treating or preventing cancer, comprising Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[0009] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting. In the case of conflict between the chemical structures and names of the compounds disclosed herein, the chemical structures will control.

[0010] Other features and advantages of the disclosure will be apparent from the following detailed description and claims.

BRIEF DESCRIPTIONS OF FIGURES

[0011] FIG. 1 is a graph showing the anti-proliferative IC_{50} values for Compound No. 1A in EGFR-WT, EGFR-Viii, EGFR-Vii, EGFR-Vvi, EGFR-A289V, and EGFR-G598V.

[0012] FIG. 2 is a graph showing the mean plasma and brain concentration of Compound No. 1A

(15 mg/kg), wherein the black bars represent plasma concentration and the gray bars represent brain concentration.

[0013] FIG. 3 is a graph showing the relationship between pEGFR (Tyr1068) and the administration of Compound No. 1A at 15 mg/kg.

[0014] FIG. 4 is a graph showing the normalized bioluminescence intensity (BLI) of GBM6 orthotopic brain patient derived xenograft tumors expressing EGFR-Viii when treated with Compound No. 1A at 50 mg/kg, 15 mg/kg, or 5 mg/kg.

[0015] FIG. 5 is a graph showing the anti-proliferative IC_{50} values for Compound No. 2B in EGFR-WT, EGFR-Viii, EGFR-Vii, EGFR-A289V, and EGFR-G598V.

[0016] FIG. 6 is a graph showing the mean plasma and brain concentration of Compound No. 2B (15 mg/kg), wherein the black bars represent plasma concentration and the gray bars represent brain concentration.

[0017] FIG. 7 is a graph showing the relationship between pEGFR (P1068) and the administration of Compound No. 2B at 50 mg/kg.

[0018] FIG. 8 is a graph showing the normalized bioluminescence intensity (BLI) of GBM6 orthotopic brain patient derived xenograft tumors expressing EGFR-Viii when treated with Compound No. 2B at 150 mg/kg, 50 mg/kg, or 15 mg/kg.

[0019] FIG. 9 is a graph showing the anti-proliferative IC_{50} values for osimertinib in EGFR-WT, EGFR-Viii, EGFR-Vii, EGFR-Vvi, and EGFR-A289V.

[0020] FIG. 10 is a graph showing mean plasma concentration of Compound No. 1A in mice when administered orally (PO) at 15 mg/kg and when administered via IV bolus at 1 mg/kg.

[0021] FIG. 11 is a graph showing mean plasma concentration of Compound No. 2B in mice when administered orally (PO) at 15 mg/kg and when administered via IV bolus at 1 mg/kg.

[0022] FIG. 12 is a graph showing the percent survival of mice expressing intracranial GBM6 patient derived tumors when treated orally with 50 mg/kg of Compound No. 1A.

[0023] FIG. 13 is a graph showing the percent survival of mice expressing intracranial GBM6 patient derived tumors when treated orally with 50 mg/kg of Compound No. 2B.

[0024] FIGS. 14A-14B are graphs showing in vitro IC_{50} values against a panel of an expanded number of EGFR mutations indicating a spectrum of Compound No. 2B.

[0025] FIG. 14C is a graph showing in vitro IC_{50} values for osimertinib against a panel of an expanded number of EGFR mutations.

[0026] FIG. 15 is a graph showing the mean concentration of Compound No. 2B in plasma and in brain in mouse when administered PO at 15 mg/kg.

[0027] FIG. 16 is a graph showing the mean concentration of Compound No. 2B in blood, brain, and in cerebrospinal fluid (CSF) in rat when administered PO at 30 mg/kg.

[0028] FIG. 17 is a graph showing the mean concentration of Compound No. 2B in blood and in cerebrospinal fluid (CSF) in dog when administered PO at 30 mg/kg.

[0029] FIG. 18 is a graph showing % phosphorylation by Compound No. 2B in Ba/F3 EGFRvIII after washout.

[0030] FIG. 19A is a graph showing the relationship between pEGFR (P1068) and the administration of Compound No. 1 in mice bearing BaF3 allograft tumors expressing EGFR-Viii when administered PO at 15 mg/kg.

[0031] FIG. 19B is a graph showing the relationship between pEGFR (P1068) and the administration of Compound No. 1A in mice bearing BaF3 allograft tumors expressing EGFR-Viii when administered PO at 50 mg/kg.

[0032] FIG. 19C is a graph showing the relationship between pEGFR (P1068) and the administration of Compound No. 2B in mice bearing Ba/F3 allograft tumors expressing EGFR-Viii when administered PO at 50 mg/kg.

[0033] FIG. 20 is a graph showing the median tumor volume (mm^3) in subcutaneous GBM46 PDX expressing EGFRvII mouse models when administered Compound No. 2B at 50 mg/kg.

[0034] FIG. 21 is a graph showing the % body weight (BW) change in a subcutaneous GBM46 PDX expressing EGFRvII mouse model when administered Compound No. 2B at 50 mg/kg.

[0035] FIG. 22 is a graph showing in vitro IC_{50} values against a panel of an expanded number of EGFR variants and mutants found in GBM.

[0036] FIG. 23 is a graph showing in vitro IC_{50} values against a panel of an expanded number of EGFR mutants of intrinsic resistance and acquired resistance in non-small cell lung cancer (NSCLC).

[0037] FIG. 24 is a graph showing the %inhibition of phosphorylation of the EGFR mutant protein in Ba/F3 cells expressing the EGFR Exon19del+C797S double mutation by Compound No. 2B at 34 nM and osimertinib at 1,000 nM, which shows that Compound No. 2B has >24 hours of inhibition of pEGFR Ex19/C797S.

[0038] FIG. 25 is a graph showing the median tumor volume (mm^3) in Ba/F3-EGFR Exon19del +

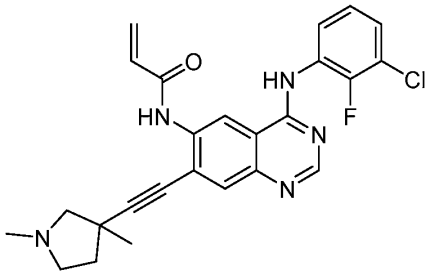
C797S mouse allograft models when administered a vehicle, osimertinib at 25 mg/kg, Compound No. 2B at 40 mg/kg, or Compound No. 2B at 120 mg/kg.

[0039] FIG. 26 is a graph showing the greatest percent change from baseline in mean tumor volume for vehicle control, osimertinib, C797S, EGFRvii, and C595F models. Vehicle control and osimertinib were tested in EGFR C797S models.

[0040] FIG. 27 is a graph depicting the schema of an exemplary study of Compound No. 2B.

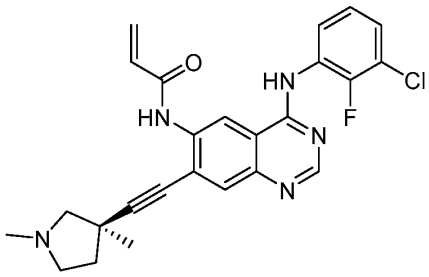
DETAILED DESCRIPTION

[0041] It is understood that the term "Compound No. 1," as used herein, refers to a compound having the following structure:



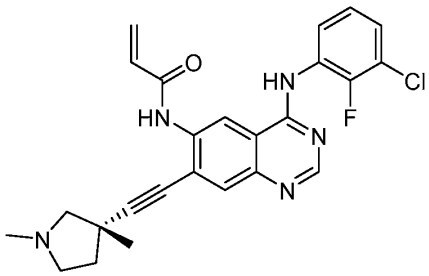
(Compound No. 1)

[0042] It is understood that the term "Compound No. 1A," as used herein, refers to a compound having the following structure:



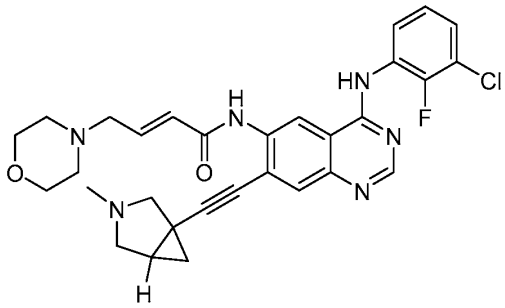
(Compound No. 1A)

[0043] It is understood that the term "Compound No. 1B," as used herein, refers to a compound having the following structure:



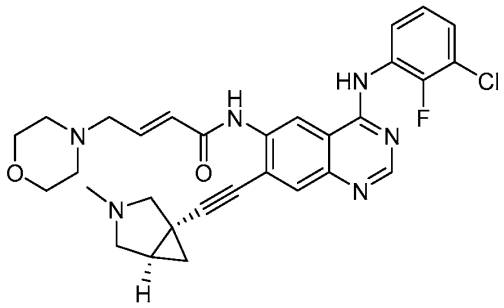
(Compound No. 1B)

[0044] It is understood that the term "Compound No. 2," as used herein, refers to a compound having the following structure:



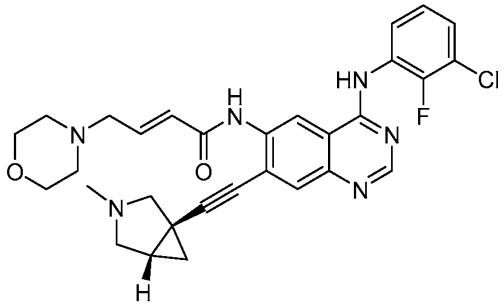
(Compound No. 2)

[0045] It is understood that the term "Compound No. 2A," as used herein, refers to a compound having the following structure:



(Compound No. 2A)

[0046] It is understood that the term "Compound No. 2B," as used herein, refers to a compound having the following structure:



(Compound No. 2B)

[0047] The present disclosure relates to compounds useful as inhibitors of receptor tyrosine kinases (RTK), in particular oncogenic mutants of ErbB-receptors. In some embodiments of the invention, oncogenic mutants of ErbB-receptors are also allosteric mutants of ErbB-receptors. In some embodiments, allosteric mutants may comprise or consist of an ErbB receptor variant having a mutation in a sequence outside of an ATP-binding site. In some embodiments, allosteric mutants may comprise or consist of an ErbB receptor variant having a mutation in a sequence within one or more of exon 18, exon 19, exon 20 or a C1-C2 extracellular dimerization interface.

[0048] Mutations affecting either the intracellular catalytic domain or extracellular ligand binding domain of an ErbB receptor can generate oncogenic activity (the ErbB protein family consists of 4 members including ErbB-1, also named epidermal growth factor receptor (EGFR) and Erb-2, also named HER2 in humans). Extracellular mutants of ErbB receptors in cancer, including EGFR-Viii (also EGFR-V3) and HER2-S310F, are constitutively activated in the absence of ligand, exhibit sustained signaling that is resistant to downregulation, and are both transforming and tumorigenic (Nishikawa, Ji et al. 1994, 2013, Francis, Zhang et al. 2014). Their expression is associated with metastasis and with poor long term overall survival.

[0049] In non-small cell lung cancer (NSCLC), which accounts for approximately 85% of lung cancer cases worldwide, NSCLC harboring EGFR mutations constitute 10-20% of all lung cancer cases in Europe and North America, and up to 50% of those in Asia. Uncommon EGFR mutations, of which EGFR-G719X, EGFR-S768I, EGFR-L861Q are amongst the most frequent, account for 10-20% of EGFR mutations in NSCLC. The common Exon19del and L858R mutations, that account for 80-90% of EGFR mutations in NSCLC, respond to current generation EGFR inhibitors, but resistance invariably emerges. For example, the exon19del combined with C797S mutation (EGFR-exon19del+C797S) and the EGFR-L858R+C797S mutations impart resistance

to first line treatment with current generation irreversible inhibitors (e.g., osimertinib or lazertinib).

[0050] In glioblastoma (also glioblastoma multiforme or GBM), EGFR-Viii is expressed by 20% of tumors (Sugawa, Ekstrand et al. 1990, Brennan, Verhaak et al. 2013). Expression of EGFR-Viii in GBM tends to be mutually exclusive with expression of other RTK oncogenes, which are co-expressed with EGFR variants in only 7% of GBM tumors (Furnari, Cloughesy et al. 2015). These data demonstrate how EGFR-Viii in GBM has a dominant and mutually exclusive expression pattern compared with other oncogenic drivers. EGFR-Viii is also expressed by approximately 30% of SCCHN tumors (Sok, Coppelli et al. 2006, Keller, Shroyer et al. 2010, Wheeler, Suzuki et al. 2010, Tinhofer, Klinghammer et al. 2011, Wheeler, Egloff et al. 2015) and 10% of squamous NSCLC (Ji, Zhao et al. 2006, Sasaki, Kawano et al. 2007), and is associated with resistance to current therapeutics including the anti-EGFR antibody cetuximab (Sok, Coppelli et al. 2006, Tinhofer, Klinghammer et al. 2011). Normal tissues do not express this oncogenic receptor variants.

[0051] RNA sequencing data has revealed that EGFR-Viii is just one of several aberrantly spliced variants of EGFR expressed in GBM tumors. Two others result in truncation of exons 12-13 (EGFR-Vvi) and 14-15 (EGFR-Vii). Like EGFR-Viii, EGFR-Vii is both transforming and tumorigenic. In addition to splice variants, GBM tumors also express a collection of EGFR point mutations including C620Y, A289V and G598V, which are transforming and tumorigenic.

[0052] HER2-S310F is the most common mutation of HER2 expressed in human tumors, expressed by approximately 0.5% of all tumors. HER2-S310F expression is mutually exclusive with expression of HER2 amplification. HER2-S310F is highly oncogenic, transforming BaF3 cells (a murine interleukin-3 (IL-3) dependent pro-B cell line) to IL-3 independence and promoting tumor growth in vivo.

[0053] Short insertions of within Exon 20 of EGFR and HER2 are expressed by lung adenocarcinoma tumors and other tumor groups. ErbB Exon 20 insertion mutants are expressed by 4-5% of lung adenocarcinoma tumors. Examples include HER2-YVMA, EGFR-SVD, and EGFR-NPH. These ErbB Exon 20 insertion mutants are highly oncogenic, transforming BaF3 cells to IL-3 independence and promoting tumor growth in vivo.

[0054] ErbB inhibitors are a known treatment for a number of cancers. However, not every patient is responsive satisfactorily to this treatment. Thus, there is a long-felt need in the art for new therapies that are able to address the variable responsiveness of cancer patients to known therapies.

The present invention is able to overcome some of these drawbacks of the standard of care, as it existed prior to the development of the compositions and methods disclosed herein.

Paradoxic ErbB Receptor Activation

[0055] Although the mechanisms described herein apply to any form of cancer in which these EGFR variants of the disclosure are expressed, the prevalence of these variants in glioblastoma (GBM) are provide by way of example. Other cancers expressing the EGFR variants of the disclosure include, but are not limited to, solid cancers, epithelial cancers and/or cancers of epithelial origin, bladder cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma (GBM), head and neck cancer, lung cancer, and non-small cell lung cancer (NSCLC).

[0056] In GBM tumors EGFR is frequently the target of genomic mutations and alternative splicing events that result in alteration of the extracellular dimer interface. Many tumors express more than one aberrant isoform. The disclosure provides the mechanism of activation for the most commonly occurring variants, EGFR-Viii, EGFR-Vii, EGFR-Vvi, EGFR-G598V and EGFR-A289V. Although each isoform/point mutant is the result of a distinct ectodomain alteration, all are activated by a common mechanism involving covalent ligand-independent dimerization.

[0057] AMG-595 (Amgen) is an EGFR-Viii isoform selective antibody that has no activity against wild type EGFR or other splice-activated variants. Rindopepimut (Celldex) is a vaccine the produces an immunological response selectively against tumor cells expressing EGFR-Viii but not wild type EGFR or other splice-activated isoforms. Other EGFR isoforms expressed in GBM tumors (EGFR-Vii and EGFR-Vvi) are constitutively active covalent receptors and their expression may limit the breadth and duration of treatment benefit for an ErbB inhibitor that is selective only for EGFR-Viii. Therefore, it may be useful to exclude patients whose tumors express EGFR-Vii, EGFR-Vvi, or EGFR ectodomain point mutants from treatment with an EGFR-Viii selective therapy.

[0058] The heterogenenic expression pattern for multiple ectodomain variants of ErbB receptors in tumors indicates that a small molecule inhibitor that inhibits all variants is preferred. The family of covalently-activated EGFR isoforms responds very differently to small molecule ErbB inhibitors compared to EGFR catalytic domain mutations observed in NSCLC. Importantly, Type I inhibitors, including erlotinib, all induce the formation of covalent EGFR dimers and increase

EGFR phosphorylation at sub-saturating concentrations, an activity that is further enhanced when ErbB inhibitor is washed away. This manifests in paradoxical activation of proliferation at sub-saturating concentrations.

[0059] The discovery of paradoxical activation of proliferation at sub-saturating concentrations of Type I ErbB inhibitors is further demonstrated for a series of extracellular variants of HER2, prevalent in a number of cancers including breast and bladder. All variants existed as covalently activated receptors, and levels of covalent dimers increased following treatment with Type I inhibitors including sapitinib and afatinib. As with covalently-activated EGFR variants, sub-saturating doses of Type I inhibitors paradoxically increased phosphorylation of HER2 variants, increasing the proliferation of cells expressing them.

[0060] In contrast to Type I inhibitors, the disclosure demonstrates that Non-Type I (e.g. Type II) inhibitors including neratinib are devoid of paradoxical activation for cells expressing ErbB ectodomain variants. Neratinib is found to exemplify a preferred molecule that is both potent and selective for each member of the covalently-activated EGFR family versus wild type EGFR.

[0061] Collectively, the disclosure provides a structure/functional relationship for predicting how structural variations affecting receptor regions distal to the active site can confer dramatically different responses to small molecule active site inhibitors. The discovery described herein of paradoxical activation of covalently-activated ErbB receptor variants by Type I inhibitors has important clinical implications. The data of the disclosure provide a mechanistic explanation for the failed clinical studies for Type I inhibitors in tumor types where expression of covalently-activated ErbB receptors is prevalent. This includes erlotinib and gefitinib in GBM tumors, erlotinib in SCCHN tumors, and sapitinib in breast tumors.

Glioblastoma

[0062] Glioblastoma (GBM), grade IV astrocytoma, is the most common form of brain cancer. The outcome for this disease is dismal. Surgery followed by a therapeutic regimen of radiation and temozolomide is standard of care, however this produces a median overall survival (OS) of only 14.6 months and few patients survive for five years. There has been little progress made in extending survival for GBM patients over the past decade. Although bevacizumab showed an improved progression free survival benefit in the recurrent setting, the addition of bevacizumab to standard of care therapy in the front-line setting did not result in an OS benefit.

[0063] EGFR is the most frequently altered oncogene in GBM. In addition to EGFR gene amplification, many tumors express variants generated by aberrant splicing or genomic mutation. The first recognized variant is EGFR-Viii, resulting from truncation of exons 2-7 and expressed by approximately 20% of GBM tumors. EGFR-Viii is oncogenic. EGFR-Viii is constitutively activated in the absence of EGF ligand, exhibiting sustained signaling that is resistant to downregulation. Therefore, EGFR-Viii is both transforming and tumorigenic. Expression of EGFR-Viii is associated with poor long term overall survival in GBM.

[0064] RNA sequencing data has revealed that EGFR-Viii is just one of several aberrantly spliced variants of EGFR expressed in GBM tumors. Two others result in truncation of exons 12-13 (EGFR-Vvi and 14-15 (EGFR-Vii). Like EGFR-Viii, EGFR-Vii is both transforming and tumorigenic. In addition to splice variants, GBM tumors also express a collection of EGFR point mutations including C620Y, A289V and G598V, which are transforming and tumorigenic. The complex landscape of EGFR alterations in GBM is further compounded by the observation that many tumors express more than one receptor variant.

[0065] Because the expression of multiple EGFR variants in GBM gives rise to transforming and tumorigenic activity and because EGFR is the most frequently altered oncogene present in GBM tumors, EGFR is an especially attractive target for small molecule ErbB inhibitors. Following the success for small molecule EGFR therapeutics against NSCLC tumors harboring activating mutations in EGFR (erlotinib, gefitinib, and afatinib), these drugs were tested in GBM. Despite intense clinical investigation of this group of ErbB inhibitors in GBM, involving >30 clinical trials and >1500 patients, all failed to produce any benefit, even for those tumors that expressed EGFR-Viii. Strikingly, some evidence suggests that erlotinib promoted disease progression. A phase 2 study evaluating erlotinib in combination with radiation and temozolomide showed median PFS (mPFS) and median OS (mOS) of 2.8 months and 8.6 months, as compared to 6.9 months and 14.6 months for patients receiving radiation and temozolomide alone. Another randomized phase II trial with erlotinib showed that patients who received erlotinib, including those whose tumors expressed EGFR-Viii, progressed more poorly as compared to those patients who received standard of care therapy. The clinical failures for ErbB inhibitors such as erlotinib in GBM tumors has cast doubt on the role of EGFR as a driver of tumor growth in GBM and led to inquiry as to why ErbB inhibitors that were so effective in treating EGFR mutations in lung cancer were so ineffective in treating EGFR variants in GBM.

[0066] A distinctive feature for the EGFR variants expressed in GBM is their location within the extracellular domain. This is in contrast to activating mutations of EGFR found in lung cancer, which often reside in the intracellular catalytic domain. EGFR is composed of four extracellular domains (two ligand binding domains and two cysteine rich regions), a transmembrane domain, and an intracellular catalytic domain. Ligand binding promotes dimerization of the extracellular cysteine rich domains (CR1 and CR2), an event that confers dimerization of the intracellular domain and activation of receptor catalytic activity. Nearly all EGFR splicing events and mutations in GBM affect the extracellular region, specifically two cysteine rich regions (CR1 and CR2) that form the extracellular dimer interface. The CR regions contain >40 cysteine residues, all of which form intramolecular disulfide bonds. In EGFR-Viii, truncation of exons 2-7 results in partial loss of sequence encoding the CR1 region. A consequence is loss of one cysteine from the Cys295-Cys307 pair, leaving Cys307 as a free unpaired cysteine. For EGFR-Viii, this cysteine can form an intermolecular disulfide bond with another EGFR monomer to drive a covalently dimerized and constitutively activated receptor. Mutation of Cysteine 307 to a Serine (C307S) prevents the formation of covalently dimerized EGFR-Viii and is inactive.

[0067] Although several recent preclinical studies have suggested that EGFR kinase inhibitors such as erlotinib are quite ineffective at inhibiting EGFR-Viii, there has been no mechanism proposed for this effect. There is also a lack in current understanding for the mechanism responsible for activation of other ectodomain variants in GBM, including EGFR-Vii and EGFR-A289V. The disclosure provides a mechanism of receptor activation and impact on ErbB inhibitor activity for a group of four of the most common ectodomain variants in GBM, EGFR-Viii, EGFR-Vii, EGFR-Vvi, EGFR-G598V and EGFR-A289V.

[0068] The disclosure demonstrates that like EGFR-Viii, an additional group of commonly occurring EGFR variants in GBM (EGFR-Vii, EGFR-Vvi, EGFR-G598V and EGFR-A289V) all exist as constitutively active covalent dimers and together form a family of EGFR isoforms that are activated by this common mechanism. Furthermore, the disclosure shows that the propensity of these variants to covalently dimerize is coupled to the conformation of the intracellular catalytic site, conferring distinct activity for classes of small molecules inhibitors binding to this distal site. Inhibitors that stabilize the active conformation of the kinase (Type I inhibitors, including erlotinib) induce the formation of covalent dimers for all covalently-activated EGFR isoforms. This is associated with the propensity of Type I inhibitors to increase EGFR phosphorylation at

sub-saturating concentrations and to paradoxically stimulate the proliferation of cells expressing covalently-activated EGFR isoforms.

[0069] Neither enhanced dimerization nor paradoxical activation of EGFR is seen with small molecule inhibitors that stabilize the inactive kinase conformation (Type II inhibitors, including lapatinib and neratinib). Examples of Type II inhibitors were identified that were potent inhibitors of covalently-activated EGFR isoforms and which were selective for this family compared to WT-EGFR.

[0070] Similar to the mutations identified for EGFR, the disclosure identifies a group of splice events and mutations affecting the CR domains of HER2 and HER4. The disclosure demonstrates that this group of splice events and mutations affecting the CR domains of HER2 and HER4 exists as covalent dimers and are paradoxically activated by agents with a Type I binding mode. These data provide a mechanistic explanation for the failure of multiple clinical trials involving Type I inhibitors, including >30 clinical trials of Type I ErbB inhibitors in GBM. Collectively these data indicate that tumors expressing covalently-activated EGFR isoforms should be excluded from treatment with Type I ErbB inhibitors such as erlotinib because of paradoxical activation. These data further demonstrate the utility for optimizing Type II ErbB inhibitors against the covalently-activated ErbB family.

Methods and Uses of the Present Disclosure

[0071] In some aspects, the present disclosure provides a method of treating or preventing (e.g., treating) cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

[0072] In some aspects, the present disclosure provides a method of treating or preventing (e.g., treating) cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or a pharmaceutically acceptable salt thereof.

[0073] In some aspects, the present disclosure provides a method of treating or preventing (e.g., treating) cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or a pharmaceutically acceptable salt thereof.

[0074] In some aspects, the present disclosure provides Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof for treating or preventing (e.g., treating) cancer in a subject in need thereof.

[0075] In some aspects, the present disclosure provides Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or a pharmaceutically acceptable salt thereof for treating or preventing (e.g., treating) cancer in a subject in need thereof.

[0076] In some aspects, the present disclosure provides Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or a pharmaceutically acceptable salt thereof for treating or preventing (e.g., treating) cancer in a subject in need thereof.

[0077] In some aspects, the present disclosure provides use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing (e.g., treating) cancer in a subject in need thereof.

[0078] In some aspects, the present disclosure provides use of Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing (e.g., treating) cancer in a subject in need thereof.

[0079] In some aspects, the present disclosure provides use of Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing (e.g., treating) cancer in a subject in need thereof.

[0080] In some embodiments, Compound No. 1A, Compound No. 1B, or the pharmaceutically acceptable salt thereof is administered.

[0081] In some embodiments, Compound No. 1A the pharmaceutically acceptable salt thereof is administered.

[0082] In some embodiments, Compound No. 1B the pharmaceutically acceptable salt thereof is administered.

[0083] In some embodiments, Compound No. 2A, Compound No. 2B, or the pharmaceutically acceptable salt thereof is administered.

[0084] In some embodiments, Compound No. 2A or the pharmaceutically acceptable salt thereof is administered.

[0085] In some embodiments, Compound No. 2B or the pharmaceutically acceptable salt thereof is administered.

Suitable Subjects and Diseases

[0086] In some embodiments, the subject is a mammal. In some embodiments, the subject is a human. In some embodiments, the subject is a human adult (e.g., being 18 years of age or order).

[0087] In some embodiments, the subject is a mouse. In some embodiments, the subject is a rat. In some embodiments, the subject is a dog.

[0088] The compounds of the disclosure inhibit or modulate the activity of a receptor tyrosine kinase, in particular extracellular mutants of ErbB-receptors, such as, but not limited to, EGFR-Viii, EGFR-Vii, EGFR-Vvi, EGFR-A289V and EGFR-G598V and HER2-S310F. Thus, the compounds and compositions of the disclosure can be useful as a medicament, i.e. as a medicament in therapy, more specifically for the prevention or treatment of cancer, as detailed below. Therefore, in a further aspect, the present disclosure provides a method of prevention or treatment of a mammal, for example, a human, suffering from cancer, as detailed below.

[0089] In some aspects, the present disclosure is directed to a method of inhibiting an oncogenic variant of an ErbB receptor (*e.g.*, an oncogenic variant of an EGFR), comprising administering the subject in need thereof a therapeutically effective amount of a compound described herein.

[0090] In some aspects, the present disclosure is directed to a method of inhibiting an oncogenic variant of an ErbB receptor (*e.g.*, an oncogenic variant of an EGFR), comprising administering the subject in need thereof a composition described herein.

[0091] In some aspects, the present disclosure is directed to a method of preventing or treating cancer, comprising administering the subject in need thereof a therapeutically effective amount of a compound described herein.

[0092] In some aspects, the present disclosure is directed to a method of preventing or treating cancer, comprising administering the subject in need thereof a composition described herein.

[0093] In some aspects, the present disclosure is directed to a compound described herein for use in the inhibition of an oncogenic variant of an ErbB receptor (*e.g.*, an oncogenic variant of an EGFR).

[0094] In some aspects, the present disclosure is directed to a compound described herein for use in the prevention or treatment of cancer.

[0095] In some aspects, the present disclosure is directed to a composition described herein for use in the inhibition of an oncogenic variant of an ErbB receptor (*e.g.*, an oncogenic variant of an EGFR).

[0096] In some aspects, the present disclosure is directed to a composition described herein for use in the prevention or treatment of cancer.

[0097] In some aspects, the present disclosure is directed to use of a compound described herein in the manufacture of a medicament for inhibiting an oncogenic variant of an ErbB receptor (*e.g.*, an oncogenic variant of an EGFR).

[0098] In some aspects, the present disclosure is directed to use of a compound described herein in the manufacture of a medicament for preventing or treating cancer.

[0099] In some embodiments, the compound is selected from the compounds described in Tables 1 and 2, pharmaceutically acceptable salts thereof, and stereoisomers thereof.

[0100] In some embodiments, the compound is selected from the compounds described in Tables 1 and 2 and pharmaceutically acceptable salts thereof.

[0101] In some embodiments, the compound is selected from the compounds described in Tables 1 and 2.

[0102] In some embodiments, cancer is a solid tumor.

[0103] In some embodiments, the cancer is a bladder cancer, a breast cancer, a cervical cancer, a colorectal cancer, an endometrial cancer, a gastric cancer, a glioblastoma (GBM), a head and neck cancer, a lung cancer, a non-small cell lung cancer (NSCLC), or any subtype thereof.

[0104] In some embodiments, the cancer is glioblastoma (GBM) or any subtype thereof. In some embodiments, the cancer is glioblastoma.

[0105] In some embodiments, the cancer is glioblastoma and the cancer is characterized by overexpression of EGFR.

[0106] In some embodiments, the cancer is methylated glioblastoma. In some embodiments, the cancer is unmethylated glioblastoma.

[0107] In some embodiments, the cancer is recurrent glioblastoma.

[0108] In some embodiments, the cancer is relapsed glioblastoma.

[0109] In some embodiments, the cancer is glioblastoma and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0110] In some embodiments, the cancer is relapsed glioblastoma and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0111] In some embodiments, the cancer is recurrent glioblastoma and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0112] In some embodiments, the cancer is non-small cell lung cancer (NSCLC) or any subtype thereof.

[0113] In some embodiments, the cancer is non-small cell lung cancer (NSCLC).

[0114] In some embodiments, the cancer is recurrent non-small cell lung cancer (NSCLC).

[0115] In some embodiments, the cancer is relapsed non-small cell lung cancer (NSCLC).

[0116] In some embodiments, the cancer is NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0117] In some embodiments, the cancer is recurrent NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0118] In some embodiments, the cancer is relapsed NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0119] In some embodiments, the cancer is advanced or metastatic NSCLC .

[0120] In some embodiments, the cancer is advanced or metastatic NSCLC and the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR.

[0121] In some embodiments, the cancer is NSCLC, wherein the cancer has metastasized to the central nervous system (CNS).

[0122] In some embodiments, the cancer is advanced or metastatic NSCLC, wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the cancer has metastasized to the central nervous system (CNS).

[0123] In some embodiments, the cancer is advanced or metastatic NSCLC, wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the cancer has not metastasized to the central nervous system (CNS).

[0124] In some embodiments, the cancer is NSCLC, wherein the cancer has not metastasized to cerebrospinal fluid (CSF).

[0125] In some embodiments, the cancer is NSCLC, wherein the cancer has metastasized to cerebrospinal fluid (CSF).

[0126] In some embodiments, the cancer is glioblastoma, wherein the cancer has not metastasized to cerebrospinal fluid (CSF).

[0127] In some embodiments, the cancer is glioblastoma, wherein the cancer has metastasized to cerebrospinal fluid (CSF).

[0128] In some embodiments, the cancer is NSCLC, wherein the cancer has not metastasized to

the brain.

[0129] In some embodiments, the cancer is NSCLC, wherein the cancer has metastasized to the brain.

[0130] In some embodiments, the subject has a central nervous system (CNS) disease.

[0131] In some embodiments, the subject does not have any CNS disease.

[0132] In some embodiments, the subject has a leptomeningeal disease.

[0133] In some embodiments, the subject does not have any leptomeningeal disease.

[0134] In some embodiments, the cancer is NSCLC and the subject has leptomeningeal disease.

[0135] In some embodiments, the cancer is glioblastoma and the subject has leptomeningeal disease.

[0136] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an ErbB receptor.

[0137] It is understood that an oncogenic variant of an ErbB receptor is an ErbB receptor protein that comprises at least one oncogenic mutation and that is produced as the result of the expression of a gene encoding the ErbB receptor that comprises at least one oncogenic mutation.

[0138] As would be appreciated by the skilled artisan, in the context of a gene (*e.g.* a gene encoding an ErbB receptor), an oncogenic mutation can include, but is not limited to a mutation that results in the substitution of one amino acid for another at a specific position within an ErbB receptor, a mutation that results in an insertion of one or more amino acids between two positions within an ErbB receptor, a mutation that results in the deletion of one more amino acids between two positions within an ErbB receptor, and mutation that results in a fusion of an ErbB receptor or portion thereof, with another protein, or portion thereof. As would be appreciated by the skilled artisan, in the context of a gene, an oncogenic mutation can include, but is not limited to, a missense mutation, a nonsynonymous mutation, an insertion of one or more nucleotides, a deletion of one or more nucleotides, an inversion and a deletion-insertion..

[0139] As would be appreciated by the skilled artisan, in the context of a protein (*e.g.* an ErbB receptor), an oncogenic mutation can include, but is not limited to, the substitution of one amino acid for another at a specific position within an ErbB receptor, an insertion of one or more amino acids between two positions within an ErbB receptor, a deletion of one more amino acids between two positions within an ErbB receptor, and a fusion of an ErbB receptor, or portion thereof, with another protein, or portion thereof.

[0140] In some embodiments, the oncogenic variant of the ErbB receptor comprises an allosteric mutation.

[0141] In some embodiments, the oncogenic variant of an ErbB receptor is is an allosteric variant of the ErbB receptor.

[0142] In some embodiments, the ErbB receptor is an an epidermal growth factor receptor (EGFR) or a human epidermal growth factor receptor 2 (HER2) receptor.

[0143] In some embodiments, the ErbB receptor is an epidermal growth factor receptor (EGFR).

[0144] In some embodiments, the ErbB receptor is a HER2 receptor.

[0145] In some embodiments, the ErbB receptor is a HER3 receptor.

[0146] In some embodiments, the ErbB receptor is a HER4 receptor.

[0147] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an epidermal growth factor receptor (EGFR).

[0148] In some embodiments, the oncogenic variant of EGFR is an allosteric variant of EGFR.

[0149] In some embodiments, the oncogenic variant of EGFR comprises an allosteric mutation.

[0150] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor.

[0151] In some embodiments, the oncogenic variant of the HER2 receptor is an allosteric variant of the HER2 receptor.

[0152] In some embodiments, the oncogenic variant of the HER2 receptor comprises an allosteric mutation.

[0153] In some embodiments, the oncogenic variant of an EGFR comprises an EGFR variant III (EGFR-Viii) mutation.

[0154] In some embodiments, the oncogenic variant of EGFR comprises an EGFR variant II (EGFR-Vii) mutation.

[0155] In some embodiments, the oncogenic variant of EGFR comprises an EGFR variant VI (EGFR-Vvi) mutation.

[0156] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a lysine (K) for an arginine (R) at position 108 of SEQ ID NO: 1.

[0157] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a cysteine (C) for an arginine (R) at position 222 of SEQ ID NO: 1.

[0158] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a

threonine (T) for an alanine (A) at position 289 of SEQ ID NO: 1.

[0159] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a valine (V) for an alanine (A) at position 289 of SEQ ID NO: 1.

[0160] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a valine (V) for a glycine (G) at position 598 of SEQ ID NO: 1.

[0161] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a phenylalanine (F) for a cysteine (C) at position 231 of SEQ ID NO: 1.

[0162] In some embodiments, the oncogenic variant of EGFR comrpises a substitution of a serine for a cysteine at position 595 of SEQ ID NO: 1.

[0163] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a valine (V) for a glycine (G) at position 598 of SEQ ID NO: 1.

[0164] In some embodiments, the oncogenic variant of EGFR comprises a substitution of a cysteine (C) for a serine (S) at position 645 of SEQ ID NO: 1.

[0165] In some embodiments, the oncogenic variant of EGFR comprises a substitution of glycine (G) at position 719 of SEQ ID NO: 1, wherein the substitution is selected from cysteine (C), aspartate (D), arginine (R), serine (S), or alanine (A).

[0166] In some embodiments, the oncogenic variant of EGFR comrpises a substitution of serine (S) for a glycine (G) at position 719 of SEQ ID NO: 1.

[0167] In some embodiments, the oncogenic variant of EGFR comprises a substitution of serine (S) for cysteine (C) at position 797 of SEQ ID NO: 1.

[0168] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an EGFR and wherein the oncogenic variant of EGFR is an allosteric variant of EGFR, the oncogenic variant of an EGFR comprises a modification of a structure of the EGFR, wherein the oncogenic variant of an EGFR is a capable of forming a covalently linked dimer, wherein the covalently linked dimer is constitutively active and wherein the covalently linked dimer enhances an activity of EGFR when contacted to a Type I ErbB inhibitor. In some embodiments, the modification of the structure of the EGFR comprises a modification of one or more of a nucleic acid sequence, an amino acid sequence, a secondary structure, a tertiary structure, and a quaternary structure. In some embodiments, the oncogenic variant comprises a mutation, a splicing event, a post-translational process, a conformational change or any combination thereof. In some embodiments, the modification of the structure of the EGFR occurs within a first cysteine rich

(CR1) and/or second cysteine rich (CR2) region of EGFR. In some embodiments, the first cysteine rich (CR1) and/or second cysteine rich (CR2) region of EGFR comprises amino acid residues T211-R334 and/or C526-S645 of SEQ ID NO: 1, respectively. In some embodiments, the oncogenic variant of an EGFR generates a physical barrier to formation of a disulfide bond within the CR1 and/or the CR2 region. In some embodiments, the oncogenic variant of an EGFR removes a physical barrier to formation of a disulfide bond within the CR1 and/or the CR2 region. In some embodiments, the oncogenic variant of an EGFR comprises one or more free or unpaired Cysteine (C) residues located at a dimer interface of the EGFR. In some embodiments, the oncogenic variant of an EGFR comprises one or more free or unpaired Cysteine (C) residues at a site selected from the group consisting of C190-C199, C194-C207, C215-C223, C219-C231, C232-C240, C236-C248, C251-C260, C264-C291, C295-C307, C311-C326, C329-C333, C506-C515, C510-C523, C526-C535, C539-C555, C558-C571, C562-C579, C582-C591, C595-C617, C620-C628 and C624-C636 according to SEQ ID NO: 1. In some embodiments, the modification occurs within 10 angstroms or less of an intramolecular disulfide bond at a site selected from the group consisting of C190-C199, C194-C207, C215-C223, C219-C231, C232-C240, C236-C248, C251-C260, C264-C291, C295-C307, C311-C326, C329-C333, C506-C515, C510-C523, C526-C535, C539-C555, C558-C571, C562-C579, C582-C591, C595-C617, C620-C628 and C624-C636 according to SEQ ID NO: 1.

[0169] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of EGFR and the oncogenic variant of EGFR is a mutation of EGFR, a nucleotide sequence encoding the oncogenic variant of an EGFR comprises a deletion or the substitution comprises one or more amino acids that encode an adenosine triphosphate (ATP) binding site. In some embodiments, the ATP binding site comprises amino acids E746 to A750 of SEQ ID NO: 1. In some embodiments, the ATP binding site or the deletion or substitution thereof comprises L858 of SEQ ID NO: 1. In some embodiments, the deletion comprises L858 of SEQ ID NO: 1. In some embodiments, an arginine (R) is substituted for the leucine (L) at position 858 (L858R) of SEQ ID NO: 1.

[0170] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an EGFR and wherein the oncogenic variant of EGFR is an allosteric variant of EGFR, a nucleotide sequence encoding the oncogenic variant of an EGFR comprises an insertion within a sequence encoding exon 20 or a portion thereof. In some embodiments, the sequence encoding

exon 20 or a portion thereof comprises a sequence encoding KEILDEAYVMASVDNPHVCAR (SEQ ID NO: 7). In some embodiments, the sequence encoding exon 20 or a portion thereof comprises a sequence encoding a C-helix, a terminal end of the C-helix or a loop following the C-helix. In some embodiments, the insertion comprises the amino acid sequence of ASV, SVD, NPH, or FQEA. In some embodiments, the sequence encoding exon 20 or a portion thereof comprises one or more of: (a) an insertion of the amino acid sequence ASV between positions V769 and D770 of SEQ ID NO: 1; (b) an insertion of the amino acid sequence SVD between positions D770 and N771 of SEQ ID NO: 1; (c) an insertion of the amino acid sequence NPH between positions H773 and V774 of SEQ ID NO: 1; (d) an insertion of the amino acid sequence FQEA between positions A763 and Y764 of SEQ ID NO: 1; (e) an insertion of the amino acid sequence PH between positions H773 and V774 of SEQ ID NO: 1; (f) an insertion of the amino acid G between positions D770 and N771 of SEQ ID NO: 1; (g) an insertion of the amino acid H between positions H773 and V774 of SEQ ID NO: 1; (h) an insertion of the amino acid sequence HV between positions V774 and C775 of SEQ ID NO: 1; (i) an insertion of the amino acid sequence AH between positions H773 and V774 of SEQ ID NO: 1; (j) an insertion of the amino acid sequence SVA between positions A767 and S768 of SEQ ID NO: 1; (k) a substitution of the amino acid sequence GYN for the DN between positions 770 and 771 of SEQ ID NO: 1; (l) an insertion of the amino acid H between positions N771 and P772 of SEQ ID NO: 1; (m) an insertion of the amino acid Y between positions H773 and V774 of SEQ ID NO: 1; (n) an insertion of the amino acid sequence PHVC between positions C775 and R776 of SEQ ID NO: 1; (o) a substitution of the amino acid sequence YNPY for the H at position 773 of SEQ ID NO: 1; (p) an insertion of the amino acid sequence DNP between positions P772 and H773 of SEQ ID NO: 1; (q) an insertion of the amino acid sequence VDS between positions S768 and V769 of SEQ ID NO: 1; (r) an insertion of the amino acid H between positions D770 and N771 of SEQ ID NO: 1; (s) an insertion of the amino acid N between positions N771 and P772 of SEQ ID NO: 1; (t) an insertion of the amino acid sequence PNP between positions P772 and H773 of SEQ ID NO: 1; (u) a substitution of the amino acid sequence GSVDN for the DN between positions 770 and 771 of SEQ ID NO: 1; (v) a substitution of the amino acid sequence GYP for the NP between positions 771 and 772 of SEQ ID NO: 1; (w) an insertion of the amino acid G between positions N771 and P772 of SEQ ID NO: 1; (x) an insertion of the amino acid sequence GNP between positions P772 and H773 of SEQ ID NO: 1; (y) an insertion of the amino acid sequence GSV between positions V769 and D770 of

SEQ ID NO: 1; (z) a substitution of the amino acid sequence GNPHVC for the VC between positions 774 and 775 of SEQ ID NO: 1; (aa) an insertion of the amino acid sequence LQEA between positions A763 and Y764 of SEQ ID NO: 1; (bb) an insertion of the amino acid sequence GL between positions D770 and N771 of SEQ ID NO: 1; (cc) an insertion of the amino acid Y between positions D770 and N771 of SEQ ID NO: 1; (dd) an insertion of the amino acid sequence NPY between positions H773 and V774 of SEQ ID NO: 1; (ee) an insertion of the amino acid sequence TH between positions H773 and V774 of SEQ ID NO: 1; (ff) a substitution of the amino acid sequence KGP for the NP between positions 771 and 772 of SEQ ID NO: 1; (gg) a substitution of the amino acid sequence SVDNP for the NP between positions 771 and 772 of SEQ ID NO: 1; (hh) an insertion of the amino acid sequence NN between positions N771 and P772 of SEQ ID NO: 1; (ii) an insertion of the amino acid T between positions N771 and P772 of SEQ ID NO: 1; and (jj) a substitution of the amino acid sequence STLASV for the SV between positions 768 and 769 of SEQ ID NO: 1.

[0171] In some embodiments, an oncogenic variant of EGFR can have or more mutations in exon 18.

[0172] In some embodiments, an oncogenic variant of EGFR can have or more mutations in exon 19.

[0173] In some embodiments, an oncogenic variant of EGFR can have or more mutations in exon 20.

[0174] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an EGFR and wherein the oncogenic variant of EGFR is an allosteric variant of EGFR.

[0175] In some embodiments, the oncogenic variant of an EGFR can be any of the following: EGFR-Viii, EGFR-Vii, EGFR-Vvi, EGFR-R222C, EGFR-R252C, EGFR-R252P, EGFR-R256Y, EGFR-T263P, EGFR-Y270C, EGFR-A289T, EGFR-A289V, EGFR-A289D, EGFR-H304Y, EGFR-G331R, EGFR-P596S, EGFR-P596L, EGFR-P596R, EGFR-G598V, EGFR-G598A, EGFR-G614D, EGFR-C620Y, EGFR-C614W, EGFR-C628F, EGFR-C628Y, EGFR-C636Y, EGFR-S645C, EGFR-Δ660, EGFR-Δ768, EGFR-C231F, EGFR-C231F, EGFR-C595S, EGFR-D761Y, EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-L858R, EGFR-E746-A750del, EGFR-E746-A750del+C797S, EGFR-E746-A750del+C797S+T790M, EGFR-C797S or any combination thereof.

[0176] In some embodiments, the oncogenic variant of an EGFR is selected from: EGFR-Viii,

EGFR-Vii, EGFR-Vvi, EGFR-R108K, EGFR-R222C, EGFR-R252C, EGFR-R252P, EGFR-R256Y, EGFR-T263P, EGFR-Y270C, EGFR-A289T, EGFR-A289V, EGFR-A289D, EGFR-H304Y, EGFR-G331R, EGFR-P596S, EGFR-P596L, EGFR-P596R, EGFR-G598V, EGFR-G598A, EGFR-G614D, EGFR-C620Y, EGFR-C614W, EGFR-C628F, EGFR-C628Y, EGFR-C636Y, EGFR-S645C, EGFR-Δ660, EGFR-Δ768, EGFR-V689M, EGFR-N700D, EGFR-E709K, EGFR-E709Q, EGFR-E709A, EGFR-E709G, EGFR-E709V, EGFR-S768I, EGFR-C231F, EGFR-C595S, EGFR-D761Y, EGFR-L718Q, EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, EGFR-G719S, EGFR-G724S, EGFR-L858R, EGFR-L858R+C797S, EGFR-L861Q, EGFR-E746-A750del, EGFR-E746-A750del+C797S, EGFR-E746-A750del+S768I, EGFR-E746-A750del+C797S+T790M, EGFR-C797S, EGFR-Δ19+C797S, EGFR- Δ19+C797S+ T790M, EGFR- Δ19+S768I, EGFR-G719C+S768I, EGFR-D716Y or any combination thereof.

[0177] In some embodiments, the oncogenic variant of EGFR comprises an insertion within exon 20, wherein the insertion comprises the amino acid sequence of ASV, SVD, NPH or FQEA.

[0178] In some embodiments, the oncogenic variant of EGFR comprises an insertion in exon 20, wherein the insertion in exon 20 is selected from the group of insertions recited in Table 1.

Table 1. EGFR Exon 20 insertions (numbering corresponding to SEQ ID NO: 1)

Insertion Description
an insertion of the amino acid sequence ASV between positions V769 and D770 (V769_D770insASV; A767_V769dup; A767-V769dupASV)
an insertion of the amino acid sequence SVD between positions D770 and N771 (D770_N771insSVD; S768_D770dup; S768_D770dupSVD)
an insertion of the amino acid sequence NPH between positions H773 and V774 (H773_V774insNPH; N771_H773dup; N771_H773dupNPH)
an insertion of the amino acid sequence FQEA between positions A763 and Y764 (A763_Y764 FQEA; A763_Y764insFQEA)
an insertion of the amino acid sequence PH between positions H773 and V774 (H773_V774insPH; P772_H773dup; P772_H773dupPH)
an insertion of the amino acid G between positions D770 and N771(D770_N771insG; D771_P772insG)
an insertion of the amino acid H between positions H773 and V774 (H773_V774insH; H773dup; H773dupH)
an insertion of the amino acid sequence HV between positions V774 and C775 (V774_C775insHV; H773_V774dup; H773_V774dupHV)
an insertion of the amino acid sequence AH between positions H773 and V774 (H773_V774insAH)

Insertion Description
an insertion of the amino acid sequence SVA between positions A767 and S768 (A767_S768insSVA; A767_V769dup; A767_V769dupSVA)
an insertion of the amino acid H between positions N771 and P772
an insertion of the amino acid Y between positions H773 and V774 (H773_V774insY)
an insertion of the amino acid sequence PHVC between positions C775 and R776 (C775_R776insPHVC)
an insertion of the amino acid sequence DNP between positions P772 and H773 (P772_H773insDNP; D770_P772dup; D770_P772dupDNP)
an insertion of the amino acid sequence VDS between positions S768 and V769 (S768_V769insVDS)
an insertion of the amino acid H between positions D770 and N771 (N771_P772insH)
an insertion of the amino acid N between positions N771 and P772
an insertion of the amino acid sequence PNP between positions P772 and H773 (P772_H773insPNP)
an insertion of the amino acid G between positions N771 and P772 (N771_P772insG)
an insertion of the amino acid sequence GNP between positions P772 and H773 (P772_H773insGNP)
an insertion of the amino acid sequence GSV between positions V769 and D770
an insertion of the amino acid sequence LQEA between positions A763 and Y764
an insertion of the amino acid sequence GL between positions D770 and N771
an insertion of the amino acid Y between positions D770 and N771
an insertion of the amino acid sequence NPY between positions H773 and V774
an insertion of the amino acid sequence TH between positions H773 and V774
an insertion of the amino acid sequence NN between positions N771 and P772
an insertion of the amino acid T between positions N771 and P772

[0179] In some embodiments, the oncogenic variant of EGFR comprises a substitution within exon 20 of EGFR.

[0180] In some embodiments, the oncogenic variant of EGFR comprises a substitution in exon 20, wherein the substitution in exon 20 is selected from the group of substitutions recited in Table 2.

Table 2. EGFR Exon 20 substitutions (numbering corresponding to SEQ ID NO: 1)

Substitution Description
a substitution of the amino acid sequence GYN for the DN between positions 770 and 771 (D770_N771 > GYN; D770_N771delinsGYN; D770_N771insGYN)
a substitution of the amino acid sequence GF for the N at position N771 (N771 > GF; N771delinsGF)
a substitution of the amino acid sequence GY for the D at position 770 (D770 > GY; D770delinsGY)

a substitution of the amino acid sequence YNPY for the H at position 773 (H773 > YNPY; H773delinsYNPY)
a substitution of the amino acid sequence GSVDN for the DN between positions 770 and 771
a substitution of the amino acid sequence GYP for the NP between positions 771 and 772
a substitution of the amino acid sequence GNPHVC for the VC between positions 774 and 775
a substitution of the amino acid sequence KGP for the NP between positions 771 and 772
a substitution of the amino acid sequence SVDNP for the NP between positions 771 and 772
a substitution of the amino acid sequence STLASV for the SV between positions 768 and 769

[0181] In some embodiments, the oncogenic variant of EGFR can be any of the EGFR variants put forth in Table 3.

Table 3. EGFR oncogenic variants

EGFR-Vii	EGFR-A289V	EGFR-C620Y
EGFR-Viii	EGFR-A289D	EGFR-C614W
EGFR-Vvi	EGFR-H304Y	EGFR-C628F
EGFR-R222C	EGFR-G331R	EGFR-C628Y
EGFR-R252C	EGFR-P596S	EGFR-C636Y
EGFR-R252P	EGFR-P596L	EGFR-S645C
EGFR-R256Y	EGFR-P596R	EGFR-Δ660
EGFR-T263P	EGFR-G598V	EGFR-Δ768
EGFR-Y270C	EGFR-G598A	EGFR-L858R
EGFR-A289T	EGFR-G614D	EGFR-Δ19 (deletion of Exon 19)
EGFR-R108K	EGFR-V689M	EGFR-N700D
EGFR-E709K	EGFR-E709Q	EGFR-E709A
EGFR-E709G	EGFR-E709V	EGFR-S768I
EGFR-L718Q	EGFR-G719A	EGFR-G719S
EGFR-G724S	EGFR-L858R+C797S	EGFR-Δ19 + C797S
EGFR-C231F	EGFR-C595S	EGFR-G719C
EGFR-G719D	EGFR-G719R	EGFR- Δ19+C797S+ T790M
EGFR-C797S	EGFR-E746-A750del+C797S	EGFR-E746-A750del
EGFR-E746-A750del+C797S+ T790M	EGFR-E746-A750del+S768I	EGFR- Δ19+S768I
EGFR-G791S	EGFR-G719C+S768I	EGFR-D716Y

[0182] In some embodiments, Δ19 can comprise the deletion of residues E746-A750 of EGFR (SEQ ID NO: 1).

[0183] In some embodiments, the cancer, or a tumor or a cell thereof, expresses one or more of: (a) a wild type human epidermal growth factor receptor 2 (HER2) receptor or an oncogenic variant of a HER2 receptor.

[0184] In some embodiments, the cancer, or a tumor or a cell thereof, expresses a wild type HER2 receptor, the wild type HER2 receptor comprises the amino acid sequence of SEQ ID NO: 2, 3, 4, 5, or 6.

[0185] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor, the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor.

[0186] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a phenylalanine (F) for a serine (S) at position 310 of SEQ ID NO: 2 or 5.

[0187] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a tyrosine (Y) for a serine (S) at position 310 of SEQ ID NO: 2 or 5.

[0188] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a glutamine (Q) for an arginine (R) at position 678 of SEQ ID NO: 2 or 5.

[0189] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a leucine (L) for a valine (V) at position 777 of SEQ ID NO: 2 or 5.

[0190] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a methionine (M) for a valine (V) at position 777 of SEQ ID NO: 2 or 5.

[0191] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric

variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of an isoleucine (I) for a valine (V) at position 842 of SEQ ID NO: 2 or 5.

[0192] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of an alanine (A) for a leucine (L) at position 755 of SEQ ID NO: 2 or 5.

[0193] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a proline (P) for a leucine (L) at position 755 of SEQ ID NO: 2 or 5.

[0194] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises a substitution of a serine (S) for a leucine (L) at position 755 of SEQ ID NO: 2 or 5.

[0195] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, a nucleotide sequence encoding the oncogenic variant of a HER2 receptor comprises an insertion within a sequence encoding exon 20 or a portion thereof. In some embodiments, the sequence encoding exon 20 or a portion thereof comprises a sequence encoding KEILDEAYVMAGVGSPYVSR(SEQ ID NO: 8). In some embodiments, the sequence encoding exon 20 or a portion thereof comprises a sequence encoding a C-helix, a terminal end of the C-helix or a loop following the C-helix. In some embodiments, the insertion comprises the amino acid sequence of GSP or YVMA. In some embodiments, the sequence encoding exon 20 or a portion thereof comprises one or more of: (a) an insertion of the amino acid sequence YVMA between positions A775 and G776 of SEQ ID NO: 2; (b) an insertion of the amino acid sequence GSP between positions P780 and Y781 of SEQ ID NO: 2; (c) an insertion of the amino acid sequence YVMA between positions A771 and Y772 of SEQ ID NO: 2; (d) an insertion of the amino acid sequence YVMA between positions A775 and G776 of SEQ ID NO: 2; (e) an insertion of the amino acid V between positions V777 and G778 of SEQ ID NO: 2; (f) an insertion of the amino acid V between positions V777 and G778 of SEQ ID NO: 2; (g) a substitution of the amino acid sequence AVGCV for the GV between positions 776 and 777 of SEQ ID NO: 2; (h) a

substitution of the amino acid sequence LC for the G between position 776 of SEQ ID NO: 2; (i) a substitution of the amino acid sequence LCV for the G between position 776 of SEQ ID NO: 2; (j) an insertion of the amino acid sequence GSP between positions V777 and G778 of SEQ ID NO: 2; (k) a substitution of the amino acid sequence PS for the LRE between positions 755 and 757 of SEQ ID NO: 2; (l) a substitution of the amino acid sequence CPGSP for the SP between positions 779 and 780 of SEQ ID NO: 2; (m) an insertion of the amino acid C between positions V777 and G778 of SEQ ID NO: 2; (n) a substitution of the amino acid sequence VVMA for the AG between positions 775 and 776 of SEQ ID NO: 2; (o) a substitution of the amino acid sequence VV for the G at position 776 of SEQ ID NO: 2; (p) a substitution of the amino acid sequence AVCV for the GV between positions 776 and 777 of SEQ ID NO: 2; (q) a substitution of the amino acid sequence VCV for the GV between positions 776 and 777 of SEQ ID NO: 2; (r) an insertion of the amino acid G between positions G778 and S779 of SEQ ID NO: 2; (s) a substitution of the amino acid sequence PK for the LRE between positions 755 and 757 of SEQ ID NO: 2; (t) an insertion of the amino acid V between positions A775 and G776 of SEQ ID NO: 2; (u) an insertion of the amino acid sequenceYAMA between positions A775 and G776 of SEQ ID NO: 2; (v) a substitution of the amino acid sequence CV for the G at position 776 of SEQ ID NO: 2; (w) a substitution of the amino acid sequence AVCGG for the GVG between positions 776 and 778 of SEQ ID NO: 2; (x) a substitution of the amino acid sequence CVCG for the GVG between positions 776 and 778 of SEQ ID NO: 2; (y) a substitution of the amino acid sequence VVVG for the GVG between positions 776 and 778 of SEQ ID NO: 2; (z) a substitution of the amino acid sequence SVGG for the GVGS between positions 776 and 779 of SEQ ID NO: 2; (aa) a substitution of the amino acid sequence VVGES for the GVGS between positions 776 and 779 of SEQ ID NO: 2; (bb) a substitution of the amino acid sequence AVGSGV for the GV between positions 776 and 777 of SEQ ID NO: 2; (cc) a substitution of the amino acid sequence CVC for the GV between positions 776 and 777 of SEQ ID NO: 2; (dd) a substitution of the amino acid sequence HVC for the GV between positions 776 and 777 of SEQ ID NO: 2; (ee) a substitution of the amino acid sequence VAAGV for the GV between positions 776 and 777 of SEQ ID NO: 2; (ff) a substitution of the amino acid sequence VAGV for the GV between positions 776 and 777 of SEQ ID NO: 2; (gg) a substitution of the amino acid sequence VVV for the GV between positions 776 and 777 of SEQ ID NO: 2; (hh) an insertion of the amino acid sequence FPG between positions G778 and S779 of SEQ ID NO: 2; (ii) an insertion of the amino acid sequence GS

between positions S779 and P780 of SEQ ID NO: 2; (jj) a substitution of the amino acid sequence VPS for the VLRE between positions 754 and 757 of SEQ ID NO: 2; (kk) an insertion of the amino acid E between positions V777 and G778 of SEQ ID NO: 2; (ll) an insertion of the amino acid sequence MAGV between positions V777 and G778 of SEQ ID NO: 2; (mm) an insertion of the amino acid S between positions V777 and G778 of SEQ ID NO: 2; (nn) an insertion of the amino acid sequence SCV between positions V777 and G778 of SEQ ID NO: 2; and (oo) an insertion of the amino acid sequence LMAY between positions Y772 and V773 of SEQ ID NO: 2.

[0196] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER2 receptor and wherein the oncogenic variant of a HER2 receptor is an allosteric variant of the HER2 receptor, the oncogenic variant of a HER2 receptor comprises HER2-Δ16, HER2-C311R, HER2-S310F, p95-HER2-M611 or any combination thereof.

[0197] In some embodiments, the oncogenic variant of HER2 comprises an insertion within exon 20, wherein the insertion comprises the amino acid sequence of GSP or YVMA.

[0198] In some embodiments, the oncogenic variant of HER2 comprises an insertion in exon 20, wherein the insertion in exon 20 is selected from the group of insertions recited in Table 4.

Table 4. HER2 Exon 20 insertions (numbering corresponding to SEQ ID NO: 2)

Insertion Description
an insertion of the amino acid sequence YVMA between positions A775 and G776 (A775_G776insYVMA; Y772_A775dup)
an insertion of the amino acid sequence YVMD between positions A775 and G776 (A775_G776insYVMD)
an insertion of the amino acid sequence SVMA between positions A775 and G776 (A775_G776insSVMA)
an insertion of the amino acid sequence GSP between positions P780 and Y781 (P780_Y781insGSP; G778_P780dup)
an insertion of the amino acid sequence YVMA between positions A771 and Y772 (A771_Y772insYVMA; Y772_A775dup)
an insertion of the amino acid V between positions V777 and G778 (V777_G778insV; V777dup)
an insertion of the amino acid sequence GSP between positions V777 and G778 (V777_G778insGSP; G778_P780dup)
an insertion of the amino acid C between positions V777 and G778 (V777_G778insC)
an insertion of the amino acid G between positions G778 and S779 (G778_S779insG; G778dup)
an insertion of the amino acid V between positions A775 and G776 (A775_G776insV)

an insertion of the amino acid sequence VVMA between positions A775 and G776 (A775_G776insVVMA)
an insertion of the amino acid sequence YAMA between positions A775 and G776(A775_G776insYAMA)
an insertion of the amino acid sequence FPG between positions G778 and S779
an insertion of the amino acid sequence CPG between positions G778 and S779 (G778_S779insCPG)
an insertion of the amino acid sequence GS between positions S779 and P780
an insertion of the amino acid E between positions V777 and G778
an insertion of the amino acid sequence MAGV between positions V777 and G778
an insertion of the amino acid S between positions V777 and G778
an insertion of the amino acid sequence SCV between positions V777 and G778
an insertion of the amino acid sequence LMAY between positions Y772 and V773
an insertion of the amino acid sequence VC at position G776 (G776insVC)

[0199] In some embodiments, the oncogenic variant of HER2 comprises a substitution within exon 20 of HER2.

[0200] In some embodiments, the oncogenic variant of EGFR comprises a substitution in exon 20, wherein the substitution in exon 20 is selected from the group of substitutions recited in Table 5.

Table 5. HER2 Exon 20 substitutions (numbering corresponding to SEQ ID NO: 2)

Substitution Description
a substitution of the amino acid sequence AVGCV for the GV between positions 776 and 777
a substitution of the amino acid sequence LC for the G at position 776 (G776delinsLC)
a substitution of the amino acid sequence VC for the G at position 776 (G776delinsVC)
a substitution of the amino acid sequence LCV for the G at position 776
a substitution of the amino acid sequence PS for the LRE between positions 755 and 757
a substitution of the amino acid sequence CPGSP for the SP between positions 779 and 780
a substitution of the amino acid sequence VVMA for the AG between positions 775 and 776
a substitution of the amino acid sequence VV for the G at position 776
a substitution of the amino acid sequence AVCV for the GV between positions 776 and 777 (G776_V777 > AVCV; G776_V777delinsAVCV)
a substitution of the amino acid sequence AVGCV for the GV between positions 776 and 777 (G776_V777 > AVGCV; G776_V777delinsAVGC)
a substitution of the amino acid sequence LCV for the GV between positions 776 and 777 (G776_V777 > LCV; G776_V777delinsLCV)
a substitution of the amino acid sequence VCV for the GV between positions 776 and 777
a substitution of the amino acid sequence PK for the LRE between positions 755 and 757
a substitution of the amino acid sequence CV for the G at position 776

a substitution of the amino acid sequence AVCGG for the GVG between positions 776 and 778
a substitution of the amino acid sequence CVCG for the GVG between positions 776 and 778
a substitution of the amino acid sequence VVVG for the GVG between positions 776 and 778
a substitution of the amino acid sequence SVGG for the GVGS between positions 776 and 779
a substitution of the amino acid sequence VVGES for the GVGS between positions 776 and 779
a substitution of the amino acid sequence AVGSGV for the GV between positions 776 and 777
a substitution of the amino acid sequence CVC for the GV between positions 776 and 777
a substitution of the amino acid sequence HVC for the GV between positions 776 and 777
a substitution of the amino acid sequence VAAGV for the GV between positions 776 and 777
a substitution of the amino acid sequence VAGV for the GV between positions 776 and 777
a substitution of the amino acid sequence VVV for the GV between positions 776 and 777
a substitution of the amino acid sequence VPS for the VLRE between positions 754 and 757

[0201] In some embodiments, the oncogenic variant of HER2 is any of the HER2 variants put forth in Table 6.

Table 6. HER2 Oncogenic Variants

HER2-S310F	HER2-G58R	HER2-V659E
HER2-S310Y	HER2-R103Q	HER2-G660D
HER2-R678Q	HER2-P122L	HER2-Q709L
HER2-V777L	HER2-V219I	HER2-T733I
HER2-V777M	HER2-G292C	HER2-D769H
HER2-V842I	HER2-G292R	HER2-D769Y
HER2-L755A	HER2-A293T	HER2-G776A
HER2-L755P	HER2-R434Q	HER2-G776V
HER2-L755S	HER2-A510T	HER2-V773M
HER2-Δ16	HER2-A588V	HER2-T862A
HER2-C311R	HER2-G603C	HER2-L869R
p95-HER2-M611	HER2-E645K	HER2-H878Y
HER2-A232V	HER2-G229R	HER2-A516T
HER2-E717V	HER2-R1230Q	

[0202] In some embodiments, the cancer, or a tumor or cell thereof, expresses an oncogenic variant of a HER3 receptor. In some embodiments, the oncogenic variant of HER3 is any of the variants put forth in Table 7.

Table 7. HER3 Oncogenic Variants

HER3-V104M
HER3-A232V
HER3-G284R
HER3-D297Y
HER3-E928G

[0203] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a HER4 receptor. In some embodiments, the oncogenic variant of the HER4 receptor is an allosteric variant of the HER4 receptor. In some embodiments, the oncogenic variant of a HER4 receptor comprises deletion of exon 16 (HER4-Δ16).

[0204] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an EGFR, wherein the sequence encoding the oncogenic variant of the EGFR comprises a deletion of exon 20 or a portion thereof and wherein the the cancer, the tumor or the cell thereof does not comprise a second oncogenic variation in a sequence other than exon 20 of EGFR. In some embodiments, the second oncogenic variation comprises a sequence encoding one or more of an EGFR kinase domain (KD), BRAF, NTRK, and KRAS.

[0205] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of an EGFR, wherein the sequence encoding the oncogenic variant of the EGFR comprises a deletion of exon 20 or a portion thereof and wherein the the cancer, the tumor or the cell thereof does not comprise a marker indicating responsiveness to immunotherapy.

[0206] In some embodiments, the oncogenic variant (e.g., allosteric variant) or the oncogenic mutation (e.g., allosteric mutation) is detected by a Food and Drug Aministration (FDA)-approved diagnosis.

[0207] In some embodiments, the cancer, or a tumor or a cell thereof, expresses an oncogenic variant of a phosphatidylinositol-3-kinase (PI3K). In some embodiments, the cancer, or a tumor or cell thereof, expresses a mutant form of a PI3K, wherein the mutant form of the PI3K differs from the wildtype sequence of the PI3K. In some embodiments, the cancer is is glioblastoma, and the cancer, or a tumor or cell thereof, expresses an oncogenic variant of a PI3K. In some embodiments, the cancer is is glioblastoma, and the cancer, or a tumor or cell thereof, expresses a mutant form of a PI3K, wherein the mutant form of the PI3K differs from the wildtype sequence of the PI3K.

[0208] It is understood that an oncogenic variant of a PI3K is a PI3K protein that comprises at least one oncogenic mutation and that is produced as the result of the expression of a gene encoding the PI3K that comprises at least one oncogenic mutation.

[0209] As would be appreciated by the skilled artisan, in the context of a gene (*e.g.* a gene encoding a PI3K), an oncogenic mutation can include, but is not limited to a mutation that results in the substitution of one amino acid for another at a specific position within a PI3K, a mutation that results in an insertion of one or more amino acids between two positions within PI3K, a mutation that results in the deletion of one more amino acids between two positions within a PI3K, and a mutation that results in a fusion of a PI3K or portion thereof, with another protein, or portion thereof. As would be appreciated by the skilled artisan, in the context of a gene, an oncogenic mutation can include, but is not limited to, a missense mutation, a nonsynonymous mutation, an insertion of one or more nucleotides, a deletion of one or more nucleotides, an inversion and a deletion-insertion.

[0210] As would be appreciated by the skilled artisan, in the context of a protein (*e.g.* a PI3K), an oncogenic mutation can include, but is not limited to, the substitution of one amino acid for another at a specific position within a PI3K, an insertion of one or more amino acids between two positions within a PI3K, a deletion of one more amino acids between two positions within a PI3K, and a fusion of a PI3K, or portion thereof, with another protein, or portion thereof.

[0211] In some embodiments, the cancer, or a tumor or cell thereof, has an amplification of the *MET* gene, which encodes the receptor tyrosine kinase c-MET (also referred to as MET).

[0212] In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFRvIII. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFRvII. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFRvVI. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-R108K. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-R222C. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-C231F. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-A289T. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-A289V. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-C595S. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-G598V. In some aspects, the cancer is glioblastoma, and the cancer, or a tumor or cell thereof, expresses EGFR-S645C.

[0213] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof expresses

EGFR-C797S. some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof expresses EGFR-G719S. In some aspects, the cancer is advanced and/or metastatic NSCLC, and the cancer, or a tumor or cell thereof expresses EGFR-C797S. In some aspects, the cancer is advanced and/or metastatic NSCLC, and the cancer, or a tumor or cell thereof expresses EGFR-G719S. In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-C797S, wherein the cancer, or a tumor or cell thereof, is insensitive or resistant to treatment with a therapeutic agent different from the compound of the present disclosure (e.g., osimertinib or lazertinib). In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-C797S as a resistance mechanism, wherein the cancer, or a tumor or cell thereof, is insensitive or resistant to treatment with a therapeutic agent different from the compound of the present disclosure (e.g., osimertinib or lazertinib).

[0214] In some aspects, a deletion of exon 19 can comprise a deletion of E746-A750 (EGFR-E746-A750del).

[0215] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses an oncogenic variant of EGFR comprising a deletion of exon 19. In some aspects, the deletion of exon 19 is a deletion of E746-A750 (EGFR-E746-A750del).

[0216] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses an oncogenic variant of EGFR comprising a deletion of exon 19 + C797S. In some aspects, the deletion of exon 19 is a deletion of E746-A750 (EGFR-E746-A750del).

[0217] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses an oncogenic variant of EGFR comprising a deletion of exon 19 + C797S, wherein the cancer, or a tumor or cell thereof, is insensitive or resistant to treatment with a therapeutic agent different from the compound of the present disclosure (e.g., osimertinib or lazertinib). In some aspects, the deletion of exon 19 is a deletion of E746-A750 (EGFR-E746-A750del).In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-L858R.

[0218] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-C797S+L858R.

[0219] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-C797S+L858R, wherein the cancer, or a tumor or cell thereof, is insensitive or resistant to treatment with a therapeutic agent different from the compound of the present disclosure (e.g., osimertinib or lazertinib).

[0220] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expreses an oncogenic variant of EGFR comprising an oncogenic mutation in Exon 18.

[0221] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, or EGFR-G719S.

[0222] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, EGFR-G719S, EGFR-S768I, EGFR-V769L, EGFR-E709G, EGFR-E709A, EGFR-D716Y or any combination thereof.

[0223] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-S768I.

[0224] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, expresses EGFR-L861Q.

[0225] In some aspects, the cancer is NSCLC, and the cancer, or a tumor or cell thereof, has an amplification of the *MET* gene.

[0226] In some embodiments, prior to the treatment with the compound of the present disclosure, the subject has not undergone any surgery for treating the cancer.

[0227] In some embodiments, prior to the treatment with the compound of the present disclosure, the subject has undergone one or more surgeries for treating the cancer.

[0228] In some embodiments, prior to the treatment with the compound of the present disclosure, the subject has received at least one chemoradiotherapy.

[0229] In some embodiments, the subject has recurrent GBM and has previously undergone one or more surgeries and have received at least one chemoradiotherapy.

[0230] In some embodiments, prior to the treatment with the compound of the present disclosure, the subject is treated with a therapeutic agent different from the compound of the present disclosure.

[0231] In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with a third-generation EGFR inhibitor.

[0232] In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with an EGFR inhibitor different from a compound of the present disclsoure.

[0233] A non-exhaustive and non-limiting list of third-generation EGFR inhibitors consists of afatinib, avitinib, dacomitinib, erlotinib, gefitinib, lazertinib, mavelertinib, naquotinib, nazartinib, olmutinib, osimertinib, and rociletinib.

[0234] In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with one or more of afatinib, avitinib, dacomitinib, erlotinib, gefitinib, lazertinib, mavelertinib, naquotinib, nazartinib, olmutinib, osimertinib, and rociletinib.

[0235] In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with osimertinib or lazertinib.

[0236] In some embodiments, the cancer is NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor. In some embodiments, the cancer is NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor in combination with a platinum containing chemotherapy.

[0237] In some embodiments, the cancer is NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor, and wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR. In some embodiments, the cancer is NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor in combination with a platinum containing chemotherapy, and wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR. In some embodiments, the oncogenic variant of EGFR can be EGFR-C797S, EGFR-L861Q, EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, EGFR-G719S, EGFR-S768I or EGFR-V769L.

[0238] In some embodiments, the cancer is advanced and/or metastatic NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor. In some embodiments, the cancer is advanced and/or metastatic NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor in combination with a platinum containing chemotherapy.

[0239] In some embodiments, the cancer is advanced and/or metastatic NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor, and wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR. In some embodiments, the cancer is advanced and/or metastatic NSCLC and is insensitive or resistant to treatment with a third-generation EGFR inhibitor in combination with a platinum containing chemotherapy, and wherein the cancer, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR. In some embodiments, the oncogenic variant of EGFR can be EGFR-C797S, EGFR-L861Q, EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, EGFR-G719S, EGFR-S768I or EGFR-V769L.

[0240] In some embodiments, the cancer is NSCLC and is insensitive or resistant to treatment with

one or more of afatinib, avitinib, dacomitinib, erlotinib, gefitinib, lazertinib, mavelertinib, naquotinib, nazartinib, olmutinib, osimertinib, and rociletinib.

[0241] In some embodiments, the cancer is NSCLC and is insensitive or resistant to treatment with osimertinib or lazertinib.

[0242] In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with a therapeutic agent different from the compound of the present disclosure. In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with a Type I inhibitor. In some embodiments, the cancer, or a tumor or a cell thereof, is insensitive or resistant to treatment with one or more of gefinitinib, erlotinib, afatinib, osimertinib, necitunumab, crizotinib, alectinib, ceritinib, dabrafenib, trametinib, afatinib, sapitinib, dacomitinib, canertinib, pelitinib, WZ4002, WZ8040, WZ3146, CO-1686 and AZD9291.

[0243] In some embodiments, the subject has an adverse reaction to treatment with a therapeutic agent different from the compound of the present disclosure. In some embodiments, the subject has an adverse reaction to treatment with a Type I inhibitor. In some embodiments, the subject has an adverse reaction to treatment with one or more of gefinitinib, erlotinib, afatinib, osimertinib, necitunumab, crizotinib, alectinib, ceritinib, dabrafenib, trametinib, afatinib, sapitinib, dacomitinib, canertinib, pelitinib, WZ4002, WZ8040, WZ3146, CO-1686 and AZD9291. In some embodiments, the adverse reaction is an activation of the oncogenic variant of an EGFR and wherein the oncogenic variant comprises a mutation in an extracellular domain of the receptor. In some embodiments, the adverse reaction is an activation of the oncogenic variant of a HER2 Receptor and wherein the oncogenic variant comprises a mutation in an extracellular domain of the receptor.

[0244] In some embodiments, the subject has been previously administered at least one initial therapy that is different from a compound of the present disclosure, and the subject has experienced disease progression despite the administration of said at least one initial therapy, wherein the initial therapy comprises the administration of at least one EGFR inhibitor different from a compound of the present disclosure, at least one platinum containing chemotherapy, at least one anti-PD-L1 therapy or any combination thereof.

[0245] In some embodiments, the subject can have NSCLC and the subject has been previously administered at least one initial therapy that is different from a compound of the present disclosure for the treatment of said NSCLC, and the subject has experienced disease progression despite the

administration of said at least one initial therapy, wherein the initial therapy comprises the administration of at least one EGFR inhibitor different from a compound of the present disclosure, at least one platinum containing chemotherapy, at least one anti-PD-L1 therapy or any combination thereof.

[0246] In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the subject has been previously administered at least one EGFR inhibitor different from a compound of the present disclosure in combination with at least one platinum containing chemotherapy. In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the subject has been previously administered at least one EGFR inhibitor different from a compound of the present disclosure in combination with at least one platinum containing chemotherapy and at least one anti-PD-L1 therapy. In some embodiments, the at least one EGFR inhibitor can be Osimertinib. In some aspects, the at least one oncogenic variant of EGFR can be EGFR-Δ19, EGFR-L858R, EGFR-L861Q, EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, EGFR-G719S, EGFR-S768I, EGFR-V769L or EGFR-C797S.

[0247] In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the subject has been previously administered at least one EGFR inhibitor different from a compound of the present disclosure in combination with at least one platinum containing chemotherapy. In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the subject has been previously administered at least one EGFR inhibitor different from a compound of the present disclosure in combination with at least one platinum containing chemotherapy and at least one anti-PD-L1 therapy. In some embodiments, the at least one EGFR inhibitor can be Osimertinib. In some aspects, the at least one oncogenic variant of EGFR can be EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, EGFR-G719S, EGFR-S768I, EGFR-V769L, EGFR-E709G, EGFR-E709A or EGFR-D716Y. In some embodiments, the NSCLC can have metastasized to the CNS. In some embodiments, the NSCLC can have not metastasized to the CNS.

[0248] In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the

NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, wherein the at least one oncogenic variant of EGFR is EGFR-C797S, and wherein the subject has been previously administered at least one EGFR inhibitor different from a compound of the present disclosure in combination with at least one platinum containing chemotherapy. In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, wherein the at least one oncogenic variant of EGFR is EGFR-C797S, and wherein the subject has been previously administered at least one EGFR inhibitor different from a compound of the present disclosure in combination with at least one platinum containing chemotherapy and at least one anti-PD-L1 therapy. In some embodiments, the at least one EGFR inhibitor can be Osimertinib. In some embodiments, the NSCLC can have metastasized to the CNS. In some embodiments, the NSCLC can have not metastasized to the CNS.

[0249] In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the subject has been previously administered at least one platinum containing chemotherapy. In some embodiments, the subject has advanced and/or metastatic NSCLC, wherein the NSCLC, or a tumor or cell thereof, expresses at least one oncogenic variant of EGFR, and wherein the subject has been previously administered at least one platinum containing chemotherapy in combination with at least one anti-PD-L1 therapy. In some embodiments, the at least one oncogenic variant of EGFR can be EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-G719A, or EGFR-G719S. In some embodiments, the NSCLC can have metastasized to the CNS. In some embodiments, the NSCLC can have not metastasized to the CNS.

[0250] Non-limiting examples of anti-PD-L1 therapy can include, but are not limited to, anti-PD-L1 antibodies known in the art (*e.g.* atezolizumab, avelumab, and durvalumab).

[0251] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of a non-Type I inhibitor. In some embodiments, the non-Type I inhibitor comprises a small molecule Type II inhibitor.

[0252] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of a non-Type I inhibitor. In some embodiments, the non-Type I inhibitor comprises a small molecule Type II inhibitor.

[0253] In some embodiments, the compound is used in combination with a therapeutically

effective amount of a non-Type I inhibitor. In some embodiments, the non-Type I inhibitor comprises a small molecule Type II inhibitor.

[0254] In some embodiments, the composition further comprises a non-Type I inhibitor. In some embodiments, the non-Type I inhibitor comprises a small molecule Type II inhibitor.

[0255] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of temozolomide.

[0256] In some embodiments, the compound is administered in combination with a therapeutically effective amount of temozolomide.

[0257] In some embodiments, the composition further comprises temozolomide.

[0258] In some embodiments, the compound is administered in combination with a therapeutically effective amount of a phosphatidylinositol-3-kinase (PI3K) inhibitor.

[0259] In some embodiments, the compound is administered in combination with a therapeutically effective amount of a phosphatidylinositol-3-kinase (PI3K) inhibitor.

[0260] In some embodiments, the composition further comprises a phosphatidylinositol-3-kinase (PI3K) inhibitor.

[0261] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of amivantamab, capmatinib, or a combination thereof.

[0262] In some embodiments, the compound is administered in combination with a therapeutically effective amount of amivantamab, capmatinib, or a combination thereof.

[0263] In some embodiments, the composition further comprises amivantamab, capmatinib, or a combination thereof.

[0264] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of osimertinib.

[0265] In some embodiments, the compound is administered in combination with a therapeutically effective amount of osimertinib.

[0266] In some embodiments, the composition further comprises osimertinib.

[0267] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of alpelisib.

[0268] In some embodiments, the compound is administered in combination with a therapeutically effective amount of alpelisib.

[0269] In some embodiments, the composition further comprises alpelisib.

[0270] In some embodiments, the method further comprises administering to the subject in need thereof a therapeutically effective amount of paxalisib.

[0271] In some embodiments, the compound is administered in combination with a therapeutically effective amount of paxalisib.

[0272] In some embodiments, the composition further comprises paxalisib.

[0273] In some embodiments, the therapeutically effective amount reduces a severity of a sign or symptom of the cancer.

[0274] In some embodiments, the sign of the cancer comprises a tumor grade and wherein a reduction of the severity of the sign comprises a decrease of the tumor grade.

[0275] In some embodiments, the sign of the cancer comprises a tumor metastasis and wherein a reduction of the severity of the sign comprises an elimination of the metastasis or a reduction in the rate or extent the metastasis.

[0276] In some embodiments, the sign of the cancer comprises a tumor volume and wherein a reduction of the severity of the sign comprises an elimination of the tumor or a reduction in the volume.

[0277] In some embodiments, the symptom of the cancer comprises pain and wherein a reduction of the severity of the sign comprises an elimination or a reduction in the pain.

[0278] In some embodiments, the therapeutically effective amount induces a period of remission.

[0279] In some embodiments, the therapeutically effective amount improves a prognosis of the subject.

[0280] Such a use (or method of prevention or treatment) of a subject comprises administering to a subject in need of such prevention or treatment a therapeutically effective amount of a compound of the disclosure or pharmaceutically acceptable salts thereof or a pharmaceutical composition thereof by targeting allosteric and/or oncogenic variants of EGFR and HER2 receptor.

Administration of Compound No. 1

[0281] In some embodiments, the subject is a human.

[0282] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is orally administered.

[0283] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage)

of:

about 15±10 mg, about 15±5 mg, about 15±4 mg, about 15±3 mg, about 15±2 mg, or about 15±1 mg (e.g., about 15 mg);

about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg);

about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg);

about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg);

about 150±20 mg, about 150±10 mg, about 150±5 mg, about 150±4 mg, about 150±3 mg, about 150±2 mg, or about 150±1 mg (e.g., about 150 mg);about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg);

about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg);

about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg);

about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg);

about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg);

about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg); or

about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

[0284] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B)

or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 15±10 mg, about 15±5 mg, about 15±4 mg, about 15±3 mg, about 15±2 mg, or about 15±1 mg (e.g., about 15 mg).

[0285] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg).

[0286] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg).

[0287] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg).

[0288] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 150±20 mg, about 150±10 mg, about 150±5 mg, about 150±4 mg, about 150±3 mg, about 150±2 mg, or about 150±1 mg (e.g., about 150 mg).

[0289] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg).

[0290] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg).

[0291] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g.,

about 400 mg).

[0292] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg).

[0293] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg).

[0294] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg).

[0295] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

[0296] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of:

about 60±10 mg/kg, about 60±5 mg/kg, about 60±4 mg/kg, about 60±3 mg/kg, about 60±2 mg/kg, or about 60±1 mg/kg (e.g., about 60 mg/kg);

about 180±20 mg/kg, about 180±10 mg/kg, about 180±5 mg/kg, about 180±4 mg/kg, about 180±3 mg/kg, about 180±2 mg/kg, or about 180±1 mg/kg (e.g., about 180 mg/kg);

about 600±50 mg/kg, about 600±40 mg/kg, about 600±30 mg/kg, about 600±20 mg/kg, about 600±10 mg/kg, about 600±5 mg/kg, about 600±4 mg/kg, about 600±3 mg/kg, about 600±2 mg/kg, or about 600±1 mg/kg (e.g., about 600 mg/kg); or

about 1800±50 mg/kg, about 1800±40 mg/kg, about 1800±30 mg/kg, about 1800±20 mg/kg, about 1800±10 mg/kg, about 1800±5 mg/kg, about 1800±4 mg/kg, about 1800±3 mg/kg, about 1800±2 mg/kg, or about 1800±1 mg/kg (e.g., about 1800 mg/kg).

[0297] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 60±10 mg/kg, about 60±5 mg/kg, about 60±4 mg/kg, about 60±3 mg/kg, about 60±2 mg/kg, or about 60±1 mg/kg (e.g., about 60 mg/kg).

[0298] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 180±20 mg/kg, about 180±10 mg/kg, about 180±5 mg/kg, about 180±4 mg/kg, about 180±3 mg/kg, about 180±2 mg/kg, or about 180±1 mg/kg (e.g., about 180 mg/kg).

[0299] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 600±50 mg/kg, about 600±40 mg/kg, about 600±30 mg/kg, about 600±20 mg/kg, about 600±10 mg/kg, about 600±5 mg/kg, about 600±4 mg/kg, about 600±3 mg/kg, about 600±2 mg/kg, or about 600±1 mg/kg (e.g., about 600 mg/kg).

[0300] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 1800±50 mg/kg, about 1800±40 mg/kg, about 1800±30 mg/kg, about 1800±20 mg/kg, about 1800±10 mg/kg, about 1800±5 mg/kg, about 1800±4 mg/kg, about 1800±3 mg/kg, about 1800±2 mg/kg, or about 1800±1 mg/kg (e.g., about 1800 mg/kg).

[0301] In some embodiments, the subject is a mouse.

[0302] In some embodiments, the subject is a rat.

[0303] In some embodiments, the subject is a dog.

[0304] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of:

about 1±3 mg/kg, about 1±2 mg/kg, about 1±1 mg/kg, or about 1±0.1 mg/kg (e.g., about 1 mg/kg);

about 5±3 mg/kg, about 5±2 mg/kg, or about 5±1 mg/kg (e.g., about 5 mg/kg);

about 15±5 mg/kg, about 15±4 mg/kg, about 15±3 mg/kg, about 15±2 mg/kg, or about

15±1 mg/kg (e.g., about 15 mg/kg);

about 30±10 mg/kg, about 30±5 mg/kg, about 30±4 mg/kg, about 30±3 mg/kg, about 30±2 mg/kg, or about 30±1 mg/kg (e.g., about 30 mg/kg);

about 50±10 mg/kg, about 50±5 mg/kg, about 50±4 mg/kg, about 50±3 mg/kg, about 50±2 mg/kg, or about 50±1 mg/kg (e.g., about 50 mg/kg); or

about 150±20 mg/kg, about 150±10 mg/kg, about 150±5 mg/kg, about 150±4 mg/kg, about 150±3 mg/kg, about 150±2 mg/kg, or about 150±1 mg/kg (e.g., about 150 mg/kg).

[0305] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 1±3 mg/kg, about 1±2 mg/kg, about 1±1 mg/kg, or about 1±0.1 mg/kg (e.g., about 1 mg/kg).

[0306] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 5±3 mg/kg, about 5±2 mg/kg, or about 5±1 mg/kg (e.g., about 5 mg/kg).

[0307] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 15±5 mg/kg, about 15±4 mg/kg, about 15±3 mg/kg, about 15±2 mg/kg, or about 15±1 mg/kg (e.g., about 15 mg/kg).

[0308] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 30±10 mg/kg, about 30±5 mg/kg, about 30±4 mg/kg, about 30±3 mg/kg, about 30±2 mg/kg, or about 30±1 mg/kg (e.g., about 30 mg/kg).

[0309] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 50±10 mg/kg, about 50±5 mg/kg, about 50±4 mg/kg, about 50±3 mg/kg, about 50±2 mg/kg, or about 50±1 mg/kg (e.g., about 50 mg/kg).

[0310] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 150±20 mg/kg, about 150±10 mg/kg, about 150±5 mg/kg, about 150±4 mg/kg, about 150±3 mg/kg, about 150±2 mg/kg, or about 150±1 mg/kg (e.g., about 150 mg/kg).

[0311] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered with one or more drug holidays.

[0312] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered without any drug holiday.

[0313] In some embodiments, prior to the administration, the subject is fasted for at least about 30 minutes, at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours, or at least about 12 hours.

[0314] In some embodiments, prior to the administration, the subject is fed with about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours.

Administration Lengths and Frequencies

[0315] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered once daily.

[0316] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered twice daily.

[0317] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered for about 21 days, about 42 days, about 63 days, about 84 days, about 105 days, about 126 days, about 147 days, about 168 days, about 189 days, or about 210 days.

[0318] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered for longer than 210 days.

[0319] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered until a progression of cancer or an adverse effect (e.g., an intolerable toxicity) is observed.

[0320] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered for about 21 days.

[0321] In some embodiments, Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof is administered for about 21 days, followed by a 30-day drug holiday.

[0322] In some embodiments, the treatment lasts about 1 month, about 2 months, about 3 months, about 6 months, about 9 months, about 12 months, about 15 months, about 18 months, about 21

months, or about 24 months.

[0323] In some embodiments, the treatment comprises one or more treatment cycles, wherein each treatment cycle comprises administering Compound No. 1 (e.g., Compound No. 1A or Compound No. 1B) or the pharmaceutically acceptable salt thereof for about 21 days, followed by a 30-day drug holiday.

Administrations of Compound No. 2

[0324] In some embodiments, the subject is a human.

[0325] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is orally administered.

[0326] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of:

about 15±10 mg, about 15±5 mg, about 15±4 mg, about 15±3 mg, about 15±2 mg, or about 15±1 mg (e.g., about 15 mg);

about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg);

about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg);

about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg);

about 150±20 mg, about 150±10 mg, about 150±5 mg, about 150±4 mg, about 150±3 mg, about 150±2 mg, or about 150±1 mg (e.g., about 150 mg);

about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg);

about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg);

about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg);

about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10

mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg);

about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg);

about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg); or

about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

[0327] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 15±10 mg, about 15±5 mg, about 15±4 mg, about 15±3 mg, about 15±2 mg, or about 15±1 mg (e.g., about 15 mg).

[0328] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg).

[0329] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg).

[0330] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg).

[0331] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 150±20 mg, about 150±10 mg, about 150±5 mg, about 150±4 mg, about 150±3 mg, about 150±2 mg, or about 150±1 mg (e.g., about 150 mg).

[0332] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg).

[0333] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg).

[0334] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg).

[0335] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg).

[0336] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg).

[0337] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg).

[0338] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10

mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

[0339] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of:

about 60±10 mg/kg, about 60±5 mg/kg, about 60±4 mg/kg, about 60±3 mg/kg, about 60±2 mg/kg, or about 60±1 mg/kg (e.g., about 60 mg/kg);

about 180±20 mg/kg, about 180±10 mg/kg, about 180±5 mg/kg, about 180±4 mg/kg, about 180±3 mg/kg, about 180±2 mg/kg, or about 180±1 mg/kg (e.g., about 180 mg/kg);

about 600±50 mg/kg, about 600±40 mg/kg, about 600±30 mg/kg, about 600±20 mg/kg, about 600±10 mg/kg, about 600±5 mg/kg, about 600±4 mg/kg, about 600±3 mg/kg, about 600±2 mg/kg, or about 600±1 mg/kg (e.g., about 600 mg/kg); or

about 1800±50 mg/kg, about 1800±40 mg/kg, about 1800±30 mg/kg, about 1800±20 mg/kg, about 1800±10 mg/kg, about 1800±5 mg/kg, about 1800±4 mg/kg, about 1800±3 mg/kg, about 1800±2 mg/kg, or about 1800±1 mg/kg (e.g., about 1800 mg/kg).

[0340] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 60±10 mg/kg, about 60±5 mg/kg, about 60±4 mg/kg, about 60±3 mg/kg, about 60±2 mg/kg, or about 60±1 mg/kg (e.g., about 60 mg/kg).

[0341] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 180±20 mg/kg, about 180±10 mg/kg, about 180±5 mg/kg, about 180±4 mg/kg, about 180±3 mg/kg, about 180±2 mg/kg, or about 180±1 mg/kg (e.g., about 180 mg/kg).

[0342] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 600±50 mg/kg, about 600±40 mg/kg, about 600±30 mg/kg, about 600±20 mg/kg, about 600±10 mg/kg, about 600±5 mg/kg, about 600±4 mg/kg, about 600±3 mg/kg, about 600±2 mg/kg, or about 600±1 mg/kg (e.g., about 600 mg/kg).

[0343] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 1800±50 mg/kg, about 1800±40 mg/kg, about 1800±30 mg/kg, about 1800±20 mg/kg, about

1800±10 mg/kg, about 1800±5 mg/kg, about 1800±4 mg/kg, about 1800±3 mg/kg, about 1800±2 mg/kg, or about 1800±1 mg/kg (e.g., about 1800 mg/kg).

[0344] In some embodiments, the subject is a mouse.

[0345] In some embodiments, the subject is a rat.

[0346] In some embodiments, the subject is a dog.

[0347] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of:

about 1±3 mg/kg, about 1±2 mg/kg, about 1±1 mg/kg, or about 1±0.1 mg/kg (e.g., about 1 mg/kg);

about 5±3 mg/kg, about 5±2 mg/kg, or about 5±1 mg/kg (e.g., about 5 mg/kg);

about 15±5 mg/kg, about 15±4 mg/kg, about 15±3 mg/kg, about 15±2 mg/kg, or about 15±1 mg/kg (e.g., about 15 mg/kg);

about 30±10 mg/kg, about 30±5 mg/kg, about 30±4 mg/kg, about 30±3 mg/kg, about 30±2 mg/kg, or about 30±1 mg/kg (e.g., about 30 mg/kg);

about 50±10 mg/kg, about 50±5 mg/kg, about 50±4 mg/kg, about 50±3 mg/kg, about 50±2 mg/kg, or about 50±1 mg/kg (e.g., about 50 mg/kg); or

about 150±20 mg/kg, about 150±10 mg/kg, about 150±5 mg/kg, about 150±4 mg/kg, about 150±3 mg/kg, about 150±2 mg/kg, or about 150±1 mg/kg (e.g., about 150 mg/kg).

[0348] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 1±3 mg/kg, about 1±2 mg/kg, about 1±1 mg/kg, or about 1±0.1 mg/kg (e.g., about 1 mg/kg).

[0349] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 5±3 mg/kg, about 5±2 mg/kg, or about 5±1 mg/kg (e.g., about 5 mg/kg).

[0350] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 15±5 mg/kg, about 15±4 mg/kg, about 15±3 mg/kg, about 15±2 mg/kg, or about 15±1 mg/kg (e.g., about 15 mg/kg).

[0351] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of

about 30±10 mg/kg, about 30±5 mg/kg, about 30±4 mg/kg, about 30±3 mg/kg, about 30±2 mg/kg, or about 30±1 mg/kg (e.g., about 30 mg/kg).

[0352] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 50±10 mg/kg, about 50±5 mg/kg, about 50±4 mg/kg, about 50±3 mg/kg, about 50±2 mg/kg, or about 50±1 mg/kg (e.g., about 50 mg/kg).

[0353] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered at a dosage (e.g., a daily dosage) of about 150±20 mg/kg, about 150±10 mg/kg, about 150±5 mg/kg, about 150±4 mg/kg, about 150±3 mg/kg, about 150±2 mg/kg, or about 150±1 mg/kg (e.g., about 150 mg/kg).

[0354] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered with one or more drug holidays.

[0355] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered without any drug holiday.

[0356] In some embodiments, prior to the administration, the subject is fasted for at least about 30 minutes, at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, at least about 10 hours, at least about 11 hours, or at least about 12 hours.

[0357] In some embodiments, prior to the administration, the subject is fed with about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, or about 12 hours.

Administration Lengths and Frequencies

[0358] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered once daily.

[0359] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered twice daily.

[0360] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered for about 21 days, about 42 days, about 63 days, about 84 days, about 105 days, about 126 days, about 147 days, about 168 days, about 189 days, or about 210 days.

[0361] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered for longer than 210 days.

[0362] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered until a progression of cancer or an adverse effect (e.g., an intolerable toxicity) is observed.

[0363] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered for about 21 days.

[0364] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered for about 21 days, followed by a 30-day drug holiday.

[0365] In some embodiments, the ttreating or preventing lasts about 1 month, about 2 months, about 3 months, about 6 months, about 9 months, about 12 months, about 15 months, about 18 months, about 21 months, or about 24 months.

[0366] In some embodiments, the treating or preventing comprises one or more treatment cycles, wherein each treatment cycle comprises administering Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof for about 21 days, followed by a 30-day drug holiday.

Combination with Temozolomide (TMZ)

[0367] In some embodiments, the method further comprises administering a therapeutically effective amount of temozolomide.

[0368] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered in combination with a therapeutically effective amount of temozolomide.

[0369] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered simultaneously, sequentially, or in alternation.

[0370] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered simultaneously.

[0371] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B),

or the pharmaceutically acceptable salt thereof, and temozolomide are administered sequentially.

[0372] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered temporal proximity.

[0373] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered in alternation.

[0374] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered in separate formulations.

[0375] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered in a co-formulation.

[0376] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered about 28 days.

[0377] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B), or the pharmaceutically acceptable salt thereof, and temozolomide are administered about 28 days, about 56 days, about 84 days, about 112 days, about 140 days, about 168 days, about 196 days, about 224 days, about 252 days, or about 280 days.

[0378] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered for longer than 280 days.

[0379] In some embodiments, Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B) or the pharmaceutically acceptable salt thereof is administered until a progression of cancer or an adverse effect (e.g., an intolerable toxicity) is observed.

Exemplary Embodiments

Exemplary Embodiment No. 1. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof.

Exemplary Embodiment No. 2. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1 or a pharmaceutically acceptable salt thereof.

Exemplary Embodiment No. 3. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 2 or a pharmaceutically acceptable salt thereof.

Exemplary Embodiment No. 4. Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof for treating or preventing cancer in a subject in need thereof.

Exemplary Embodiment No. 5. Compound No. 1 or a pharmaceutically acceptable salt thereof for treating or preventing cancer in a subject in need thereof.

Exemplary Embodiment No. 6. Compound No. 2 or a pharmaceutically acceptable salt thereof for treating or preventing cancer in a subject in need thereof.

Exemplary Embodiment No. 7. Use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

Exemplary Embodiment No. 8. Use of Compound No. 1 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

Exemplary Embodiment No. 9. Use of Compound No. 2 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

Exemplary Embodiment No. 10. The method, compound, or use of any one of the preceding Embodiments, wherein the cancer is glioblastoma (GBM) or any subtype thereof.

Exemplary Embodiment No. 11. The method, compound, or use of any one of the preceding Embodiments, wherein the cancer is glioblastoma.

Exemplary Embodiment No. 12. The method, compound, or use of any one of the preceding Embodiments, wherein the cancer is non-small cell lung cancer (NSCLC) or any subtype thereof.

Exemplary Embodiment No. 13. The method, compound, or use of any one of the preceding Embodiments, wherein the cancer is non-small cell lung cancer (NSCLC).

Exemplary Embodiment No. 14. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 1A, Compound No. 1B, or the pharmaceutically acceptable salt thereof is administered.

Exemplary Embodiment No. 15. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 1A the pharmaceutically acceptable salt thereof is

administered.

Exemplary Embodiment No. 16. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 1B the pharmaceutically acceptable salt thereof is administered.

Exemplary Embodiment No. 17. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 2A, Compound No. 2B, or the pharmaceutically acceptable salt thereof is administered.

Exemplary Embodiment No. 18. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 2A the pharmaceutically acceptable salt thereof is administered.

Exemplary Embodiment No. 19. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 2B the pharmaceutically acceptable salt thereof is administered.

Exemplary Embodiment No. 20. The method, compound, or use of any one of the preceding Embodiments, wherein the subject is a human.

Exemplary Embodiment No. 21. The method, compound, or use of any one of the preceding Embodiments, wherein the subject is a mouse.

Exemplary Embodiment No. 22. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg);

about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg);

about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg);

about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg);

about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg);

about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10

mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg);

about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg);

about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg);

about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg); or

about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

Exemplary Embodiment No. 23. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 60±10 mg/kg, about 60±5 mg/kg, about 60±4 mg/kg, about 60±3 mg/kg, about 60±2 mg/kg, or about 60±1 mg/kg;

about 180±20 mg/kg, about 180±10 mg/kg, about 180±5 mg/kg, about 180±4 mg/kg, about 180±3 mg/kg, about 180±2 mg/kg, or about 180±1 mg/kg;

about 600±50 mg/kg, about 600±40 mg/kg, about 600±30 mg/kg, about 600±20 mg/kg, about 600±10 mg/kg, about 600±5 mg/kg, about 600±4 mg/kg, about 600±3 mg/kg, about 600±2 mg/kg, or about 600±1 mg/kg; or

about 1800±50 mg/kg, about 1800±40 mg/kg, about 1800±30 mg/kg, about 1800±20 mg/kg, about 1800±10 mg/kg, about 1800±5 mg/kg, about 1800±4 mg/kg, about 1800±3 mg/kg, about 1800±2 mg/kg, or about 1800±1 mg/kg.

Exemplary Embodiment No. 24. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 1 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 1±3 mg/kg, about 1±2 mg/kg, about 1±1 mg/kg, or about 1±0.1 mg/kg (e.g., about 1

mg/kg);

about 5±3 mg/kg, about 5±2 mg/kg, or about 5±1 mg/kg;

about 15±5 mg/kg, about 15±4 mg/kg, about 15±3 mg/kg, about 15±2 mg/kg, or about 15±1 mg/kg;

about 30±10 mg/kg, about 30±5 mg/kg, about 30±4 mg/kg, about 30±3 mg/kg, or about 30±2 mg/kg, or about 30±1 mg/kg (e.g., about 30 mg/kg);

about 50±10 mg/kg, about 50±5 mg/kg, about 50±4 mg/kg, about 50±3 mg/kg, about 50±2 mg/kg, or about 50±1 mg/kg; or

about 150±20 mg/kg, about 150±10 mg/kg, about 150±5 mg/kg, about 150±4 mg/kg, about 150±3 mg/kg, about 150±2 mg/kg, or about 150±1 mg/kg.

Exemplary Embodiment No. 25. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg);

about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg);

about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg);

about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg);

about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg);

about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg);

about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg);

about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg

(e.g., about 600 mg);

about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg); or

about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

Exemplary Embodiment No. 26. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 60±10 mg/kg, about 60±5 mg/kg, about 60±4 mg/kg, about 60±3 mg/kg, about 60±2 mg/kg, or about 60±1 mg/kg;

about 180±20 mg/kg, about 180±10 mg/kg, about 180±5 mg/kg, about 180±4 mg/kg, about 180±3 mg/kg, about 180±2 mg/kg, or about 180±1 mg/kg;

about 600±50 mg/kg, about 600±40 mg/kg, about 600±30 mg/kg, about 600±20 mg/kg, about 600±10 mg/kg, about 600±5 mg/kg, about 600±4 mg/kg, about 600±3 mg/kg, about 600±2 mg/kg, or about 600±1 mg/kg; or

about 1800±50 mg/kg, about 1800±40 mg/kg, about 1800±30 mg/kg, about 1800±20 mg/kg, about 1800±10 mg/kg, about 1800±5 mg/kg, about 1800±4 mg/kg, about 1800±3 mg/kg, about 1800±2 mg/kg, or about 1800±1 mg/kg.

Exemplary Embodiment No. 27. The method, compound, or use of any one of the preceding Embodiments, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 1±3 mg/kg, about 1±2 mg/kg, about 1±1 mg/kg, or about 1±0.1 mg/kg (e.g., about 1 mg/kg);

about 5±3 mg/kg, about 5±2 mg/kg, or about 5±1 mg/kg;

about 15±5 mg/kg, about 15±4 mg/kg, about 15±3 mg/kg, about 15±2 mg/kg, or about 15±1 mg/kg;

about 30±10 mg/kg, about 30±5 mg/kg, about 30±4 mg/kg, about 30±3 mg/kg, or about 30±2 mg/kg, or about 30±1 mg/kg (e.g., about 30 mg/kg);

about 50±10 mg/kg, about 50±5 mg/kg, about 50±4 mg/kg, about 50±3 mg/kg, about 50±2

mg/kg, or about 50±1 mg/kg; or

about 150±20 mg/kg, about 150±10 mg/kg, about 150±5 mg/kg, about 150±4 mg/kg, about 150±3 mg/kg, about 150±2 mg/kg, or about 150±1 mg/kg.

Exemplary Embodiment No. 28. The method of any one of the preceding Embodiments, further comprising administering to the subject in need thereof a therapeutically effective amount of temozolomide.

Exemplary Embodiment No. 29. The compound of any one of the preceding Embodiments, wherein the compound is used in combination with a therapeutically effective amount of temozolomide.

Exemplary Embodiment No. 30. The method of any one of the preceding Embodiments, further comprising administering to the subject in need thereof a therapeutically effective amount of a phosphatidylinositol-3-kinase (PI3K) inhibitor.

Exemplary Embodiment No. 31. The compound of any one of the preceding Embodiments, wherein the compound is used in combination with a therapeutically effective amount of a phosphatidylinositol-3-kinase (PI3K) inhibitor.

Exemplary Embodiment No. 32. The method of any one of the preceding Embodiments, further comprising administering to the subject in need thereof a therapeutically effective amount of amivantamab, capmatinib, or a combination thereof.

Exemplary Embodiment No. 33. The compound of any one of the preceding Embodiments, wherein the compound is used in combination with a therapeutically effective amount of amivantamab, capmatinib, or a combination thereof.

Exemplary Embodiment No. 34. The method of any one of the preceding Embodiments, further comprising administering to the subject in need thereof a therapeutically effective amount of osimertinib.

Exemplary Embodiment No. 35. The compound of any one of the preceding Embodiments, wherein the compound is used in combination with a therapeutically effective amount of osimertinib.

Exemplary Embodiment No. 36. The method of any one of the preceding Embodiments, further comprising administering to the subject in need thereof a therapeutically effective amount of alpelisib.

Exemplary Embodiment No. 37. The compound of any one of the preceding Embodiments, wherein the compound is used in combination with a therapeutically effective amount of alpelisib.

Exemplary Embodiment No. 38. The method of any one of the preceding Embodiments, further comprising administering to the subject in need thereof a therapeutically effective amount of paxalisib.

Exemplary Embodiment No. 39. The compound of any one of the preceding Embodiments, wherein the compound is used in combination with a therapeutically effective amount of paxalisib.

Definitions

[0380] It will be understood that while compounds disclosed herein may be presented in one particular configuration. Such particular configuration is not to be construed as limiting the disclosure to one or another isomer, tautomer, regioisomer or stereoisomer, nor does it exclude mixtures of isomers, tautomers, regioisomers or stereoisomers. In some embodiments, the presentation of a compound herein in a particular configuration intends to encompass, and to refer to, each of the available isomers, tautomers, regioisomers, and stereoisomers of the compound, or any mixture thereof; while the presentation further intends to refer to the specific configuration of the compound.

[0381] Further, it will be understood that while compounds disclosed herein may be presented without specified configuration (e.g., without specified stereochemistry). Such presentation intends to encompass all available isomers, tautomers, regioisomers, and stereoisomers of the compound. In some embodiments, the presentation of a compound herein without specified configuration intends to refer to each of the available isomers, tautomers, regioisomers, and stereoisomers of the compound, or any mixture thereof.

[0382] As used herein, the term “isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[0383] As used herein, the term “chiral centre” refers to a carbon atom bonded to four nonidentical

substituents.

[0384] As used herein, the term "chiral isomer" means a compound with at least one chiral centre. Compounds with more than one chiral centre may exist either as an individual diastereomer or as a mixture of diastereomers, termed "diastereomeric mixture." When one chiral centre is present, a stereoisomer may be characterised by the absolute configuration (R or S) of that chiral centre. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral centre. The substituents attached to the chiral centre under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0385] As used herein, the term "geometric isomer" means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0386] The terms "nucleic acid" and "polynucleotide" are used interchangeably herein to refer to single- or double-stranded RNA, DNA, or mixed polymers. Polynucleotides may include genomic sequences, extra-genomic and plasmid sequences, and smaller engineered gene segments that express, or may be adapted to express polypeptides.

[0387] An "isolated nucleic acid" is a nucleic acid that is substantially separated from other genome DNA sequences as well as proteins or complexes such as ribosomes and polymerases, which naturally accompany a native sequence. The term embraces a nucleic acid sequence that has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogues or analogues biologically synthesized by heterologous systems. A substantially pure nucleic acid includes isolated forms of the nucleic acid. Of course, this refers to the nucleic acid as originally isolated and does not exclude genes or sequences later added to the isolated nucleic acid by the hand of man.

[0388] The term "polypeptide" is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product. Peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or

exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof.

[0389] An "isolated polypeptide" is one that has been identified and separated and/or recovered from a component of its natural environment. In preferred embodiments, the isolated polypeptide will be purified (1) to greater than 95% by weight of polypeptide as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes the polypeptide *in situ* within recombinant cells since at least one component of the polypeptide's natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

[0390] A "native sequence" polynucleotide is one that has the same nucleotide sequence as a polynucleotide derived from nature. A "native sequence" polypeptide is one that has the same amino acid sequence as a polypeptide (e.g. EGFR) derived from nature (*e.g.*, from any species). Such native sequence polynucleotides and polypeptides can be isolated from nature or can be produced by recombinant or synthetic means.

[0391] A polynucleotide "variant," as the term is used herein, is a polynucleotide that typically differs from a polynucleotide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions.

[0392] A polypeptide "variant," as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions, or inversions. Such variants may be naturally occurring, non-naturally occurring, or may be synthetically generated.

[0393] EGFR mutations (or variants) of the disclosure may comprise one or more substitutions, deletions, additions and/or insertions, or inversions of the amino acid sequence that are alter the function of the resultant protein. Mutations may be detected, for example, by comparison or alignment of a nucleic or amino acid sequence with a wild type sequence.

[0394] When comparing polynucleotide and polypeptide sequences, two sequences are said to be

"identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

[0395] Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS 5*:151-153; Myers, E.W. and Muller W. (1988) *CABIOS 4*:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol. 4*:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA 80*:726-730.

[0396] Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

[0397] One preferred example of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters

described herein, to determine percent sequence identity for the polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

[0398] In one illustrative example, cumulative scores can be calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

[0399] For amino acid sequences, a scoring matrix can be used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T and X determine the sensitivity and speed of the alignment.

[0400] In one approach, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.,* gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residues occur in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.,* the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

[0401] A wild type EGFR sequence of the disclosure may comprise or consist of the amino acid

sequence of:

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 1 mrpsgtagaa llallaalcp asraleekkv cqgtsnkltq lgtfedhfls lqrmfnncev
 61 vlgnleityv qrnydlsflk tiqevagyvl ialntverip lenlqiirgn myyensyala
121 vlsnydankt glkelpmrnl qeilhgavrf snnpalcnve siqwrdivss dflsnmsmdf
181 qnhlgscqkc dpscpngscw gageencqkl tkiicaqqcs grcrgkspsd cchnqcaagc
241 tgpresdclv crkfrdeatc kdtcpplmly npttyqmdvn pegkysfgat cvkkcprnyv
301 vtdhgscvra cgadsyemee dgvrkckkce gpcrkvcngi gigefkdsls inatnikhfk
361 nctsisgdlh ilpvafrgds fthtppldpq eldilktvke itgflliqaw penrtdlhaf
421 enleiirgrt kqhgqfslav vslnitslgl rslkeisdgd viisgnknlc yantinwkkl
481 fgtsgqktki isnrgensck atgqvchalc spegcwgpep rdcvscrnvs rgrecvdkck
541 llegeprefv enseciqchp eclpqamnit ctgrgpdnci qcahyidgph cvktcpagvm
601 genntlvwky adaghvchlc hpnctygctg pglegcptng pkipsiatgm vgalllllvv
661 algiglfmrr rhivrkrtlr rllqerelve pltpsgeapn qallrilket efkkikvlgs
721 gafgtvykgl wipegekvki pvaikelrea tspkankeil deayvmasvd nphvcrllgi
781 cltstvqlit qlmpfgclld yvrehkdnig sqyllnwcvq iakgmnyled rrlvhrdlaa
841 rnvlvktpqh vkitdfglak llgaeekeyh aeggkvpikw malesilhri ythqsdvwsy
901 gvtvwelmtf gskpydgipa seissilekg erlpqppict idvymimvkc wmidadsrpk
961 freliiefsk mardpqrylv iqgdermhlp sptdsnfyra lmdeedmddv vdadeylipq
1021 qgffsspsts rtpllsslsa tsnnstvaci drnglqscpi kedsflqrys sdptgalted
1081 siddtflpvp eyinqsvpkr pagsvqnpvy hnqplnpaps rdphyqdphs tavgnpeyln
1141 tvqptcvnst fdspahwaqk gshqisldnp dyqqdffpke akpngifkgs taenaeylrv
1201 apqssefiga
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(SEQ ID NO: 1, corresponding to epidermal growth factor receptor [Homo sapiens] and Genbank Accession No. CAA25240).

[0402] A wild type HER2 Receptor sequence of the disclosure may comprise or consist of the amino acid sequence of:

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 1 melaalcrwg lllallppga astqvctgtd mklrlpaspe thldmlrhly qgcqvvqgnl
 61 eltylptnas lsflqdiqev qgyvliahnq vrqvplqrlr ivrgtqlfed nyalavldng
121 dplnnttpvt gaspgglrel qlrslteilk ggvliqrnpq lcyqdtilwk difhknnqla
181 ltlidtnrsr achpcspmck gsrcwgesse dcqsltrtvc aggcarckgp lptdccheqc
241 aagctgpkhs dclaclhfnh sgicelhcpa lvtyntdtfe smpnpegryt fgascvtacp
301 ynylstdvgs ctlvcplhnq evtaedgtqr cekcskpcar vcyglgmehl revravtsan
361 iqefagckki fgslaflpes fdgdpasnta plqpeqlqvf etleeitgyl yisawpdslp
421 dlsvfqnlqv irgrilhnga ysltlqglgi swlglrslre lgsglalihh nthlcfvhtv
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481 pwdqlfrnph qallhtanrp edecvgegla chqlcarghc wgpgptqcvn csqflrgqec
541 veecrvlqgl preyvnarhc lpchpecqpq ngsvtcfgpe adqcvacahy kdppfcvarc
601 psgvkpdlsy mpiwkfpdee gacqpcpinc thscvdlddk gcpaeqrasp ltsiisavvg
661 illvvvlgvv fgilikrrqq kirkytmrrl lqetelvepl tpsgampnqa qmrilketel
721 rkvkvlgsga fgtvykgiwi pdgenvkipv aikvlrents pkankeilde ayvmagvgsp
781 yvsrllgicl tstvqlvtql mpygclldhv renrgrlgsq dllnwcmqia kgmsyledvr
841 lvhrdlaarn vlvkspnhvk itdfglarll dideteyhad ggkvpikwma lesilrrrft
901 hqsdvwsygv tvwelmtfga kpydgipare ipdllekger lpqppictid vymimvkcwm
961 idsecrprfr elvsefsrma rdpqrfvviq nedlgpaspl dstfyrslle dddmgdlvda
1021 eeylvpqqgf fcpdpapgag gmvhhrhrss strsgggdlt lglepseeea prsplapseg
1081 agsdvfdgdl gmgaakglqs lpthdpsplq rysedptvpl psetdgyvap ltcspqpeyv
1141 nqpdvrpqpp spregplpaa rpagatlerp ktlspgkngv vkdvfafgga venpeyltpq
1201 ggaapqphpp pafspafdnl yywdqdpper gappstfkgt ptaenpeylg ldvpv (SEQ ID NO: 2, corresponding to receptor tyrosine-protein kinase erbB-2 isoform a precursor [Homo sapiens] and GenBank Accession No. NP_004439).

[0403] A wild type HER2 Receptor sequence of the disclosure may comprise or consist of the amino acid sequence of:

1 mklrlpaspe thldmlrhly qgcqvvqgnl eltylptnas lsflqdiqev qgyvliahnq
61 vrqvplqrlr ivrgtqlfed nyalavldng dplnnttpvt gaspgglrel qlrslteilk
121 ggvliqrnpq lcyqdtilwk difhknnqla ltlidtnrsr achpcspmck gsrcwgesse
181 dcqsltrtvc aggcarckgp lptdccheqc aagctgpkhs dclaclhfnh sgicelhcpa
241 lvtyntdtfe smpnpegryt fgascvtacp ynylstdvgs ctlvcplhnq evtaedgtqr
301 cekcskpcar vcyglgmehl revravtsan iqefagckki fgslaflpes fdgdpasnta
361 plqpeqlqvf etleeitgyl yisawpdslp dlsvfqnlqv irgrilhnga ysltlqglgi
421 swlglrslre lgsglalihh nthlcfvhtv pwdqlfrnph qallhtanrp edecvgegla
481 chqlcarghc wgpgptqcvn csqflrgqec veecrvlqgl preyvnarhc lpchpecqpq
541 ngsvtcfgpe adqcvacahy kdppfcvarc psgvkpdlsy mpiwkfpdee gacqpcpinc
601 thscvdlddk gcpaeqrasp ltsiisavvg illvvvlgvv fgilikrrqq kirkytmrrl
661 lqetelvepl tpsgampnqa qmrilketel rkvkvlgsga fgtvykgiwi pdgenvkipv
721 aikvlrents pkankeilde ayvmagvgsp yvsrllgicl tstvqlvtql mpygclldhv
781 renrgrlgsq dllnwcmqia kgmsyledvr lvhrdlaarn vlvkspnhvk itdfglarll
841 dideteyhad ggkvpikwma lesilrrrft hqsdvwsygv tvwelmtfga kpydgipare
901 ipdllekger lpqppictid vymimvkcwm idsecrprfr elvsefsrma rdpqrfvviq

961 nedlgpaspl dstfyrslle dddmgdlvda eeylvpqqgf fcpdpapgag gmvhhrhrss
1021 strsgggdlt lglepseeea prsplapseg agsdvfdgdl gmgaakglqs lpthdpsplq
1081 rysedptvpl psetdgyvap ltcspqpeyv nqpdvrpqpp spregplpaa rpagatlerp
1141 ktlspgkngv vkdvfafgga venpeyltpq ggaapqphpp pafspafdnl yywdqdpper
1201 gappstfkgt ptaenpeylg ldvpv (SEQ ID NO: 3, corresponding to receptor tyrosine-protein kinase erbB-2 isoform b [Homo sapiens] and GenBank Accession No. NP_001005862).

[0404] A wild type HER2 Receptor sequence of the disclosure may comprise or consist of the amino acid sequence of:

1 mprgswkpqv ctgtdmklrl paspethldm lrhlyqgcqv vqgnleltyl ptnaslsflq
61 diqevqgyvl iahnqvrqvp lqrlrivrgt qlfednyala vldngdplnn ttpvtgaspg
121 glrelqlrsl teilkggvli qrnpqlcyqd tilwkdifhk nnqlaltlid tnrsrachpc
181 spmckgsrcw gessedcqsl trtvcaggca rckgplptdc cheqcaagct gpkhsdclac
241 lhfnhsgice lhcpalvtyn tdtfesmpnp egrytfgasc vtacpynyls tdvgsctlvc
301 plhnqevtae dgtqrcekcs kpcarvcygl gmehlrevra vtsaniqefa gckkifgsla
361 flpesfdgdp asntaplqpe qlqvfetlee itgylyisaw pdslpdlsvf qnlqvirgri
421 lhngaysltl qglgiswlgl rslrelgsgl alihhnthlc fvhtvpwdql frnphqallh
481 tanrpedecv geglachqlc arghcwgpgp tqcvncsqfl rgqecveecr vlqglpreyv
541 narhclpchp ecqpqngsvt cfgpeadqcv acahykdppf cvarcpsgvk pdlsympiwk
601 fpdeegacqp cpincthscv dlddkgcpae qraspltsii savvgillvv vlgvvfgili
661 krrqqkirky tmrrllqete lvepltpsga mpnqaqmril ketelrkvkv lgsgafgtvy
721 kgiwipdgen vkipvaikvl rentspkank eildeayvma gvgspyvsrl lgicltstvq
781 lvtqlmpygc lldhvrenrg rlgsqdllnw cmqiakgmsy ledvrlvhrd laarnvlvks
841 pnhvkitdfg larlldidet eyhadggkvp ikwmalesil rrrfthqsdv wsygvtvwel
901 mtfgakpydg ipareipdll ekgerlpqpp ictidvymim vkcwmidsec rprfrelvse
961 fsrmardpqr fvviqnedlg paspldstfy rslledddmg dlvdaeeylv pqqgffcpdp
1021 apgaggmvhh rhrssstrsg ggdltlglep seeeaprspl apsegagsdv fdgdlgmgaa
1081 kglqslpthd psplqrysed ptvplpsetd gyvapltcsp qpeyvnqpdv rpqppspreg
1141 plpaarpaga tlerpktlsp gkngvvkdvf afggavenpe yltpqggaap qphpppafsp
1201 afdnlyywdq dppergapps tfkgtptaen peylgldvpv (SEQ ID NO: 4, corresponding to receptor tyrosine-protein kinase erbB-2 isoform c [Homo sapiens] and GenBank Accession No. NP_001276865).

[0405] A wild type HER2 Receptor sequence of the disclosure may comprise or consist of the amino acid sequence of:

1 melaalcrwg lllallppga astqvctgtd mklrlpaspe thldmlrhly qgcqvvqgnl
61 eltylptnas lsflqdiqev qgyvliahnq vrqvplqrlr ivrgtqlfed nyalavldng
121 dplnnttpvt gaspgglrel qlrslteilk ggvliqrnpq lcyqdtilwk difhknnqla
181 ltlidtnrsr achpcspmck gsrcwgesse dcqsltrtvc aggcarckgp lptdccheqc
241 aagctgpkhs dclaclhfnh sgicelhcpa lvtyntdtfe smpnpegryt fgascvtacp
301 ynylstdvgs ctlvcplhnq evtaedgtqr cekcskpcar vcyglgmehl revravtsan
361 iqefagckki fgslaflpes fdgdpasnta plqpeqlqvf etleeitgyl yisawpdslp
421 dlsvfqnlqv irgrilhnga ysltlqglgi swlglrslre lgsglalihh nthlcfvhtv
481 pwdqlfrnph qallhtanrp edecvgegla chqlcarghc wgpgptqcvn csqflrgqec
541 veecrvlqgl preyvnarhc lpchpecqpq ngsvtcfgpe adqcvacahy kdppfcvarc
601 psgvkpdlsy mpiwkfpdee gacqpcpinc thscvdlddk gcpaeqrasp ltsiisavvg
661 illvvvlgvv fgilikrrqq kirkytmrrl lqetelvepl tpsgampnqa qmrilketel
721 rkvkvlgsga fgtvykgiwi pdgenvkipv aikvlrents pkankeilde ayvmagvgsp
781 yvsrllgicl tstvqlvtql mpygclldhv renrgrlgsq dllnwcmqia kgmsyledvr
841 lvhrdlaarn vlvkspnhvk itdfglarll dideteyhad ggkvpikwma lesilrrrft
901 hqsdvwsygv tvwelmtfga kpydgipare ipdllekger lpqppictid vymimvkcwm
961 idsecrprfr elvsefsrma rdpqrfvviq nedlgpaspl dstfyrslle dddmgdlvda
1021 eeylvpqqgf fcpdpapgag gmvhhrhrss strnm (SEQ ID NO: 5, corresponding to receptor tyrosine-protein kinase erbB-2 isoform d precursor [Homo sapiens] and GenBank Accession No. NP_001276866).

[0406] A wild type HER2 Receptor sequence of the disclosure may comprise or consist of the amino acid sequence of:

1 mklrlpaspe thldmlrhly qgcqvvqgnl eltylptnas lsflqdiqev qgyvliahnq
61 vrqvplqrlr ivrgtqlfed nyalavldng dplnnttpvt gaspgglrel qlrslteilk
121 ggvliqrnpq lcyqdtilwk difhknnqla ltlidtnrsr achpcspmck gsrcwgesse
181 dcqsltrtvc aggcarckgp lptdccheqc aagctgpkhs dclaclhfnh sgicelhcpa
241 lvtyntdtfe smpnpegryt fgascvtacp ynylstdvgs ctlvcplhnq evtaedgtqr
301 cekcskpcar vcyglgmehl revravtsan iqefagckki fgslaflpes fdgdpasnta
361 plqpeqlqvf etleeitgyl yisawpdslp dlsvfqnlqv irgrilhnga ysltlqglgi

421 swlglrslre lgsglalihh nthlcfvhtv pwdqlfrnph qallhtanrp edecvgegla
481 chqlcarghc wgpgptqcvn csqflrgqec veecrvlqgl preyvnarhc lpchpecqpq
541 ngsvtcfgpe adqcvacahy kdppfcvarc psgvkpdlsy mpiwkfpdee gacqpcpinc
601 ths (SEQ ID NO: 6, corresponding to receptor tyrosine-protein kinase erbB-2 isoform e [Homo sapiens] and GenBank Accession No. NP_001276867).

[0407] Based on the definitions given throughout the application the skilled person knows which combinations are synthetically feasible and realistic, e.g. typically combinations of groups leading to heteroatoms directly linked to each other are not contemplated.

[0408] As used herein, the term "about" refers to a range covering any normal fluctuations appreciated by one of ordinary skill in the relevant art. In some embodiments, the term "about" refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[0409] As used herein, the term "pharmaceutically acceptable salt" refers to a derivative of the compound of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc. Other examples of pharmaceutically

acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ratio other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3. It is to be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0410] It is understood that the compounds described herein include the compounds themselves, as well as their pharmaceutically acceptable salts, and their solvates, if applicable. A pharmaceutically acceptable salt, for example, can be formed between a pharmaceutically acceptable anion and a positively charged group (e.g., amino) on a compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (e.g., trifluoroacetate).

[0411] It is understood that the compounds of the present disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates and dihydrates. Nonlimiting examples of solvates include ethanol solvates and acetone solvates.

[0412] As used herein, the expressions “one or more of A, B, or C,” “one or more A, B, or C,” “one or more of A, B, and C,” “one or more A, B, and C,” “selected from the group consisting of A, B, and C”, “selected from A, B, and C”, and the like are used interchangeably and all refer to a selection from a group consisting of A, B, and/or C, i.e., one or more As, one or more Bs, one or more Cs, or any combination thereof, unless indicated otherwise.

[0413] It is understood that, throughout the description, where compositions are described as having, including, or comprising specific components, it is contemplated that compositions also

consist essentially of, or consist of, the recited components. Similarly, where methods or processes are described as having, including, or comprising specific process steps, the processes also consist essentially of, or consist of, the recited processing steps. Further, it should be understood that the order of steps or order for performing certain actions is immaterial so long as the invention remains operable. Moreover, two or more steps or actions can be conducted simultaneously.

[0414] It is understood that compounds of the present disclosure can be prepared in a variety of ways using commercially available starting materials, compounds known in the literature, or from readily prepared intermediates, by employing standard synthetic methods and procedures either known to those skilled in the art, or which will be apparent to the skilled artisan in light of the teachings herein. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be obtained from the relevant scientific literature or from standard textbooks in the field. Although not limited to any one or several sources, classic texts such as Smith, M. B., March, J., *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th edition, John Wiley & Sons: New York, 2001; Greene, T.W., Wuts, P.G. M., *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons: New York, 1999; R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995), incorporated by reference herein, are useful and recognized reference textbooks of organic synthesis known to those in the art.

[0415] As used herein, the term "subject" includes human and non-human mammal, as well as cell lines, cell culture, tissues, and organs. In some embodiments, the subject is a mammal. The mammal can be *e.g.*, a human or appropriate non-human mammal, such as primate, mouse, rat, dog, cat, cow, horse, goat, camel, sheep or a pig. The subject can also be a bird or fowl. In some embodiments, the subject is a human.

[0416] As used herein, the term "subject in need thereof", refers to a subject having a disease (to be treated) or having an increased risk of developing the disease (to be prevented). A subject in need thereof can be one who has been previously diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who has (e.g., is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (*i.e.*, a

subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant a disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that doesn't respond or hasn't yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0417] As used herein, the term "treating" or "treat" describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder. The term "treat" can also include treatment of a cell *in vitro* or an animal model.

[0418] It is understood that a compound of the present disclosure, or a pharmaceutically acceptable salt, polymorph or solvate thereof, can or may also be used to prevent a relevant disease, condition or disorder, or used to identify suitable candidates for such purposes.

[0419] As used herein, the term "preventing," "prevent," or "protecting against" describes reducing or eliminating the onset of the symptoms or complications of such disease, condition or disorder.

[0420] As used herein, the term "temporal proximity" refers to that administration of one therapeutic agent (Compound No. 2 (e.g., Compound No. 2A or Compound No. 2B)) occurs within a time period before or after the administration of another therapeutic agent (e.g., temozolomide), such that the therapeutic effect of the one therapeutic agent overlaps with the therapeutic effect of the other therapeutic agent. In some embodiments, the therapeutic effect of the one therapeutic agent completely overlaps with the therapeutic effect of the other therapeutic agent. In some embodiments, "temporal proximity" means that administration of one therapeutic agent occurs within a time period before or after the administration of another therapeutic agent, such that there is a synergistic effect between the one therapeutic agent and the other therapeutic agent. "Temporal proximity" may vary according to various factors, including but not limited to, the age, gender, weight, genetic background, medical condition, disease history, and treatment history of the subject to which the therapeutic agents are to be administered; the disease or condition to be

treated or ameliorated; the therapeutic outcome to be achieved; the dosage, dosing frequency, and dosing duration of the therapeutic agents; the pharmacokinetics and pharmacodynamics of the therapeutic agents; and the route(s) through which the therapeutic agents are administered. In some embodiments, "temporal proximity" means within 15 minutes, within 30 minutes, within an hour, within two hours, within four hours, within six hours, within eight hours, within 12 hours, within 18 hours, or within 24 hours. In some embodiments, multiple administration of one therapeutic agent can occur in temporal proximity to a single administration of another therapeutic agent. In some embodiments, temporal proximity may change during a treatment cycle or within a dosing regimen.

[0421] As used herein, the term "pharmaceutically acceptable" refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0422] As used herein, the term "pharmaceutically effective amount", refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject's body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Pharmaceutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician.

[0423] It is understood that, for the compounds of the present disclosure beingcapable of further forming salts, all of these forms are also contemplated within the scope of the claimed disclosure.

[0424] As used herein, the term "pharmaceutically acceptable salts" refer to derivatives of the compounds of the present disclosure wherein the parent compound is modified by making acid or base salts thereof. In some embodiments, the pharmaceutically acceptable salt of a compound is also a prodrug of the compound. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional

non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0425] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The present disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0426] It is understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates) or crystal forms (polymorphs) as defined herein, of the same salt.

[0427] As used herein, the term “prodrug” refers to any agent which, when administered to a mammal, is converted in whole or in part to a targeted compound. In some embodiments, the prodrug of a compound is also a pharmaceutically acceptable salt of the compound.

[0428] It is understood that the compounds of the present disclosure can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, acetate, propionate or other ester.

[0429] The compounds, or pharmaceutically acceptable salts thereof, are administered orally,

nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In one embodiment, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0430] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0431] Techniques for formulation and administration of the disclosed compounds of the disclosure can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In an embodiment, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0432] Various *in vitro* or *in vivo* biological assays are may be suitable for detecting the effect of the compounds of the present disclosure. These *in vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0433] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the present disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the present disclosure. The examples do not limit the claimed disclosure. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the present disclosure.

[0434] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission

that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow.

EXAMPLES

Example 1. Selectivity of Compound No. 1A for allosteric EGFR variants expressed in GBM

[0435] To assess the selectivity for Compound No. 1A for EGFR allosteric mutants, anti-proliferative IC_{50} values were deteremined for Compound No. 1A in EGFR-WT, EGFR-Viii, EGFR-Vii, EGFR-Vvi, EGFR-A289V, and EGFR-G598V. See, e.g., FIG. 1.

Example 2. Plasma and brain concentration for Compound No. 1A

[0436] To assess the ability for Compound No. 1A to penetrate the brain, mean plasma and brain concentration was deteremined for Compound No. 1A when dosed at 15 mg/kg. The unbound partition coefficient (K_{puu}) was determined to be 0.19. See, e.g., FIG. 2. FIG. 10 shows the mean plasma concentration of Compound No. 1A in mice when administered orally (PO) at 15 mg/kg and when administered via IV bolus at 1 mg/kg. Pharmacokinetic (PK) parameters were measured for mice after being administered Compound No. 1A orally (PO) at 15 mg/kg and when administered via IV bolus at 1 mg/kg as shown in Table A below.

Table A

	Mouse (BalbC)
IV Dose	**1 mg/kg[a]**
C_0 (ng/mL)	4241
$T_{1/2}$ (h)	1.15
Vd_{ss} (L/kg)	0.60
Cl (mL/min/kg)	14
$AUC_{0\text{-last}}$ (ng·h/mL)	1184
PO Dose	**15 mg/kg[b]**
C_{max} (ng/mL)	855
T_{max} (h)	0.5
$T_{1/2}$ (h)	1.7
$AUC_{0\text{-last}}$ (ng·h/mL)	1716

Bioavailability (%)	13
AUClast_brain/AUClast_plasma	0.375

[a]0.5 mg/ml in 50%PEG400/50%water, clear solution; [b]1.5 mg/ml in 0.5% methylcellulose and 0.4% Tween 80, clear solution. The data presented in Table A are approximate and subject to experimental and instrumental variations.

Example 3. Engagement of allosteric EGFR mutants in vivo with Compound No. 1A

[0437] The relationship between pEGFR and administration of Compound No. 1A was determined in BaF3-EGFR V2 Xenografts MI4029. See, e.g., FIG. 3.

Example 4. Compound No. 1A inhibits tumor growth of intracranial PDX tumors expressing allosteric EGFR mutants

[0438] To assess the ability of Compound No. 1A to inhibit tumor growth, the normalized bioluminescence intensity (BLI) of GBM6 orthotopic brain patient derived xenograft tumors expressing EGFR-Viii was deteremined when treated with Compound No. 1A at 50 mg/kg, 15 mg/kg, or 5 mg/kg. See, e.g., FIG. 4.

Example 5. Selectivity of Compound No. 2B for allosteric EGFR variants expressed in GBM

[0439] To assess the selectivity for Compound No. 2B for EGFR allosteric mutants, anti-proliferative IC_{50} values were determined for Compound No. 2B in EGFR-WT, EGFR-Viii, EGFR-Vii, EGFR-A289V, and EGFR-G598V. See, e.g., FIG. 5.

Example 6. Plasma and brain concentration for Compound No. 2B

[0440] To assess the ability for Compound No. 2B to penetrate the brain, mean plasma and brain concentration was deteremined for Compound No. 2B when dosed at 15 mg/kg. See, e.g., FIG. 6. FIG. 11 shows the mean plasma concentration of Compound No. 2B in mice when administered orally (PO) at 15 mg/kg and when administered via IV bolus at 1 mg/kg. Pharmacokinetic (PK) parameters were measured for mice after being administered Compound No. 2B orally (PO) at 15 mg/kg and when administered via IV bolus at 1 mg/kg as shown in Table B below.

Table B

	Mouse (BalbC)

IV Dose	**1 mg/kg[a]**
C_0 (ng/mL)	624
$T_{1/2}$ (h)	1.6
Vd_{ss} (L/kg)	3.15
Cl (mL/min/kg)	39
$AUC_{0\text{-last}}$ (ng·h/mL)	419
PO Dose	**15 mg/kg[b]**
C_{max} (ng/mL)	653
T_{max} (h)	0.25
$T_{1/2}$ (h)	3.7
$AUC_{0\text{-last}}$ (ng·h/mL)	1510
Bioavailability (%)	25
AUClast_brain/AUClast_plasma	0.379

[a]0.50 mg/mL in 10% DMA: 40% PEG400: 50% water, clear solution; [b]1.50 mg/mL in 10% DMA: 40% PEG400:50% water, clear solution. The data presented in Table B are approximate and subject to experimental and instrumental variations.

Example 7. Engagement of allosteric EGFR mutants in vivo with Compound No. 2B

[0441] The relationship between pEGFR and administration of Compound No. 2B was determined in BaF3-EGFR V3 Xenografts MI4415. See, e.g., FIG. 7.

Example 8. Compound No. 2B inhibits tumor growth of intracranial PDX tumors expressing allosteric EGFR mutants

[0442] To assess the ability of Compound No. 2B to inhibit tumor growth, the normalized bioluminescence intensity (BLI) of GBM6 orthotopic brain patient derived xenograft tumors expressing EGFR-Viii was deteremined when treated with Compound No. 2B at 150 mg/kg, 50 mg/kg, or 15 mg/kg. See, e.g., FIG. 8.

Example 9. Selectivity of osimertinib for allosteric EGFR variants expressed in GBM

[0443] To assess the selectivity for osimertinib for EGFR allosteric mutants, anti-proliferative IC_{50} values were deteremined for osimertinib in EGFR-WT, EGFR-Viii, EGFR-Vii, EGFR-Vvi, and EGFR-A289V. See, e.g., FIG. 9. Potency and selectivity is not similarly captured by Osimertinib compared to Compound No. 1A and Compound No. 2B.

Example 10. Compound No. 1A inceases survival rate in mice expressing intracranial GBM6 patient derived tumors

[0444] To assess the efficacy for Compound No. 1A, percent survival of mice expressing intracranial GBM6 patient derived tumors when treated orally with 50 mg/kg of Compound No. 1A was determined. FIG. 12 shows percent survival increased over longer dosing periods.

Example 11. Compound No. 2B inceases survival rate in mice expressing intracranial GBM6 patient derived tumors

[0445] To assess the efficacy for Compound No. 2B, percent survival of mice expressing intracranial GBM6 patient derived tumors when treated orally with 50 mg/kg of Compound No. 2B was determined. FIG. 13 shows percent survival increased over longer dosing periods.

Example 12. Compound No. 2B shown to achieve potent and selective inhibition of a spectrum of allosteric EGFR variants

[0446] To assess the potency of Compound No. 2B for inhibition of allosteric EGFR variants expressed in GBM and/or NSCLC, anti-proliferative IC_{50} values were determined for Compound No. 2B inhibiting wild-type EGFR (H292), amplified wild-type EGFR (A431), EGFRvIII, EGFRvII, EGFRvV1, EGFR-R222C, EGFR-C231F, EGFR-A289V, EGFR-C595S, EGFR-G598V, EGFR-D761Y, EGFR-G719C, EGFR-G719D, EGFR-G719R, EGFR-E746-A750del, EGFR-L858R, EGFR-E746-A750del+C797, and EGFR-E746-A750del+C797S+T790M. See, *e.g.,* FIG. 14A. Compound No. 2B was further demonstrated to inhibit EGFR-R108K, EGFR-A298T, EGFR-S645C with an anti-proliferative IC_{50} of less than 10 nM. See, *e.g.,* FIG. 14B. Compound No. 2B was demonstrated to have low activity against wild-type EGFR (H292) and moderate activity against amplified wild-type EGFR (A431). Anti-proliferative IC_{50} values were also determined for osimertinib. See, e.g., FIG. 14C. Compound No. 2B was found to have increased potency and selectivity against EGFR mutations that occur in GBM compared to osimertinib. Additionally, Compound No. 2B demonstrated activity aginast the C797S resistance mutation. FIG. 22 and FIG. 23 also show greater than 10-fold selectivity in EGFR variants and mutants found in GBM and of intrinsic resistance and acquired resistance in NSCLC.

Example 13. Compound No. 2B shows favorable preclinical CNS PK profiles across species

[0447] PK parameters of were measured for PO administration of Compound No. 2B in mouse (15 mg/kg), rat (30 mg/kg), and dog (30 mg/kg). See, *e.g.*, FIGs. 15-17. The unbound partition coefficient (K_{puu}) was determined to be 0.19 in the brain for mouse. The K_{puu} was determined to be 0.81 in the brain and 0.90 in cerebrospinal fluid (CSF) for rat. The K_{puu} was determined to be 0.22 in CSF for dog.

Example 14. Clinical Study of Compound No. 2B.

[0448] This study is comprised of modules in which Compound No. 2B is be evaluated as either a single agent or in combination with other therapies for the treatment of patients with GBM or NSCLC.

[0449] Each module consists of a Dose Escalation and Dose Expansion phase. Patients are enrolled in each module are as follows:

Module 1: GBM that has relapsed/refractory (RR) following initial surgery or NSCLC with an EGFR C797S or E18 mutation.

Module 2: GBM in patients who are eligible for treatment with temozolomide (TMZ).

Module 3: GBM or NSCLC with an EGFR C797S or E18 mutation eligible for surgical resection.

[0450] NSCLC patients have documented EGFR C797S or Exon 18 mutation status as confirmed by a validated NGS assay routinely used by each institution. In addition, a baseline tumor sample is provided for retrospective concordance testing by a companion diagnostic test.

Example 15. Irreversible Inhibition in vitro with Compound No. 2B

[0451] The irreversibility of Compound No. 2B was determined in a washout study in Ba/F3 EGFRvIII. See, e.g. FIG. 18.

[0452] The irreversibility of Compound No. 2B was also determined against C797S mutant, which has >24 hour inhibition of pEGFR Ex19/C797S at 34 nM, whereas Osimertinib at 1,000 nM shows complete washout after 0.5 hours. See, e.g., FIG. 24.

Example 16. Irreversible Inhibition in vivo with Compound No. 1

[0453] The relationship between pEGFR (p1068) and administration of Compound No. 1 was

determined in mice bearing BaF3 allograft tumors expressing EGFR-Viii. See, e.g., FIG. 19A.

Example 17. Irreversible Inhibition in vivo with Compound No. 1A

[0454] The relationship between pEGFR (p1068) and administration of Compound No. 1A was determined in mice bearing BaF3 allograft tumors expressing EGFR-Viii. See, e.g., FIG. 19B.

Example 18. Irreversible Inhibition in vivo with Compound No. 2B

[0455] The relationship between pEGFR (p1068) and administration of Compound No. 2B was determined in mice bearing BaF3 allograft tumors expressing EGFR-Viii. See, e.g., FIG. 19C.

Example 19. Tumour Growth Inhibition in vivo with Compound No. 2B

[0456] The relationship between the median tumor volume (mm^3) and administration of Compound No. 2B was determined in a subcutaneous GBM46 PDX expressing EGFRvII mouse model. See, e.g., FIG. 20. The relationship between the mean tumor volume (mm^3) and administration of Compound No. 2B was determined in Ba/F3-EGFR Exon19del + C797S mouse allograft models when administered Compound No. 2B at 40 mg/kg or at 120 mg/kg. See, e.g., FIG. 25 and FIG. 26.

Example 20. Compound No. 2B Inhibits EGFR Ex19del and Ex19del/C797S-driven Cell Lines

[0457] The ability for Compound No. 2B to selectively bind EGFR Ex19del and Ex19del/C797S-driven cell lines without sacrificing selectivity over EGFR WT is shown in Table C below. Compound No. 2B is an irreversible EGFR inhibitor that is selective for EGFR Ex19del and Ex19del/C797S over EGFR WT. The data presented in Table C are approximate and subject to experimental and instrumental variations.

Table C

	Erlotinib	**Gefitinib**	**Afatinib**	**Dacomitinib**	**Osimertinib**	**Compound No. 2B**
MOA	Reversible	Reversible	Irreversible	Irreversible	Irreversible	Irreversible
CNS Kpuu (r)	0.08	0.29	-	0.21	0.29	0.45
EGFR-WT (H292) IC_{50} (nM)	878	418	29	28	454	119
EGFR Ex19del (Ba/F3) IC_{50} (nM)	19	10	0.5	0.3	2.5	0.6

EGFR Ex19del/C797S (Ba/F3) IC_{50} (nM)	15	11	8	9	>1000	3.1

Example 21. Bodyweight is unimpacted with Compound No. 2B

[0458] The relationship between the % bodyweight and administration of Compound No. 2B was determined in a subcutaneous GBM46 PDX expressing EGFRvII mouse model. See, e.g., FIG. 21.

Dose Escalation

[0459] Within each module, patients are initially enrolled in a Dose Escalation stage.

[0460] All modules use a Bayesian optimal interval (BOIN) dose escalation design using dose levels of 400 mg, 600 mg, 800 mg, and 1000 mg QD (n=7 for each dose level).

[0461] In Module 1 only, the dose escalation of Compound No. 2B initially starts as an accelerated titration of 25 mg, 50 mg, and 100 mg QD (n=1 for each dose). Potential doses are explored using the BOIN design include 200 mg, 400 mg, 600 mg, and 800 mg QD as well as 200 mg, 300 mg, 400 mg, and 500 mg BID dose levels.

[0462] In addition, 12 patients in Module 1 participate in a food or enzyme-inducing antiepileptic drug (EIAD) drug-drug interaction (DDI) evaluation (n=12 per treatment) using either a dose regimen of either 400 mg or 600 mg QD.

[0463] To evaluate the pharmacodynamic effect of Compound No. 2B in backfilled pharmacodynamic (PDc) cohorts (n=3), select GBM patients are enrolled in Module 1.

[0464] For Modules 2 and 3, three dose levels may be explored with the first dose being 1 dose level lower than the RP2D determined for Module 1.

[0465] The primary objective of the Dose Escalation stage of each Module is to identify the MTD of Compound No. 2B as a single agent or combination therapy and determine RP2D for single agent or combination agent. The safety and PK profile of Compound No. 2B are reviewed to determine whether the Dose Expansion phase of the module should be initiated, and if so, recommend an MTD.

Dose Expansion

[0466] The Dose Expansion stage assess the antitumor effect of Compound No. 2B single or combination therapy at the RP2D. The cohorts that are evaluated in each module are provided

below.

[0467] *Module 1:* GBM patients that has relapsed/refractory (RR) disease following initial tumor resection; and NSCLC patients with an EGFR C797S or exon 18 mutation for whom standard therapy is either not available or not appropriate.

[0468] *Module 2:* GBM in patients who are eligible for treatment with temozolomide (TMZ).

[0469] *Module 3:* Newly diagnosed GBM (prior to initial tumor resection); and NSCLC with an EGFR C797S or E18 mutation

Study Treatment

[0470] Compound No. 2B is administered orally in 21-day treatment cycles. Depending on the results of the food effect evaluation portion of Module 1 Dose Escalation stage, Compound No. 2B may be administered with food.

[0471] Study treatment continues until disease progression (PD), unacceptable drug-related toxicity, death, the start of new anticancer therapy, consent withdrawal, or are lost to follow up. Study treatment is discontinued 52 weeks after the last patient first study visit unless the patient is tolerating the study drug and deriving clinical benefit. Study treatment is discontinued in patients who have confirmed PD or who start a subsequent anticancer therapy.

[0472] Patients who complete the initial cycle of therapy without evidence of significant toxicity or clinical evidence of progressive disease) may receive additional 21-day cycles of treatment at the same dose level.

Study Assessments

[0473] Patients are required to attend clinic visits during the treatment and post-treatment periods for collection of study assessments.

[0474] Tumor imaging is performed once every 6 weeks for 1st 8 cycles and once every 12 weeks thereafter, with the tumor response assessed using RECIST, version 1.1 or by RANO, as appropriate.

[0475] Safety and tolerability are assessed through the reporting of adverse events (AEs); clinical laboratory tests; and electrocardiogram (ECG), echocardiogram (or MUGA), and physical exam findings. Dose-limiting toxicities are assessed using the NCI CTCAE, version 5.0.

[0476] Pharmacokinetic sampling is collected on Days 1 and 15 of Cycle 1 and Day 1 of each

subsequent cycle.

[0477] Exploratory biomarker assessments are performed on plasma ctDNA samples collected once each treatment cycle. In GBM patients, assessments are performed on CSF ctDNA collected at baseline and EOT.

Study Drug/Treatment Groups, Dose, and Mode of Administration

[0478] Patients receive the following treatments in the respective modules:

Module 1: Single-agent Compound No. 2B

Module 2: Compound No. 2B in combination with temozolimide

Module 3: Compound No. 2B either as single agent or combination therapy

[0479] Compound No. 2B is administered orally.

Duration of Treatment/Study:

[0480] Each patient continues study treatment until progressive disease (PD), death, or discontinuation based on the patient's or Investigator's decision. The expected duration of treatment for each patient is 6 months.

[0481] The overall duration of the study is approximately 4 years.

Example 22. Clinical Study of Compound No. 2B

[0482] A Phase 1, open-label, multicenter study of Compound No. 2B in patients with recurrent GBM harboring EGFR alterations or locally advanced or metastatic NSCLC with specific EGFR mutations was performed. The study schema is shown in FIG. 27.

[0483] The monotherapy dose escalation portion of this study evaluates Compound No. 2B in patients with either recurrent GBM expressing EGFR alterations or advanced/metastatic NSCLC harboring sensitive EGFR mutations, with or without CNS disease. The phase 1 study also includes a pilot food effect cohort as well as a leptomeningeal disease (LMD) cohort to further assess CNS drug penetration and target related changes or ctDNA in CSF of patients with leptomeningeal disease. Once a provisional RP2D is established based on safety, PK, PDx, and tolerability data, Compound No. 2B monotherapy is explored in disease specific to further evaluate safety, PK, and preliminary assessment of efficacy. The disease specific expansions include: 1) patents with GBM with EGFR mutations and other variants, and 2) patents with advanced/metastatic NSCLC with

uncommon mutations such as G719S or acquired mutations such as C797S. Once monotherapy safety is established, Compound No. 2B is administered in combination with TMZ to assess safety, tolerability, and recommended combination dose for the treatment of patients with recurrent GBM harboring EGFR mutations or variants.

Monotherapy Dose Escalation

[0484] The maximum tolerated dose (MTD) of Compound No. 2B as monotherapy is estimated using accelerated titration followed by a Bayesian optimal interval (BOIN) design. The starting dose is 15mg once daily oral dosing. Initial dose escalation is proposed as an accelerated titration with single patient cohorts at 15 mg, 25 mg, 50 mg, and 100 mg once daily (QD) in order to minimize the number of patients receiving potentially subtherapeutic dose levels.

[0485] Multi-patient dose cohorts begin at 200 mg QD or at earlier dose levels if grade 2 or higher drug-related adverse events are observed. Additional incremental doses are explored using the BOIN design to identify an MTD. The prespecified dose levels include 200 mg, 400 mg, 600 mg, and 800 mg QD. Further expansion of previously enrolled dose levels and assessment of intermediate dose levels are conducted to further evaluate the safety, PK, preliminary efficacy, and PDx activity of Compound No. 2B.

Leptomeningeal Disease (LMD) Cohort

[0486] The LMD cohort allows patients with leptomeningeal disease to receive Compound No. 2B treatment at dose levels identified as tolerable in the monotherapy dose escalation (in patients without LMD). CSF sampling is utilized to follow CSF malignant cell count in patients with LMD and enable assessment of study drug PK in the CSF as well as target-specific changes in malignant cells or ctDNA. The LMD cohort open for enrollment only after a monotherapy multi-patient dose level is deemed tolerable by the SRC. LMD patients receive daily dosing of Compound No. 2B and assessments as per the monotherapy dose escalation.

Pilot Food Effect (FE) Cohort

[0487] A pilot FE cohort is evaluated to gain preliminary information about the effect of food on the PK of Compound No. 2B. Patients are be dosed in the fed/fasted state. PK is be obtained at 200 mg QD or a different dose as based on emerging PK and safety data. A dose level is not be

tested in the FE cohort unless at least one dose level above it has been deemed tolerable in the monotherapy dose expansion cohorts. If data from high-fat FE indicates, the effect of a low-fat meal on the PK of Compound No. 2B is assessed as part of this cohort.

Dose Expansion Cohorts

Once the RP2D is provisionally established in the monotherapy dose escalation, confirmation of the RP2D and assessment of the preliminary efficacy are followed in disease specific expansion cohorts. Dose expansion enrolls patients in the following disease specific cohorts:

- Recurrent GBM with confirmed *EGFR* alterations
- Locally Advanced or Metastatic NSCLC with an acquired resistance EGFR mutation (C797S) following 3rd generation EGFR inhibitor (eg osimertinib) in the 1st line setting and platinum standard of care therapy, with and without CNS metastases.
- Locally advanced or metastatic NSCLC with oncogenic uncommon *EGFR* mutations (G719A/C/D/R/S, S768I, V769L, E709G/A, D716Y or other mutations validated by the Sponsor) which have progressed following EGFR inhibitor and platinum standard of care therapies, with and without CNS metastases.

[0488] A single RP2D is anticipated from dose escalations across both GBM and NSCLC. However, if disease specific dose escalation is recommended based on emerging data, then further dose adjustments occur within specific arms of patients. The RP2D, whether overall or if disease specific as needed, is selected based on overall safety and tolerability, PK, PDx and preliminary antitumor activity.

Temozolomide (TMZ) Combination

[0489] A dose-finding evaluation is performed with Compound No. 2B in combination with TMZ in patients with recurrent GBM harboring EGFR alterations. The initial dose of Compound No. 2B begins at least one dose level lower than the preliminary RP2D identified during monotherapy dose escalation. The maximum dose of Compound No. 2B in combination with TMZ does not exceed the monotherapy MTD. TMZ is administered per standard of care, in this setting: 150 mg/m^2 PO on Days 1 to 5 of each cycle (28 days).

[0490] Recommendations for Compound No. 2B dose escalation or de-escalation are based on the DLTs observed during Cycle 1 of combination treatment using the BOIN design and review of the

totality of safety, tolerability, and available PK on the combination. The combination MTD is defined as a dose level with at least 9 patients enrolled and de-escalation is not recommended as the next step.

Study Treatment

[0491] Compound No. 2B is administered orally daily as monotherapy in 21-day treatment cycles or in combination with TMZ in 28-day treatment cycles. Study treatment continues until disease progression (PD), unacceptable drug-related toxicity, death, the start of new anticancer therapy, consent withdrawal, or lost to follow up.

Study Assessments

[0492] Tumor imaging is collected. Tumor response is assessed using RECIST, version 1.1, or by RANO, as appropriate. Safety and tolerability are assessed through the reporting of adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), echocardiogram (or MUGA), and physical exam findings. Pharmacokinetic sampling is collected and assessed during treatment cycles. Exploratory biomarker assessments are performed on plasma ctDNA, CTC, and serum samples collected during each treatment cycle. In patients with CNS disease, assessments are performed on CSF collected.

Study Drug/Treatment Groups, Dose, and Mode of Administration

[0493] Patients receive oral daily Compound No. 2B either as a single agent or in combination with TMZ administered orally.

[0494] Doses are evaluated during the Dose Escalation portion include:

- Compound No. 2B as a single agent: 15, 25, 50, 100, 200, 400, 600, and 800 mg QD administered in the fasted state. Intermediate dose levels are evaluated depending on safety and PK.
- For the Food Effect evaluation, Compound No. 2B is dosed at least 1 dose level below what has been deemed tolerable as monotherapy and will be administered in a fasted or fed (low- or high-fat meal) state. The pre-specified nominal dose for food effect cohort is 200 mg or 400 mg of Compound No. 2B depending on the emerging safety and PK data.

- For Compound No. 2B in combination with TMZ, the initial dose of Compound No. 2B in combination with TMZ begins at least one dose level lower than the preliminary RP2D identified during monotherapy dose escalation. The maximum dose of Compound No. 2B in combination with TMZ does not exceed the monotherapy MTD. TMZ is administered per standard of care in this setting: 150 mg/m^2 PO on days 1 to 5 of each 28-day cycle..

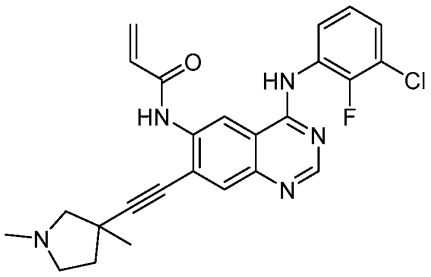
[0495] The provisional RP2D dose identified from the Dose Escalation portion of study is used for the dose expansion cohorts.

EQUIVALENTS

[0496] The details of one or more embodiments of the disclosure are set forth in the accompanying description above. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, the preferred methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms include plural referents unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated by reference. The foregoing description has been presented only for the purposes of illustration and is not intended to limit the disclosure to the precise form disclosed, but by the claims appended hereto.

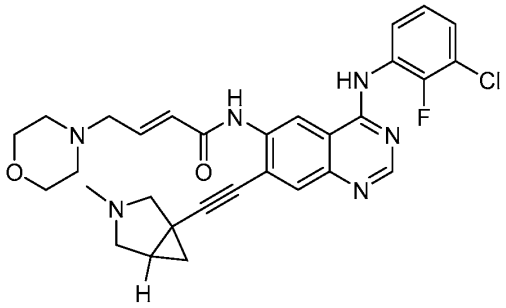
CLAIMS

1. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 1:



;

Compound No. 2:



;

or a pharmaceutically acceptable salt thereof.

2. A method of treating or preventing cancer in a subject in need thereof, comprising administering to the subject a pharmaceutically effective amount of Compound No. 2 or a pharmaceutically acceptable salt thereof.

3. Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof for treating or preventing cancer in a subject in need thereof.

4. Compound No. 2 or a pharmaceutically acceptable salt thereof for treating or preventing cancer in a subject in need thereof.

5. Use of Compound No. 1, Compound No. 2, or a pharmaceutically acceptable salt thereof,

in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

6. Use of Compound No. 2 or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating or preventing cancer in a subject in need thereof.

7. The method, compound, or use of any one of the preceding claims, wherein the cancer is glioblastoma (GBM) or any subtype thereof.

8. The method, compound, or use of any one of the preceding claims, wherein the cancer is glioblastoma.

9. The method, compound, or use of any one of the preceding claims, wherein the cancer is recurrent glioblastoma.

10. The method, compound, or use of any one of the preceding claims, wherein the cancer is non-small cell lung cancer (NSCLC) or any subtype thereof.

11. The method, compound, or use of any one of the preceding claims, wherein the cancer is non-small cell lung cancer (NSCLC).

12. The method, compound, or use of any one of the preceding claims, wherein the cancer is advanced or metastatic NSCLC.

13. The method, compound, or use of any one of the preceding claims, wherein the cancer is NSCLC, wherein the cancer has metastasized to cerebrospinal fluid (CSF).

14. The method, compound, or use of any one of the preceding claims, wherein the cancer is NSCLC, wherein the cancer has metastasized to the brain.

15. The method, compound, or use of any one of the preceding claims, wherein the subject has a central nervous system (CNS) disease.

16. The method, compound, or use of any one of the preceding claims, wherein the subject has a leptomeningeal disease.

17. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2A, Compound No. 2B, or the pharmaceutically acceptable salt thereof is administered.

18. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2A the pharmaceutically acceptable salt thereof is administered.

19. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2B the pharmaceutically acceptable salt thereof is administered.

20. The method, compound, or use of any one of the preceding claims, wherein the subject is a human.

21. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of:

about 15±10 mg, about 15±5 mg, about 15±4 mg, about 15±3 mg, about 15±2 mg, or about 15±1 mg (e.g., about 15 mg);

about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg);

about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about 50 mg);

about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg);

about 150±20 mg, about 150±10 mg, about 150±5 mg, about 150±4 mg, about 150±3 mg, about 150±2 mg, or about 150±1 mg (e.g., about 150 mg);about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg);

about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg,

about 300±2 mg, or about 300±1 mg (e.g., about 300 mg);

about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg);

about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg);

about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg);

about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg); or

about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

22. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 15±10 mg, about 15±5 mg, about 15±4 mg, about 15±3 mg, about 15±2 mg, or about 15±1 mg (e.g., about 15 mg).

23. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 25±10 mg, about 25±5 mg, about 25±4 mg, about 25±3 mg, about 25±2 mg, or about 25±1 mg (e.g., about 25 mg).

24. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 50±10 mg, about 50±5 mg, about 50±4 mg, about 50±3 mg, about 50±2 mg, or about 50±1 mg (e.g., about

50 mg).

25. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 100±20 mg, about 100±10 mg, about 100±5 mg, about 100±4 mg, about 100±3 mg, about 100±2 mg, or about 100±1 mg (e.g., about 100 mg).

26. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 150±20 mg, about 150±10 mg, about 150±5 mg, about 150±4 mg, about 150±3 mg, about 150±2 mg, or about 150±1 mg (e.g., about 150 mg).

27. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 200±20 mg, about 200±10 mg, about 200±5 mg, about 200±4 mg, about 200±3 mg, about 200±2 mg, or about 200±1 mg (e.g., about 200 mg).

28. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 300±20 mg, about 300±10 mg, about 300±5 mg, about 300±4 mg, about 300±3 mg, about 300±2 mg, or about 300±1 mg (e.g., about 300 mg).

29. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 400±50 mg, about 400±40 mg, about 400±30 mg, about 400±20 mg, about 400±10 mg, about 400±5 mg, about 400±4 mg, about 400±3 mg, about 400±2 mg, or about 400±1 mg (e.g., about 400 mg).

30. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 500±50 mg, about 500±40 mg, about 500±30 mg, about 500±20 mg, about 500±10 mg, about 500±5 mg, about 500±4 mg, about 500±3 mg, about 500±2 mg, or about 500±1 mg (e.g., about 500 mg).

31. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 600±50 mg, about 600±40 mg, about 600±30 mg, about 600±20 mg, about 600±10 mg, about 600±5 mg, about 600±4 mg, about 600±3 mg, about 600±2 mg, or about 600±1 mg (e.g., about 600 mg).

32. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 800±50 mg, about 800±40 mg, about 800±30 mg, about 800±20 mg, about 800±10 mg, about 800±5 mg, about 800±4 mg, about 800±3 mg, about 800±2 mg, or about 800±1 mg (e.g., about 800 mg).

33. The method, compound, or use of any one of the preceding claims, wherein Compound No. 2 or the pharmaceutically acceptable salt thereof is administered at a daily dosage of about 1000±50 mg, about 1000±40 mg, about 1000±30 mg, about 1000±20 mg, about 1000±10 mg, about 1000±5 mg, about 1000±4 mg, about 1000±3 mg, about 1000±2 mg, or about 1000±1 mg (e.g., about 1000 mg).

34. The method of any one of the preceding claims, further comprising administering to the subject in need thereof a therapeutically effective amount of temozolomide.

35. The method, compound, or use of any one of the preceding claims, wherein the compound is administered in combination with a therapeutically effective amount of temozolomide.